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The Ulster Medical Journal

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THE ULSTER MEDICAL JOURNAL

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THE ULSTER MEDICAL SOCIETY

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The Ulster Medical Journal, Volume 70, No. 2, pp. 79-88, November 2001

Editorial

Insurance, genetic testing and familial cancer:

Recent policy changes in the United Kingdom

P J Morrison

In the United Kingdom, concerns about the consequences of genetic testing and the eligibility for life assurance have worried families wanting to pursue genetic testing for later onset disorders such as familial cancers and neurological disease. The recent history and development of the insurance and genetic testing guidelines in the UK is interesting and relevant, because it is the only country in Europe to have had a recent major change in insurance recommendations. Insurance companies have driven the changes, which culminated in the agreement of the UK Government and the Association of British Insurers on a five-year moratorium announced at the end of October 2001. This review details the events leading to the introduction of a moratorium, and the implications for families with a family history of a familial cancer.

BACKGROUND

A family history of cancer is now universally recognised as a major risk factor for developing cancer and demand for appropriate clinical services is fuelled by publicity in both the popular media and the professional literature. Within the past few years, cancer genetic clinics have sprung up in almost every major medical centre and all are hard pressed to cope with the numbers of referrals[1-3]. The insurance implications of genetic testing are complex and this review serves to reflect recent changes in government policy and in the thinking of the insurance industry in the United Kingdom. The situation in the USA is different as within a private healthcare system, insurers often encourage or fund genetic testing as they can see the preventative value of such tests in helping initiate cancer screening programmes. The situation in the Republic of Ireland is *de facto* the same as the UK as most insurers in Ireland have head offices in the UK or vice versa and operate the same policy on genetic testing and insurance.

INSURANCE ISSUES

Fisher predicted the use of genetic information in assessing insurance risks as long ago as 1935[4]. Several cancer genetic tests are now available routinely. For testing in familial breast and ovarian cancer, the main tests asked for are BRCA1 and BRCA2, and less frequently PTEN and TP53. In familial colorectal cancer, familial adenomatous polyposis coli (FAP) and hereditary non-polyposis colon cancer (HNPCC) tests are in common use. Huntington's disease (HD), an autosomal dominant neurodegenerative disorder, has been a role model for this type of testing in adult genetic diseases. Several ethical and legal problems already have been recognised[5,6]. Clearly, there is a difference between more highly penetrant autosomal dominant diseases such as HD, and such diseases as breast and colon cancer. Life tables and penetrance have been worked out for HD and it is possible to predict the age of death within a narrow range. Cancers due to single genes such as breast cancer, which constitute only 5-10% of a predominantly non familial common cancer, present more difficulty, as few accurate lifetime risk tables are available or are difficult to compile with limited accurate penetrance data[7,8]. If genetic tests such as BRCA1 and BRCA2 are used in insurance, they should only be used in conjunction with other information.

DEFINITION OF A GENETIC TEST

A genetic test has been defined as *"an examination of the chromosome, DNA or RNA to find out if there is an otherwise undetectable disease related is genotype, which may indicate an increased chance of that individual developing a specific disease in the future"*[9].

The UK advisory committee on genetic testing (ACGT) definition[10] defines it as *"a test to detect the presence or absence of, or change in, a particular gene or chromosome"*.

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Family history data has been used for years and is generally accepted by insurance companies although there may be considerable inaccuracy in family history data. Using such history without good validated reasons is bad practice and should be challenged - further evidence needs to be collected to demonstrate whether such use is really fair or effective.

In the UK, 95-97% of life insurance policies are accepted at no increased premium. Only about 1% are declined, and 2-4% are rated up[11, 12]. There is no analysis of these figures for specific diseases. The main reason for refusal or 'loaded' premiums is the above average sum assured, and not the type of 'high risk' individual assessed. Risks for insurers will be small if the policy value is low[13], for example under £100,000.

THE RECENT UK POLICY DEVELOPMENTS IN INSURANCE AND GENETIC TESTING

In the UK the main concern is about the consequences of cancer genetic testing on the eligibility for life assurance[14,15]. The recent history and development of the insurance and genetic testing situation in the UK is interesting and relevant, because it is the only country in Europe to have had a recent major change in insurance recommendations. Insurance companies have driven the changes. Before 1995, the insurance industry paid little attention to progression of genetic testing. A House of Commons Science and Technology Select Committee reported on human genetics in 1995,[16] and included insurance issues. The committee found a lack of published research on underwriting and adverse selection, with the insurance industry relying on the principle of the 'right to underwrite'.

Shortly after the publication of the report, the UK Government gave the ABI one year to formulate proposals that would meet demands for access to insurance. At the same time, they announced the formation of a Human Genetics Advisory Commission (HGAC). The HGAC was established in December 1996 as a non-statutory advisory body to report to the government on various developments in genetics. It concentrated on insurance as its first task. The insurance industry in 1997 announced the appointment of a genetics adviser and drafted a code of practice. The first HGAC report was published in December 1997[13]. The report recommended a two-year moratorium on genetic testing. Its conclusions are shown in Table 1. The Association of British Insurers (ABI), a body representing around 95% of insurers in the UK, also reported their recommendations at the same time as the HGAC[8]. The ABI code of practice for genetic testing came into effect in January 1998. The code had several important features (Table 2) and applied to all insurance, including life, permanent health, critical illness, and long-term care and medical expenses. Most 'relevant' UK insurance is predominantly life insurance linked to personal pensions, and property insurance (mortgage cover). As the UK National Health Service provides free health care, health insurance is less frequently purchased than in the USA, although there has been a recent increase in sales of personal health insurance cover policies. The situation

TABLE 1:

Recommendations on genetic testing & insurance of the Human Genetics Advisory Commission of the UK (1998).

1. A permanent ban on the use of genetic testing is not appropriate. Recommendation is for introduction of a moratorium on genetic testing for at least 2 years.
2. There is not sufficient predictive ability of genetic tests at the moment to allow accurate risk assessment.
3. The life insurance industry could currently withstand limited adverse selection if nondisclosure of test results was current policy.
4. There is a perception of unacceptable discrimination - this may deter testing that may lead to beneficial treatment.
5. Arrangements for confidentiality of data are adequate under current practice.
6. No company should require taking of a test as a prerequisite of obtaining cover.
7. Increased research and collaboration between industry and science is required to improve knowledge of actuarial implications of genetic factors.
8. There should be a robust appeals procedure as part of any new system.
9. Recommendations are primarily relating to life insurance but the principles above should appl apply to other types of health insurance.

TABLE 2:

Association of British Insurers code of practice for genetic testing (1998).

1. Insurance companies will not insist on genetic tests.
2. Genetic test results will only affect insurance if they show a clearly increased risk of illness or death. A low increase in risk will not necessarily affect the premium.
3. Insurance companies will always seek expert medical advice when assessing the impact of genetic test results on insurance.
4. Insurers may take account of a test result only when reliability and relevance have been established.
5. Applicants for insurance will not be asked to take a genetic test, but existing test results should be given to the insurance company when it asks a relevant question, unless it has said this information is not required.
6. Existing genetic test results need not be disclosed in applications for life insurance up to £100,000* which are directly linked to a new mortgage for the purchase of a house to be occupied by the applicant(s).
7. An applicant will not be required to disclose the result of a genetic test undertaken by another person (such as a blood relative), and one person's test information will not affect another person's application.
8. The reason for an increased premium or rejection of an insurance application will be provided to the applicant's doctor on request.
9. Insurers will not "cherry pick" by offering a "preferred life" lower than normal premiums on the basis of their genetic test results.
10. An independent adjudication tribunal is being set up to consider complaints, which are unresolved.
11. Each year chief executives will need to demonstrate how they have complied with the code.

* Extended to £300,000 for all classes of insurance in May 2001 and to £500,000 for life insurance in October 2001

differs greatly from the USA insurance market, which is dominated by private health insurance.

The Government responded to the HGAC in late 1998 and although it didn't accept the proposed moratorium, it established a genetics and insurance advisory committee (GAIC in April 1999 in an attempt to validate genetic tests proposed by the Association of British Insurers. The ABI had listed matrices of autosomal dominant, autosomal recessive and X-linked recessive diseases for potential validation. Initially a list of around 30 tests was drafted, and then shortened to eight Autosomal dominant diseases. Adult polycystic kidney disease was then dropped as a test as ultrasound scanning was found to be reliable and easier to institute than a genetic test The list of seven conditions (see Table 3) includes Huntington's disease, multiple endocrine neoplasia (MEN-2), breast cancer (BRCAI & 2 genes), familial adenomatous polyposis coli (FAP), Alzheimer disease, hereditary motor and sensory neuropathy (HMSN) and myotonic dystrophy. The list was never openly published.

TABLE 3.

List of seven conditions and genetic tests recommended by the ABI as relevant for insurance purposes genetic tests of ABI

Condition	**Genes tested for**
*Huntington disease	HD
*Early onset familial Alzheimer disease	APP, PS1 and PS2
*Hereditary breast and ovarian cancer	*BRCA1 and BRCA2*
Myotonic Dystrophy	*MDPK*
Familial adenomatous polyposis	*APC*
Multiple endocrine neoplasia	*RET*
Hereditary motor and sensory neuropathy	*PMP22*

* Reduced to only these three by end December 2000

The role of GAIC was in validating the tests proposed by the ABI. It deemed a test suitable for use in assessing insurance proposals if it met three conditions:

1. Technical relevance - is the test technically reliable and does it accurately detect the specific changes sought for the named condition?
2. Clinical relevance - does a positive result in the test have any implications for the health of the individual?
3. Actuarial relevance - do the health implications make any difference to the likelihood of a claim under the proposed insurance product?

The first condition for validation, Huntington's Disease, was approved in October 2000 as reliable and relevant for the purposes of life insurance policies. The insurance companies accepted this ruling and disclosed that they would not use tests, which were not received for approval by GAIC by the end of 2000. Two more conditions were submitted and are currently being processed - early onset familial Alzheimer disease and hereditary breast/ovarian cancer. Regrettably, the insurance companies took the view that although they had withdrawn other tests including the cancers FAP and MEN-2 as they felt genetic testing by middle age was not going to add much to family history and clinical examination, they refused to allow the results of negative (i.e. not carrying a family mutation) tests which would have been advantageous in securing normal rates in those penalised by family history of these disease. Although there was a large amount of public opposition to the first approval of HD by GAIC, the role of GAIC has been useful in that it forced the ABI to consider the topic seriously, rather that its' previous view that no problem existed. It also put the onus on insurers to produce facts and a case to submit evidence to GAIC regarding reliability and for just these reasons, 5 of the 8 tests have now been dropped. GAIC has all types of insurance as its remit and not just life insurance, which is most problematic in the UK and has forced the consideration of health and critical illness and long term care issue onto the agenda (issues which are particularly relevant in the USA).

Other issues including ethical and social issues in relation to insurance are not covered by GAIC and are the remit of the Human Genetics Commission (HGC). The HGC was established in May 1999 following a major government reorganisation of committees and it absorbed several predecessor committees including the HGAC, which stopped functioning in December 1999. In December 2000, the HGC published a consultation on public opinion on several issues and showed that there was strong opposition to the use of genetic test results by insurance companies[17]. This was confirmed in a MORI opinion survey published by the HGC in March 2001[18] and the HGC concluded that the level of public concern over the issue required a response. This information coincided with the new House of Commons Committee on Science and technology report[19] also in March 2001. The committee took both oral and written evidence from several bodies including the insurance companies within and outside the ABI. The report was severely critical of the insurance companies and the conclusions (including recommending a two year moratorium) are listed in table 4.

The HGC published a statement in May 2001 recommending interim recommendations on the use of genetic information in insurance (Table 5). These included an immediate moratorium on the use of genetic tests by the insurance companies for a period of not less than 3 years. This would allow time for a full review of evidence and regulatory options. The use of family history information was allowed but the HGC specified that they would discuss this and address how insurers use family history information. They also placed a ceiling on the recommended moratorium of £500,000, to protect the insurance industry from significant financial loss. They recommended that legislation might be needed to enforce the moratorium because of the failings of the current system. The ABI responded by issuing on the same day, an extension to their existing moratorium to include all classes of insurance up to £300,000 (previously only mortgage related policies up to £100,000).

The UK government response to both the House of Commons select committee report and the HGC interim recommendations was published on 23rd October 2001[20]. The key features are summarized in table 6. The Government and the ABI have announced a 5-year moratorium on the use of genetic test results by insurers. The moratorium will apply to life insurance policies up to £500,000 and critical illness, long-term care insurance and income protection up to £300,000 for each type of policy. In policy applications above these limits, the insurance industry may use genetic test results where these tests have been approved by GAIC. Legislation

TABLE 4.

Some of the House of Commons Science and technology committee recommendations May 2001

1. Insurance companies should detail exactly what genetic tests they will consider (both positive and negative) for what conditions and under which circumstances as soon as possible.
2. Commercial insurance companies should have access to the same information as applicants, where it is relevant and reliable - but only if there are no adverse consequences for society.
3. It is not certain at present that the information obtained from positive genetic tests is relevant to the insurance industry.
4. Insurers have given test results a predictive significance that cannot at present be justified.
5. Insurers appear to be more interested in establishing their future right to use genetic test results in assessing premiums than in whether or not they are reliable or relevant
6. Insurers must publish more data, which unequivocally supports the changes made to insurance premiums based on positive genetic test results.
7. Insurers should publish clear explanations as to exactly how such factors as early diagnosis and treatment are factored into their actuarial calculations
8. The small number of cases involving genetic test results could allow insurers to ignore all genetic test results until their scientific and actuarial relevance is firmly established.
9. The view that ignoring genetic test results is costly is contradicted by the actions of at least 3 insurers who choose to ignore tests for the short term.
10. We recommend that insurers take into account negative test results.
11. Insurers should explain and publish how they use family history in assessing premiums.
12. Adequate independent research to discern the impact of the use of genetic test results by insurance companies should be carried out.
13. The distinction between research and diagnostic tests should be clearly understood by those seeking to use the results and the statement that results from research will not be used should be incorporated into the ABI code of practice.
14. The ABI must act to convince the government and public that the code of practice is being complied with, and insurers must prove that they are capable of regulating themselves effectively and thoroughly.

TABLE 5.

HGC moratorium recommendations May 2001

1. No insurance company should require disclosure of adverse results of any genetic tests, or use such results in determining the availability or terms of all classes of insurance.
2. Recommendation is for introduction of a moratorium on genetic testing for not less than three years. This will allow time for a full review of regulatory options and afford the opportunity to collect data, which is not currently available. The moratorium should continue if the issues have not been resolved satisfactorily within this period.
3. The moratorium will not affect the current ability of insurance companies to take into account favourable results of any genetic test result, which the applicant has chosen to disclose.
4. HGC will address the issue as to how family history information is used by insurers.
5. An exception is made for policies greater than £500,000. as protection from significant financial loss.
6. Only genetic tests approved by the genetics and insurance committee (GAIC) should be taken onto account for these high value policies. There remains a need for an expert body of this kind.
7. In view of the failings of self-regulation, independent enforcement of the moratorium will be needed. The HGC believes that legislation will be necessary to achieve this.

has not been introduced; however independent monitoring of the ABI code of conduct will take place possibly through an enhanced role for GAIC in monitoring both insurance compliance and customer complaints. It is also to review the composition of the GAIC committee with extension of its' membership. The moratorium has not been extended to use of family history data, and the whole moratorium will be reviewed after 3 years. An important note from the patients' perspective is that the use of negative test results is encouraged by the insurer subject to confirmation in most cases by a geneticist of the relevance of the result.

TABLE 6.

Government and ABI agreed moratorium October 2001

1. There will be a five year moratorium on the use of genetic test results by insurers.
2. The moratorium will apply to life insurance policies up to £500,000 and critical illness, long term care insurance and income protection up to £300,000 for each type of policy.
3. In policy applications above these limits, the insurance industry may use genetic test results where these tests have been approved by GAIC.
4. Legislation has not been introduced, however independent monitoring of the ABI code of conduct will take place through an enhanced role for GAIC in monitoring both insurance compliance and customer complaints.
5. The moratorium has not been extended to use of family history data
6. The whole moratorium will be reviewed after 3 years.
7. The use of negative test results in obtaining normal premiums is encouraged by the insurer subject to confirmation in most cases by a geneticist of the relevance of the result.

THE SITUATION IN OTHER EUROPEAN COUNTRIES

Several European countries have no legislation or guidelines on insurance and genetic testing. Countries that have some guidelines have a moratorium on the use of genetic tests. For example, in France, the moratorium is up to five years, whilst in the Netherlands, it has been extended indefinitely. Once a moratorium has been introduced, it is difficult to find sufficient scientific evidence to justify lifting a ban on the use of genetic testing in underwriting practice[14].

In Austria, the 1994 gene technology law states that employers and insurers are forbidden to obtain, request, accept or use results of genetic analyses. In Belgium, a 1992 Non-marine insurance law allows medical examinations etc. to be based only on past medical history establishing the applicant's medical state, and not on genetic analysis techniques capable of determining future state of health. In Denmark, the amendment to the insurance contracts act 1997, allows insurers only to ask for HIV tests and family history when the sum insured is high and over a certain level. In France, the 1994 French federation of Insurance Companies (FFSA) issued a statement saying that for 5 years, the FFSA will not use genetic information when determining applicants' insurability, even if applicants bring favourable information.

In the Netherlands, it is considered that strict regulation will be needed. In 1995, a 5-year moratorium was extended indefinitely and insurers have agreed not to use genetic tests or existing genetic information for policies below NLG 300'000. Individual responsibility is seen as being extremely important. Limitations on the collection and use of genetic information are derived from the medical treatment and medical checks acts.

In Norway, a 1994 biotechnology law allows strict use of genetic tests. It states that it is 'forbidden to request, receive, retain or make use of genetic information from a genetic test result, and it is forbidden to ascertain if a genetic test has been performed'. In 1997, Poland introduced a law, which established a general inspectorate for personal data protection. In Sweden, Genetic discrimination can be subject to penalty by fine or prison sentence up to a maximum of six months. An agreement was reached with the insurance companies in 1999 not to require insurance applications to undergo genetic tests up until 2002. Following a referendum in Switzerland in June 1998, insurers are not allowed to demand presymptomatic or prenatal investigations as a condition of insurance.

There is no legislation in Finland, Germany, Greece, Hungary, Iceland, Italy, Portugal or Spain. In Ireland the situation is similar to the UK and although there is no specific legislation, most Irish insurance companies have organisational links to the ABI and follow the ABI code where possible.

REGULATION OF GENETIC TESTING AND INSURANCE IN OTHER COUNTRIES

In the USA and other countries without national health services the main concern is about health insurance where a positive predictive test would have great relevance although predictive genetic

tests are rarely able to determine the time at which someone will become ill. In the USA most health insurance is purchased on a group basis by employers and the unemployed or low income groups are often not insured. There is no obligation on an employer to insure a high-risk employee who would raise their costs. Thus 31-36 million people in the USA have no health insurance[21]. The most significant legislation is the health insurance portability and accountability act 1996 (HIPAA). This federal law provides some protection from genetic discrimination but only to employer based and commercially issued group health insurance. President Clinton in February 2000[22] signed an executive order forbidding the USA federal government from using genetic information in general employment decisions. Eventually national legislation in the USA is likely in order to prevent discrimination. Indeed this has been proposed for some time[23]. In the interim 28 states have already introduced fairly restrictive legislation, including the recent Massachusetts law, which prohibits genetic discrimination by employers and health insurance agents[24]. Interestingly there does not appear to be any advantage taken of the gap in those states without laws. The situation in the USA is covered partly by the Discrimination act, 1996. Current bills passing through the US government include one on genetic information & non-discrimination in health insurance[25].

Australia has an Insurance contracts act 1984, which allows insurers to take into account existing genetic information as well as family history. Insurers generally are against forcing individuals to take genetic tests. The Life, Investment, and Superannuation Association of Australia (LISA) are currently revising further guidelines in 1997. The genetic privacy and nondiscrimination bill 1998 explicitly prohibits genetic discrimination by insurers. Canada has no legislation. New Zealand issued guidelines in April 1997 on insurance and genetic tests.

BENEFITS OF CANCER GENETIC TESTING

As in Huntington's disease, if the genetic nature of the condition is well enough defined individuals may be unable to obtain insurance because they are at 50% risk, irrespective of DNA tests[6]. This may prompt those at risk to request testing in the hope that their 50% prior risk will be reduced to the point of being able to obtain insurance. This has not been found to be a particularly important reason for opting for a test[26], nonetheless some women who test positive for BRCA1 have had premiums reduced to normal after prophylactic mastectomy and oophorectomy.

The finding of negative test results (i.e. non gene carriers) has been used to lower already high premiums. In the UK, insurance companies cannot insist that applicants should have genetic tests. Many individuals at risk and on a higher premium will organise genetic tests at their own expense. Confirmation by genetic testing of a genetic cause for a cancer in an already affected person does not automatically increase the existing premium, as this may be based on existing family history or current health status, but a negative test result has led to a reduced premium for some applicants.

Some insurers consider that genetic information is not essential for underwriting life insurance, and are not requesting information about genetic tests. Most applicants who were requested to provide further information were not rated at a higher premium or rejected. Some companies consider they can absorb this small extra load. Overall only 1 in 20 policies are actually claimed on death, which is not an excessive amount.

EVIDENCE OF DISCRIMINATION

A survey of European genetic centres involved in breast cancer testing showed that all the UK centres surveyed had had patients who refused testing because of fear of penalty or being unable to obtain insurance. Two (40%) of the UK centres had experience of patients who refused genetic testing because of fear of employment discrimination[27]. Interestingly, although Norway has extremely strict laws, and there is no particular need to discuss insurance issues prior to testing, instances of refusal of testing due to both fear and employment were seen. This may reflect anxiety because of strict legislation, as people may consider there must be something behind the legislation. The non-UK centres did not appear to have any major discrimination problems.

Cases of actual discrimination were documented, all from UK centres. Some examples cited include a 40 year-old female with relatives with breast and ovarian cancer who could not obtain insurance, but was able to do so after preventative mastectomy and oophorectomy, and a 39 year-old female with a BRCA1 family history, who divorced from her husband, was denied insurance and mortgage cover for a new house unless she had a negative BRCA1 test. Cases were also documented in which on application for health

insurance, excessive details of other family history and genetic test results were requested[28].

A postal survey found that up to 33% of respondents in patient support groups may have experienced problems when applying for life insurance[29]. Such findings can easily be overinterpreted due to a high non-response rate by more satisfied customers.

In the rest of Europe where most countries have restrictive legislation there is little evidence of discrimination[28], although in Norway, there is evidence of increased premiums for HNPCC, but not for BRCA1/2[30].

There is little evidence of discrimination in obtaining health insurance in the USA for presymptomatic individuals[23], nonetheless health insurers are unwilling to pay for testing of for instance BRCA1, with only 15% covering the costs[24] and this is likely to increase if the tests are targeted in the high-risk situation, such as a family with a known mutation[31]. Unless more is done to encourage insurers they may not to be prepared to pay for, for example, an FAP predictive test, thus denying those on lower incomes the opportunity for testing in the first place. Further work in the USA has also shown that insurance industry's fears about adverse selection may be groundless. Women testing positive for BRCAl mutations did not take out higher levels of life insurance[32].

In Australia, families with hereditary bowel cancer experienced genetic discrimination. In a survey of families on the hereditary bowel cancer register, Barlow-Stewart found 8% discrimination - predominantly HNPCC related, and included a number of areas including refusal of life insurance, denial of an increase in life insurance for a pre-existing policy, refusal of income protection and trauma insurance, reduction of superannuation and loading on premiums for travel insurance[33]. One interesting case was that of a civil servant who reported that her application for a senior position in the public service was subject to a negative FAP test result. She had to discontinue her application, as she would have been forced to have a test that would have revealed her mutation status. The issue had been picked up following her ticking of a regular colonoscopy box on the health form.

As a result of release of this evidence, the Australian government has initiated several enquiries to determine the direction for future law or other policy development.

HOW CAN PATIENTS WITH A FAMILY HISTORY OF CANCER ENSURE THE BEST POSSIBLE MANAGEMENT OF THEIR CONDITION?

Patients, and their clinicians, should be aware of the regulations on insurance and genetic testing, the relevant contents of the ABI report and the recent moratorium on insurance and genetic testing within the UK. Most of these issues are complex and patients with a history of familial cancer need access to a clinical genetics service either by direct telephone or clinic contact or through secondary contact via their medical practitioner or hospital clinician. This is particularly useful if the risk is being based on family history, as often patients' knowledge of their own family history of cancer may be inaccurate. The introduction of the recent moratorium and the safeguards contained both within it and by external monitoring of the genetic testing aspects by GAIC and the ethical and social aspects by HGC, is an encouraging step. Increased use of normal test results in setting normal premiums and industry competition should improve access to reasonable insurance cover for hereditary illnesses and as not all insurance companies belong to the ABI, good advice is to 'shop around' using an independent advisor who may be able to negotiate very competitive rates.

CONCLUSION

The rapidly evolving practice of clinical genetics is producing many questions to which we do not yet have clear answers. This is nowhere more apparent than in the genetics of common cancers, including breast cancer, which is the fastest growing area of genetic medicine. Worry about misuse of genetic test information by insurers is a real occurrence and the recent discussions between the Government and the insurance industry leading to their moratorium is to be welcomed. Little evidence exists on which to base a lot of risk assessment by insurers on either the predictive power of cancer genetic tests or on the use of family history as a rating factor. Further high quality actuarial research evidence will provide a better understanding of insurance risk estimation and allow better actuarial practice in calculation of insurance premiums in families with a history of cancer.

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CONFLICT OF INTEREST

The author is a member of the Human Genetics Commission. Although his views have shaped the HGC recommendations on insurance submitted to the UK government, the views expressed in this article are those of the author and may not reflect official Government policy.

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The clinical outcome of non-RhD antibody affected pregnancies in Northern Ireland

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SUMMARY

We assessed the clinical outcome of pregnancies with non-Rh-D antibody in Northern Ireland using retrospective case note review.

During the study period (April 1999- March 2000) 186 women with clinically significant antibodies were identified from the records of the antenatal laboratory of the Northern Ireland Blood Transfusion Service. Eighty-five women were included in the study using the criteria mentioned above. None of the fetuses required intrauterine transfusion during this period. One baby required exchange transfusion, three were given top-up transfusions and 17 had phototherapy. Nine babies with a positive direct antiglobulin test (DAT) received no treatment.

The incidence of anti-Kell could be reduced by transfusing Kell negative red cells to premenopausal women. It is important that all pregnant women are tested at least twice in their pregnancy to detect the antibodies formed late in the pregnancy. It is useful to formulate a standard protocol for antenatal interventions. Non Rh-D antibodies can cause significant anaemia for up to six weeks in the neonatal period, hence early detection of maternal antibodies is important so that the neonates are followed up for an appropriate length of time.

INTRODUCTION

Although the prevalence of anti-D has significantly declined in relation to other red cell antibodies, anti-D still remains the major cause of morbidity and mortality associated with haemolytic disease of the newborn (HDN) and the fetus. The fetal and neonatal outcomes of anti-D affected pregnancies in Northern Ireland have been reported recently[2]. This study was undertaken to assess the management and outcome of pregnancies in women who had other clinically significant antibodies.

METHODS

The Northern Ireland Blood Transfusion Service (NIBTS) provides centralised antibody testing for most of the antenatal clinics in the Province. Blood samples from pregnant women are tested for ABO and Rh-D group and screened for atypical antibodies. Antibody screening is performed using solid phase methodology (capture R assay) following the manufacturer's methods. The specificity of the antibody is identified by further testing of those samples that give positive reaction on initial screening.

The antibodies are classified into three groups:

Group I: anti-D, anti-c, anti-Kell

Group II: anti-Fy^a, anti-Fy^b, anti-Jk^a, anti-Jk^b, anti-C, anti-Ce, anti-e, anti-E, anti-C^w, anti- M, anti-N, anti-S, anti-s, anti-LU^a

Group III: anti-Le^a, anti-Le^b, anti-P1, anti-I, anti HI, cold agglutinins, enzyme agglutinins (clinically not significant)

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A sample is requested from her partner if a woman has either a group I or group II antibody in her plasma to assess the risk to the fetus. All pregnant women with group I antibodies are monitored monthly up to 28 weeks gestation and every two weeks thereafter. The interval of follow up for group II antibodies depends on the initial titre, subsequent rise in titre, and the antigen status of the partner. All the others are tested at least twice, once at booking and once between 28-32 weeks.

All the women who had group I (other than anti-D) and women with group II antibodies with a titre of 1/16 or above anytime during the pregnancy were included in the study. The case notes were examined after obtaining permission from the obstetricians responsible for the care of these women. The following details were obtained: history of blood transfusion, indication for transfusion, previous obstetric history, antenatal interventions (if any), time of delivery, baby's birth weight, blood group, DAT, bilirubin, haemoglobin and details of management.

RESULTS

NIBTS tested 34,913 samples between April 1999 and March 2000. During the study period 186 women were found to have non Rh-D clinically significant antibodies. The antibody identification details are given in Table 1. 85 women fulfilled the inclusion criteria described above (Table 2). The antigen status of the partners are given in figure 1. Ten women could not be followed up for the following reasons: seven case notes were not available, one woman moved to England during pregnancy, two women were tested only once by their general practitioners and no further information was available.

There was a definitive history of transfusion in 46 (61.3%) women, and the antibody was pregnancy induced (not previously transfused) in 10 (13.3%) women. Transfusion history was not recorded in 19 cases, but 7 of these women had antigen-negative partners, indicating that the antibody was most likely transfusion-induced. It was difficult to classify the remaining 12 women (Fig 2). 36 (48%) women were transfused in one of their previous pregnancies following primary postpartum haemorrhage, retained placenta, ruptured ectopic pregnancy or miscarriage; two were transfused following non-obstetric surgery, two following trauma, two had transfusion to correct anaemia and the reason for transfusion was not recorded for the remaining four women.

Previous obstetric history was noted in detail in women who were at risk of an affected infant i.e., women with homozygous/heterozygous partners or whose partners were not tested. 22 women had a positive antibody screen in their previous pregnancy/pregnancies and at least six of them had previously affected babies treated with phototherapy for neonatal jaundice or top-up transfusions for anaemia. Amniocentesis was

TABLE 1:

Antibody specificities (other than anti-D) of antenatal women tested during study period

Rh Group (other than anti-D)

Antibody specificity	No
anti-c (alone)	12
anti-c + others	11
anti-C (alone)	2
anti-C + others	5
anti-C (alone)	42
anti-E + others	7
anti-C^w	20
TOTAL	**99**

Non Rh Group

Antibody specificity	No
anti-Kell (alone) + others	34
anti-Kell + others	7
anti-Fy^a (alone)	9
anti-Fy^a + others	2
anti-S	6
anti-s	3
anti-Jk^a	6
Others(anti-M 13: anti-N 3: anti-Bga 3: anti-Kpa 1)	20
TOTAL	**87**

Rh = Rhesus blood group system

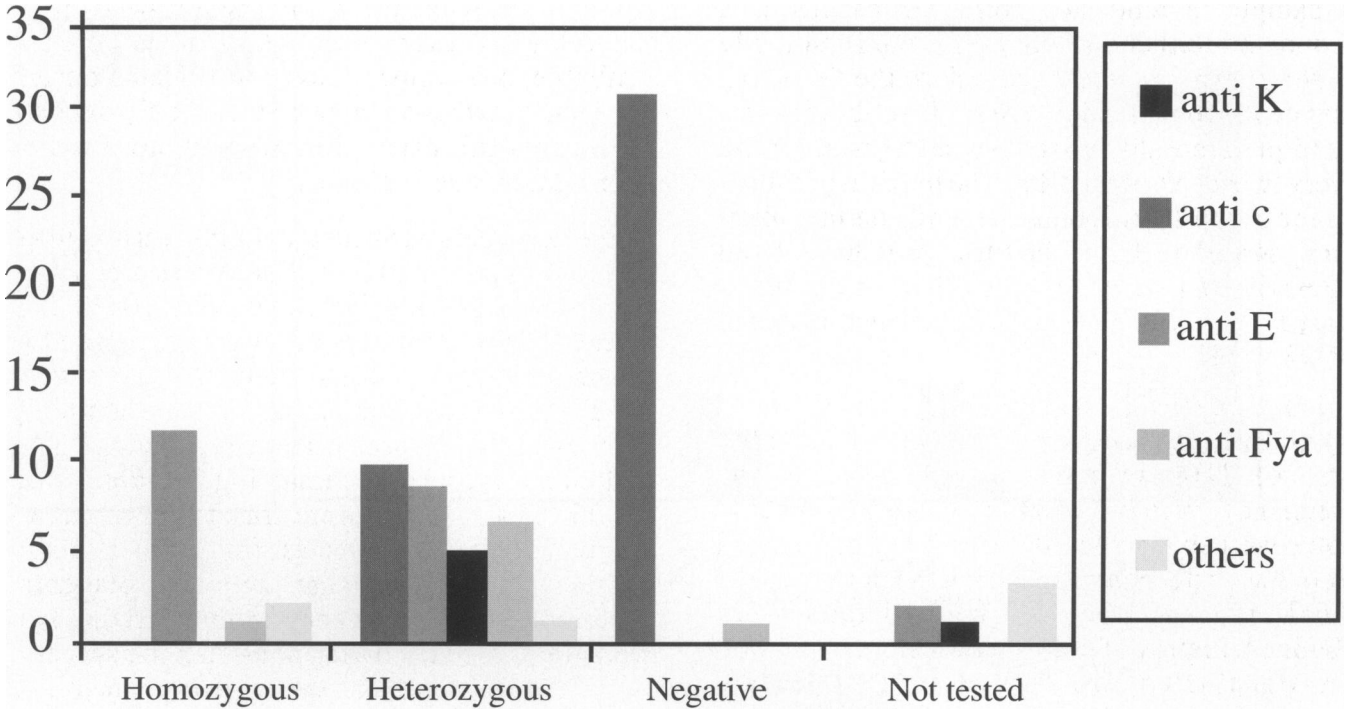

Fig 1. Autigen Status of Partners.

TABLE 2:
Number and specificity of the red cell antibodies in the study group

Antibody specificity	Number
anti-Kell	41
anti-c	23
anti-Fy^a	9
anti-E	6
others (anti-C^w 2: anti-Jk^a 1: anti-s 1: anti-e 1, anti-E + Jk^a 1	6
TOTAL	**85**

performed in one woman with anti-Kell in her three previous pregnancies and also in the current pregnancy. Five women with anti-c also had a history of amniocentesis in their previous pregnancies.

Eleven women (excluding one who had amniocentesis to assess risk of Down syndrome) had invasive antenatal interventions in this pregnancy. A woman with anti-Kell titre of 1/512 went into premature labour at 32 weeks after the second amniocentesis and the baby required exchange transfusion for neonatal jaundice. Cordocentesis was performed in one woman with anti-Kell and anti-Jk^a due to increase in titres. The fetus was typed Kell-negative and Jk^a-positive and hence further interventions were not required. The baby was DAT positive due to anti-Jk^a but did not require treatment. A woman with anti-Fy^a titre of 1/16 had an amniocentesis done but the reason for this intervention could not be ascertained from her records. Her previous three babies were treated with phototherapy for neonatal jaundice and this infant was also treated with phototherapy for 24 hours (cord bilirubin 56μmol/l).

The clinical outcome of the antibody-affected pregnancies is shown in table 3.

During the study period there were no fetal or neonatal deaths directly attributed to the red cell allommunisation and none of the fetuses required intrauterine transfusions. Among the 38 women who had anti-Kell detected in their sera, for whom case notes were available, only ten had antigen-positive (heterozygous) partners. We decided to include the women with negative partners in the study group when we noted a significant rise in titres (1/64 to 1/2048) in two women. The increase in titres could have been due to underlying systemic lupus erythematosus (SLE) in one of them. The results were discussed

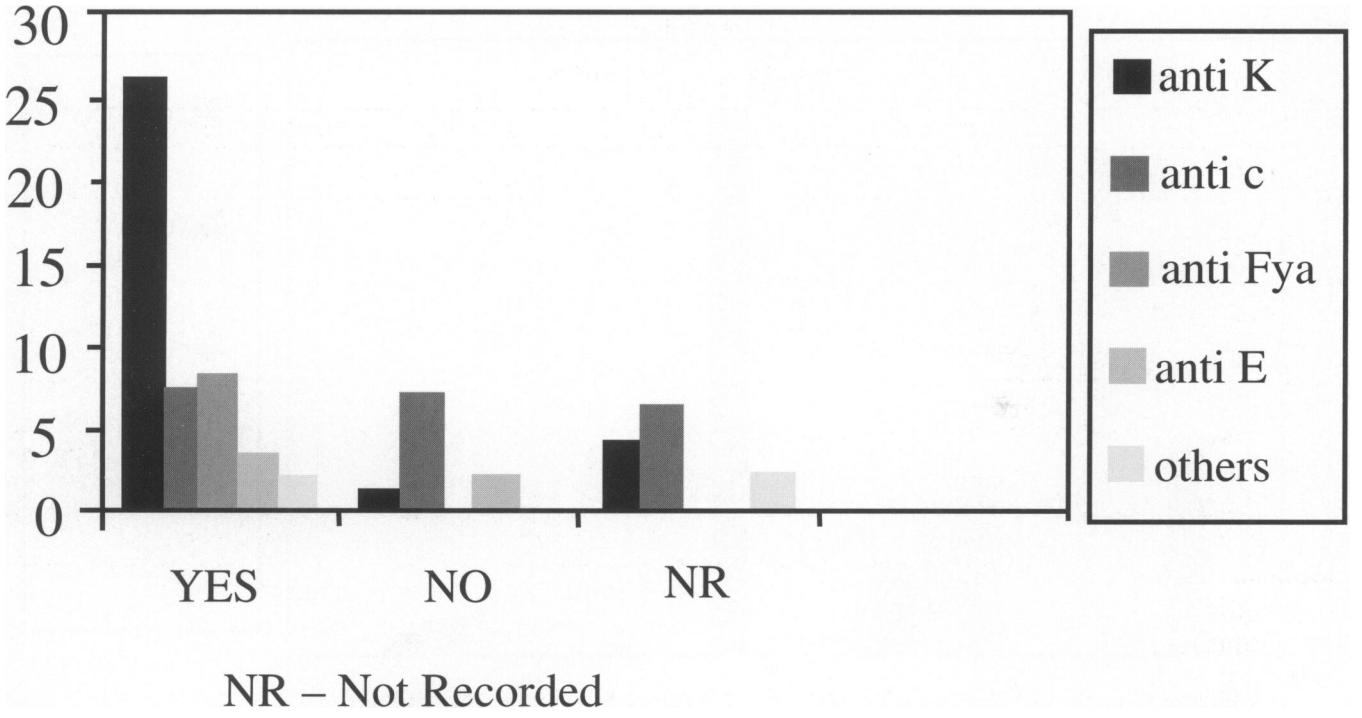

Fig 2. History of Transfusion.

with the women by their obstetricians and it was decided not to do invasive antenatal investigations. The two babies were DAT negative. Similarly all the other babies born to Kell-negative fathers were DAT negative as expected (DAT was not done in one case).

In this study, 10 of the 17 babies who needed phototherapy were born to mothers with anti-c and two babies needed top-up transfusions. One of these babies was noted to be jaundiced on the day of birth and found to be DAT positive and phototherapy was commenced. The mother was tested only once during pregnancy. She had only non-specific cold antibodies in this sample. Anti-c and anti-Jk^{a} were demonstrated in the postnatal maternal sample and the same antibodies were eluted from the red cells of her baby. The infant needed top-up transfusion due to a fall in haemoglobin level (from 12 g/dl on day-1 to 6.7 g/dI on day-10). The late appearance of antibodies is well recognised and the "guidelines for antibody testing during pregnancy" [7] recommend testing all pregnant women twice in pregnancy, once at booking and once between 28-32 weeks to allow detection of late appearance of clinically significant antibodies.

DISCUSSION

Among the non Rh-D antibodies, anti-c and anti-Kell are those most likely to cause severe HDN. Antibodies like anti-Fy^{a} , anti-E, anti-Ce, anti-e and anti-Jk^{a} have also the potential to cause significant HDN[7]. Other antibodies may rarely cause clinically relevant HDN.

Anti-Kell differs from other red cell antibodies because the maternal antibody titres and amniotic fluid spectrophotometric estimation usually do not correlate with fetal anaemia[3,4]. Anti-Kell antibodies cause fetal anaemia by suppression of erythropoiesis rather than red cell destruction[5,6]. Amniocentesis remains useful for identification of fetal Kell genotype by polymerase chain reaction (PCR)[6] when the father has undetermined or heterozygous Kell antigen status. PCR results enable the clinician to exclude the mothers with Kell negative babies from further invasive interventions. Blood group genotyping was not used as a diagnostic tool in any of the cases in this series. It should be noted that 26/41 women with anti-Kell had a history of transfusion and further 10 had negative partners and hence the antibody was most likely to be transfusion induced (Fig 2). Most of the transfusions were given for obstetric causes. NIBTS has started routine phenotyping of donor units for Kell and other Rh antigens in addition to ABO and Rh D typing. Northern Ireland has a population of 562,900 pre menopausal (age 0-45) female subjects (source: Department of Demography and Methodology, Northern Ireland, April 1999) and it is practically

TABLE 3:

Outcome of Pregnancies

	anti-K	anti-c	anti-E	anti-Fy[a]	others	Total
DAT Negative	32[a]	5[b,c]	2	2[d]	2[c]	43
DAT Positive, No treatment	2	3	1	3	0	9
Phototheraphy	1	10	1	3[f]	2[g]	17
Top up Tx	0	2	1	0	0	3
Exchange Tx	1	0	0	0	0	1
Fetal loss <16 weeks	2[h]	0	0	0	0	2
TOTAL	38	20	5	8	4	75

Figures include:

a: DAT not done in one baby, father Kell negative.
b: DAT negative, c positive.
c: DAT negative, c negative, father homozygous cc.
d: DAT negative, Fy^a positive.
e: father homozygous ss.
f: prophylactic phototherapy: DAT positive, Fy^a negative, ABO incompatability.
g: parents C^w negative, baby DAT positive, C^w positive, given prophylactic phototherapy.
h: cause for spontaneous abortion, one had antigen negative partner.
DAT = Direct Antiglobulin Test. Tx = Transfusion.

possible to provide Kell negative blood to those female recipients (in the absence of anti-cellano) without depleting the blood stocks. Ninety-one percent of the population are Kell negative; 91% of recipients will be Kell negative. NIBTS currently provides an inventory of Kell negative typed units to all hospital blood banks. The female population, aged birth to 45, is not an intensively transfused group and there will be little impact on the Kell negative inventory because of the balance of Kell negative to Kell positive in our population. Ideally all female recipients aged 0 to 45 should be Kell typed and this will have to be done in hospital blood banks because not all women present as antenatal cases to NIBTS for antenatal testing in the laboratory. If this recommendation is routinely implemented, the number of anti-Kell antibodies in pregnancies should decline slowly.

However, in the case of anti-c antibodies, 50% of the women were not previously transfused in this study (Fig 2). Hence, provision of c-antigen negative red cells to c-antigen negative recipients would be expected to make less impact on the number of cases affected with anti-c because unlike anti-Kell, most of the partners are c-antigen positive and induction of immunisation in pregnancy can still occur. Furthermore, this will also involve additional testing of all Rh-D positive pregnant women for their c-antigen status. Bowell et al [10] expressed a similar opinion after a retrospective study of 177 women with anti-c over an 8-year period and concluded that routine c-antigen typing of premenopausal women was not justifiable. Kozlowski *et al*[9] pointed out that 50% of the women with anti-c in their study had been transfused (similar to our figures) compared to 5% in unselected antenatal population. Hence they felt it was worthwhile to perform antenatal c antigen typing of all Rh D positive women and provide antigen selected blood to cover obstetric emergencies.

There was no major institutional variation in the care of the neonates as there is a uniform policy among the neonatal units for the management of neonatal jaundice. All the babies were treated in

accordance with the "guide charts for the management of hyperbilirubinaemia" which give guidance for treatment for babies in different birth weight ranges. There are no specific British Committee Standards in Haematology (BCSH) guidelines related to management of hyperbilirubinaemia in newborns. As part of any investigation protocol however direct antiglobulin tests (DAT) should be performed on the baby and an antibody screen on maternal plasma to exclude red cell allo antibodies as a cause of hyperbilirubinaemia. Where the DAT is positive and the maternal antibody screen is negative it is necessary to perform a maternal v paternal compatibility test to exclude private or low incidence antigens as a cause of undetected haemolytic disease of the newborn.

The indications for antenatal interventions varied among different hospitals. Anti c antibody as well as group II antibodies do not cause significant HDN when detected below the titre of 1/32[7] and hence may be monitored by non-invasive methods. NIBTS is planning to conduct a pilot study to do quantitation of anti-c to provide assistance to the obstetrician in decision-making. In a study conducted in Manchester[9], none of the babies born to mothers with anti-c level below 9.5 iu/ml required exchange transfusion. Based on this observation, the authors suggested that invasive antenatal intervention is not necessary if the anti-c level is below 7.5 iu/ml, allowing for inherent error in quantitation method.

This study highlights the fact that the clinical outcome of non Rh-D antibodies affected pregnancies is good due to careful monitoring of pregnancy and effective neonatal care. Red cell alloimmunisation remains one of the major causes of neonatal hyperbilirubinaemia resulting in intensive neonatal care admission. Haemolysis due to antibodies can continue to occur for up to six weeks, and the babies have to be followed up during this period to detect anaemia. It is important that laboratories undertaking antenatal testing maintain an effective working relationship and communication with the midwives, obstetricians and paediatricians to provide optimal perinatal care for the patients.

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The history of Obstetrics in Northern Ireland 1921-1992

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SUMMARY

In 1921 there was little provision for the care of the pregnant woman in Northern Ireland where there were only two hospitals staffed by specialist obstetricians. The mortality statistics reflected this, the province having the highest maternal mortality and the second highest infant mortality rates in the United Kingdom. There was little progress until the establishment of the National Health Service in 1948. Within a short time, excellent hospital specialist and domiciliary midwifery services were developed. Scientific advances, mainly during the 1970's, led to further expansion of the specialist service and the disappearance of the general practitioner service. These advances have again been reflected in the statistics. The maternal mortality is now zero and the perinatal mortality 8 per 1,000 births.

INTRODUCTION

When Northern Ireland was established in 1921, provision for the care of the pregnant woman was governed by the Irish Poor Law Act (1838).[1] This Act had established Boards of Guardians throughout the country in order to provide workhouses for the destitute able-bodied. Later, in 1851, the Guardians were made responsible for the existing dispensary service and were directed to develop it. Dispensary doctors and midwives were appointed in areas throughout the country. Among their duties was the care of destitute pregnant women during labour and the puerperium.

In 1898, rural and urban district councils were set up and made responsible for the care of all other pregnant women and their children at health clinics. Midwives employed at these clinics did not attend women in labour. In 1921, only 21 of the 64 councils which now formed Northern Ireland provided this service.[2]

DEVELOPMENTS 1921-1948

In 1924, Sir Dawson Bates set up a Commission to examine the provision of health services in the province. In May 1928 the Minister stated that there was no money available to carry out any of the recommendations.[3] The inadequacy of health care was especially apparent with regard to maternity and child services. The mortality statistics reflected this; the province had the highest maternal mortality and second highest infant mortality rates in the United Kingdom.[4]

During the period until the National Health Service was established there was little progress in health care. Several Boards of Guardians converted the infirmaries attached to the workhouses into district hospitals. Thirteen were thus converted and many were staffed by local general practitioners. Pregnant women with complications could be admitted from home to these new institutions as fee-paying patients.

The only specialist maternity hospitals in the province were in Belfast. In 1934, the Royal Maternity Hospital, built entirely by private donations, opened in the grounds of the Royal Victoria Hospital. This replaced the old maternity hospital in Townsend Street.[5] In 1935, the Belfast Board of Guardians opened the Jubilee Maternity Hospital in the grounds of the Infirmary. This replaced the original maternity hospital 'Ivy Cottage' which is still used as a neonatal nursery.[6] In 1946, the Board of Management of the Mater Infirmorum Hospital opened a 24-bed maternity unit adjacent to the main hospital.[7]

At that time there were six obstetricians attached to the Royal Maternity Hospital and two to the Mater maternity unit. These men did not receive

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any salary. Two obstetricians attached to the Jubilee Maternity Hospital were paid on the same basis as visiting medical officers attending Union infirmaries.

In 1936, Sir Dawson Bates set up a Committee of Enquiry into maternal mortality and morbidity in Northern Ireland. In that year the maternal mortality was 7.3 per 1,000 live births, while in England and Wales the figure was 4.9 per 1,000 live births. The report was presented to the Minister in 1942 but was not made public at that time. However, after repeated criticism by Dr Lyle, a dispensary doctor from County Tyrone and Unionist MP for The Queen's University of Belfast, the report was published in 1943.

Following passage of the Ministries Act (Northern Ireland) 1944,[9] a Ministry of Health with its own Minister was established. Others were also concerned about the state of the maternity services. On 11 January 1941, the editor of the 'Newsletter' reported that Belfast Corporation had spent only 21 per cent of the Government grant allocated for the provision and maintenance of maternity and child welfare clinics.[10] Members of Belfast Corporation Health Committee then invited Dr T Carnwath, former Deputy Chief Medical Officer of Health for England and Wales, to investigate the many health problems in the city. His report [11] was accepted by the Committee. Dr Carnwath pointed out many grave deficiencies in the care of the pregnant woman, and recommended the establishment of an emergency obstetric service, the 'Flying Squad'. This service was to be provided by the Royal and Jubilee Maternity Hospitals and the cost was to be borne by the Corporation.

Another group also expressed concern about health care. In October 1942, the Nuffield Provincial Hospitals Regional Council for Northern Ireland was set up under the chairmanship of Dr Lindsay Keir, Vice Chancellor of The Queen's University of Belfast. This Council invited three eminent physicians from Great Britain to visit all the hospitals and clinics in the province. These doctors made recommendations which were studied by the Council, which later published its own proposals for the future development of hospital services in the province.[12] Among the proposals was the provision of beds in hospital for 70 per cent of pregnant women. Nursery facilities were also to be provided.

The report was also submitted to officials of the newly formed Ministry of Health who rejected it in its entirety. These officials later carried out their own survey but their findings and recommendations were not made public.

At about that time most pregnant women were delivered at home. For many, pregnancy was a cause of great anxiety, mainly because of financial worries. Therefore, in order to save money, the majority did not seek antenatal care and often called a private midwife only after labour had started. Dispensary midwives did not offer antenatal care, being responsible only for the care of women in labour and in the puerperium. However, they were permitted to accept non-compensatory patients on a private fee-paying basis and many did offer care during pregnancy.

Many family doctors did not offer a service to pregnant women, attending only in response to a midwife's request for medical assistance during labour. In 1921, Dr Janet Campbell, an officer in the Ministry of Health, London, made recommendations about the frequency of antenatal visits and these remained standard practice in the province until recent times. However, Mr Hardy Greer [13] a senior obstetrician in the Royal Maternity Hospital did not agree and in 1936 wrote that he saw patients only four times during pregnancy rather than the 12 times recommended by Dr Campbell.

Conditions in many of the houses in which women were delivered have been described by Nic Suibhne [14] and Ballard [15] and in an article entitled 'Reflections of a Ligoniel Midwife'.[16] Many women in labour were looked after by 'handywomen'. This practice was made illegal in Belfast in 1907 and later throughout Ireland by the Midwives Act 1917.[17] Many 'handywomen' were still in practice when the National Health Service began in 1948.[18] These women were held in high esteem by those who requested their services. Fees were not charged. The women usually received a small financial gift and were content with the respect given to them by members of the local community. Many offered an excellent service but lack of knowledge and poor hygiene led to many deaths due to puerperal sepsis.

Analgesia in labour was rarely available. If a family doctor was in attendance the use of intermittent inhalation of chloroform was practised. If the woman attended a specialist as a private patient in Belfast then 'twilight sleep'

was given as a form of analgesia using morphine and scopolamine.[19]

Postpartum haemorrhage was common and resulted in many maternal deaths. Liquid ergot by mouth was absorbed irregularly and was unsatisfactory. The intramuscular preparation of the drug did not become available until 1936. Fetal loss was very high, especially among premature babies.[19]

Despite all these shortcomings in the service, the world-famous work on the conservative management of placenta praevia was started in the Royal Maternity Hospital, Belfast, by Macafee in 1937 and his findings were published in 1945.[20] This is still the method of choice in the management of this complication.

The training of medical and midwifery staff was either non-existent or of short duration. Family doctors had no formal training apart from lectures and supervised practical work while they were students. Prior to 1950, many Queen's University medical students attended the Dublin maternity hospitals for practical experience. A few doctors spent some time as housemen in the two Belfast specialist maternity hospitals. Likewise, there was no course of training for specialists. The Royal College of Surgeons in Edinburgh held an examination in obstetrics and gynaecology. In 1929, a College (later Royal College) of Obstetricians and Gynaecologists was founded in London. Professor C G Lowry of The Queen's University was one of the founder members. Examinations were introduced in 1932 and training in recognised hospitals began in 1936. The Royal Victoria, Royal Maternity, Samaritan and Jubilee Maternity Hospitals were not inspected and recognised until 1947.

In the province, midwives trained in the Belfast City Hospital (known as the Union Infirmary until 1942), Lurgan and Portadown Infirmary, Malone Place Hospital and the Royal Maternity Hospital (prior to 1934 the Belfast Lying-In Hospital, Townsend Street).

In 1921, the duration of midwifery training was four months. This was increased to six months in 1926, while for women who were not already trained in general nursing the course was one year. From 1937 all staff had to train for one year.

After qualification many midwives did not practise. In a submission to the Committee of Enquiry on Maternal Mortality and Morbidity in 1936, Professor Lowry stated that he considered the work expected from midwives was really 'slave labour'. Those who were employed as dispensary midwives had no off-duty time or annual leave. It was compulsory for the midwife to leave a written message on her front door stating where she could be contacted while out on duty or on a social visit. There was no pension scheme so there was no age limit for retirement. Many of these midwives struggled to maintain a service when they were no longer fit to do so. The salary for a dispensary midwife in 1948 was only £40 per year.

DEVELOPMENTS 1948-1992

The Health Services Act (NI) 1946 [21] swept away all piecemeal health care. A free National Health Service was established in July 1948. The Act resulted in the establishment of the Northern Ireland Hospitals Authority, Northern Ireland Tuberculosis Authority, General Health Services Board, two County Borough and six County Health Committees. The Northern Ireland Act differed in many aspects from that of England and Wales.

With money guaranteed for the first time by the Chancellor of the Exchequer in London to provide a health service equal to that in the rest of the United Kingdom, all the new Authorities made great efforts to do so. The County Health Committees were now responsible for the domiciliary midwifery service and the employment of midwives. Fees for maternity care were paid to family doctors by these committees. The Hospitals Authority became responsible for all midwifery services in hospital, both specialist and general practitioner.

Officers and members of the Health Committees were appalled at the standard of care offered to the pregnant woman in her home. Good antenatal care was immediately introduced by doctors and midwives. All visits to patients were recorded by the Medical Officers of Health.

There was an immediate demand for the service which, for the first time, was free to all. Likewise, drugs and sterile packs were obtained free of charge. If complications developed in pregnancy a 'home-help' service, also free of charge, was provided to look after the patient and her family. A maternity grant (£5.00 in 1948) was paid to all women. Those women who had sufficient insurance stamps were granted a maternity benefit

for 18 weeks during the statutory period of maternity leave. However, in many occupations at that time there was a marriage bar for women, so few obtained this benefit. Later, in an attempt to reduce the demand for hospital confinement, the Government paid a higher grant to any woman who was delivered at home, and eventually abolished the grant to hospital patients. These measures failed and demand for hospital confinement continued apace. The problem of insufficient beds was overcome by the early discharge of mothers and their babies from hospital. Unfortunately, this action was frequently carried out in a haphazard way and often led to conflict between hospital and domiciliary staffs.

Despite all the changes, Medical Officers regularly reported that there was a hard core of women who still did not seek antenatal care, summoning help only when in labour. On the other hand, Macafee, working in a hospital where there was a policy of selective booking, stated that women were attending for antenatal care much earlier than was the norm in the 1930's.[22] He attributed this change to the provision of additional food rations to pregnant women, a policy which had been introduced during the War years.

The County Medical Officers of Health expanded their services. All domiciliary midwives became full-time employees of Health Committees. They were guaranteed annual leave and were paid a bicycle allowance, later replaced by a motor car allowance. All were supplied with new equipment which included sphygmomanometers. Prior to 1948 midwives had to supply their own instruments.

Inhalation analgesia, 'gas and air', had been introduced in some maternity hospitals in England during the 1930's. Training in its use started in the Belfast midwife training schools in 1946. However problems still existed because for many years there were insufficient 'Minnit' gas and air machines available, or a lack of cylinders containing the gas.

Another problem on the district was the care of premature babies. There were no nurseries in hospitals. The County Health Committees eventually provided wooden incubators for home use. These were heated by two 60 watt bulbs if the house had an electricity supply or alternatively by hot water bottles.

Expansion was slower in the hospital services. In 1946, after the War, trainee specialists, both service and supernumerary, were appointed to the Belfast hospitals. When the Hospitals Authority was established there were two major problems – building materials were not available to upgrade and expand hospitals, and there were no trained specialists to staff peripheral hospitals. By 1951, eight provincial hospitals had a specialist obstetrician on the staff. The expansion of this service was completed in 1963.

At the same time the general practitioner hospital maternity service was developed. Most provincial towns had some facility, either in a separate building such as the Cottage Hospital in Ballymena, or shared with a consultant obstetrician, eg in the Erne Hospital, Enniskillen. The development of this service gradually led to the virtual disappearance of the domiciliary service. The expansion of general practitioner hospital units was completed in 1973.

At the beginning of the Health Service all family doctors who wished were included on the obstetric list. From 1 January 1967 it was compulsory to have served as a houseman for six months in a recognised hospital post before admission to the list was granted. Thereafter, the doctor had to be responsible for a certain number of deliveries and to attend refresher courses in order to remain on the list. These regulations had to be altered from time to time as the number of births decreased.

The 1970's saw a tremendous expansion in medical knowledge, the development of new equipment and the introduction of new drugs. These produced great changes in the care of the pregnant woman. Modern electronic fetal monitoring had been introduced by Hon in the USA in 1950.[23] and was first used in the Belfast teaching hospitals in 1970. Dr (later Professor) Charles Whitfield had been sent by Professor Pinkerton to work with Hon.[24]

Ultrasound scanning had been introduced in Glasgow by Donald in 1958.[25] The first commercial machine became available in the province in 1973. Northern Ireland has led the way in the United Kingdom in providing this service because, in the province, it is based in the maternity department and not in the radiology department. Ultrasound scans could be performed at any time by experienced obstetricians so there was no delay in treatment.

Another major advance reduced the number of stillbirths and neonatal deaths. At one time 15 per

cent of patients delivered in the Royal Maternity Hospital carried Rhesus antibodies. Their babies were treated after birth by exchange transfusion of their affected blood. Anti-D prophylaxis was introduced into clinical practice in 1969 and Rhesus disease has now virtually disappeared. [26]

Obstetricians in the British Isles, for long known as obstetric physicians, were very conservative. The motto adopted for the management of labour was 'masterly inactivity'. A more active approach was introduced in the early 1960's and their motto was changed to 'active intervention'. Active management of labour, which includes artificial rupture of the membranes and augmentation of uterine contractions by the intravenous infusion of Syntocinon, has now abolished prolonged labour with its attendant high risk of complications to both mother and baby. Progress in labour was more readily assessed by the introduction of graphic representation of dilatation of the cervix and descent of the baby's head. This technique was introduced in 1954 by Friedman [27] in the USA and popularised by Philpott in Rhodesia in 1970.[28] It was introduced in the Belfast maternity hospitals by Ritchie in 1973.[29]

Intramuscular pethidine was first used as an analgesic in labour in 1940.[30] It was soon used throughout the province and replaced the other forms of analgesia. In 1950, domiciliary midwives were permitted to prescribe and administer up to a maximum of 200 mg pethidine. This is still the drug of choice, now being supplemented by inhalation of nitrous oxide and oxygen. TENS, a non-invasive form of analgesia, has been widely used in the province. Epidural analgesia is now available in many hospitals. It is the wish of the Government that there will be few large maternity hospitals so that a 24-hour epidural service would be available to all women.

FAMILY PLANNING

The first attempt to establish a family-planning service in the province was made by Marie Stopes when she visited Belfast in 1934.[31] A clinic established by her in The Mount offered this service between 1936 and 1947. A family-planning clinic was started in the Royal Maternity Hospital in 1940 and another in Malone Place Hospital in 1951.

Birth control was revolutionised when the 'pill' was introduced into clinical practice in 1963. A further major step was the provision of free family planning as part of the National Health Service in 1974. There was no controversy when this was done, as the service was introduced by means of the 'parity' formula by Mr Paddy Devlin, then Minister of Health for Northern Ireland.[32] There was no public debate.

CARE OF THE NEWBORN

During this time there had been little advance in the care of the newborn. In 1958 and 1970 perinatal surveys were carried out in England and Wales (Northern Ireland being included in the 1970 survey). Dr Muriel Frazer, appointed to Jubilee Maternity Hospital in 1945, could be regarded as the first neonatologist in the province. The major impetus to the expansion of this service was the appointment of Dr (now Professor) Garth McClure as lecturer in Neonatology in 1973, followed by the appointment of Dr Knox Ritchie as Lecturer in Perinatal Medicine in the Department of Obstetrics in 1976.

In 1976, these doctors and their colleagues carried out a survey of neonatal services and perinatal mortality in the province.[33] There were two outcomes, a) the appointment of a committee to investigate infant mortality and handicap in Northern Ireland, and b) a conscious effort was made by consultant obstetricians to transfer women in premature labour to hospitals where neonatal intensive care facilities were available. Neonatal intensive care units were established in Altnagelvin, Craigavon and Ballymena/Antrim Hospitals. A highly sophisticated regional neonatal intensive care unit was set up in the Royal Maternity Hospital.

Much research into the problems of the newborn has been undertaken in Belfast. The work has been supported by the Northern Ireland Mother and Baby Appeal (NIMBA). Professor Henry Halliday was appointed co-ordinator for research in Europe into the management of lung complications using the product 'Surfactant'. Preliminary trials had already been carried out here. Work was also carried out on the nutrition of premature babies. Following research in the Royal Maternity Hospital, manufacturers of infant food produced special high calorie 'milks' for premature babies. This work has shown excellent results.

In 1943, Allen reported a loss of 25% of all babies weighing under $5\frac{1}{2}$ lb (2495 g) born in the Royal Maternity Hospital.[19] In contrast, in 1979,

Halliday reported that 40% of babies weighing less than 2½ lb (1134 g) survived.[34]

CONCLUSIONS

In 1936, the maternal mortality was 7.3/1,000 live births, in 1948 it had fallen to 1.52/1,000, and by 1992 it was zero. The estimated perinatal mortality, based on notification of births, was 50/1,000 in 1948. In 1976 this had fallen to 25/1,000, while in 1992 the figure had fallen further to 8/1,000.

These remarkable results could not have been achieved without a marked alteration in facilities. In 1948, only 30% of women were delivered in hospital – specialist and family-doctor units. In 1992, almost 100% of deliveries took place in specialist hospitals. Advances in technology have led to the disappearance of the family doctor being involved in the management of labour.

The continued compulsory education of specialists and midwives has been of the utmost importance. Neonatology has developed and is now recognised as a specialty in its own right, and all obstetricians rely on and appreciate the unselfish efforts of their new colleagues.

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Occurrence of *Campylobacter* spp. in water in Northern Ireland: implications for public health

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SUMMARY

The occurrence of *Campylobacter* spp was examined in a variety of waters in Northern Ireland. Conventional cultural techniques were employed with 768 water specimens, including drinking waters (tap, spring, bore hole and bottled) and recreational waters (swimming pool, lough, river and sea). Positive waters included 1/11 (9.1%) drinking water from untreated well water, as well as 5/12 (41.7%) untreated surface waters from loughs and 7/8 (87.5%) untreated river waters.

Overall, untreated surface waters may represent a source of contamination with *Campylobacter* spp. in Northern Ireland, where they have a recreational involvement or are used as a drinking source by man or agricultural livestock. Therefore waterborne campylobacteriosis should be considered in patients presenting with acute enteritis and a history of participation in water sports/activities. As faecal coliform organisms have been previously shown to be poor markers of water quality, especially for *Campylobacter* spp, new criteria should be established to assess the risk of this infection and to evaluate and monitor the quality of water used for recreational purposes.

INTRODUCTION

The past three decades have seen the rise of *Campylobacter* enteritis in man from virtual obscurity to notoriety, with present isolation rates superseding those of other enteric pathogens such as *Salmonella* spp. and *Shigella* spp. in most developed countries. Unlike the salmonellae and other enteric pathogens, the majority (c.99%) of clinical reports concerning *Campylobacter* are sporadic and *Campylobacter* enteritis outbreaks are rare. The lack of well-developed typing schemes has hindered the epidemiological investigations seeking natural reservoirs of the organism and modes of transmission from these sources to man. Only about 15% of clinical isolates are identified to species level thus making epidemiological investigations extremely difficult to perform.

Although campylobacters are not completely new to applied bacteriology, they have evaded traditional techniques used for the isolation of pure cultures, apart from single isolations that were free from competing organisms. However it was not until 1957, when King[1] reported on infection in man caused by a closely "related vibrio", that more awareness was given to the disease potential of *Campylobacter* spp. King observed two distinctly different types of vibrio organisms being isolated from blood cultures of infected patients. The first were typical of the organisms designated as *Vibrio fetus*, but the second group were distinctly different in that they had a much higher optimal growth temperature (42°C) and all were isolated from patients with gastrointestinal disease. She concluded that these "related vibrios" were the causative agents of the gastroenteritis, and such organisms were a more common cause of gastroenteritis than was recognised at that time.

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King concluded that the relative absence of microaerophilic vibrios from stools was due to the organisms being fastidious in nature and slow-growing.

A major breakthrough occurred when Dekeyser *et al.*[2] developed a procedure to selectively isolate microaerophilic vibrios from stool specimens. The isolation technique involved filtering suspensions of stools through 0.65μm membrane filters and inoculating the filtrate on to selective agar. Since King first described human infection with the "related vibrios" only 14 cases were reported until the discovery of a selective medium for the isolation of enteropathogenic *Campylobacter* spp. However it was not until 1977, when Skirrow [3] described a more direct technique for the isolation of campylobacters from stool samples from individuals with diarrhoea that the true importance of *Campylobacter* as a causative agent for acute human gastroenteritis was fully revealed. Skirrow employed selective antibiotics in the media formulation in order to eliminate competing flora and to promote the isolation of campylobacters. From this work it was established that campylobacters were indeed a very frequent, if not the most frequent, cause of diarrhoea, particularly amongst paediatric patients.

Since the development of more sophisticated isolation techniques, the true disease potential of these organisms has become apparent, and today campylobacteriosis is regarded as a zoonosis which is capable of being transmitted to man by a wide range of domestic animals.[4] At present the laboratory isolation of these organisms has become routine from clinical as well as from environmental specimens, and although relatively complicated to perform routine isolation has been carried out with success for the past 20 years or so. Until recently, *Campylobacter* has been known mainly as an human pathogen generally of zoonotic origins; however there have been several reports of waterborne acquisition of this organism. Therefore, it was the aim of this study to examine the occurrence of *Campylobacter* spp in waters in Northern Ireland and to assess subsequently their importance to public health.

MATERIALS AND METHODS

Collection and processing of water specimens

All samples (1000 ml) were collected by Environmental Health Officers from the 26 local council authorities within Northern Ireland in sterile plastic disposable containers. The samples were collected as part of a routine programme from various domestic and commercial premises (Table 1). In addition, samples were collected from various leisure facilities, such as public leisure centres and hotel leisure complexes. Surface waters from lakes, reservoirs, springs and wells were also analysed. All samples were transported and maintained at 4°C prior to analysis and were processed within 24 hours following collection.

Conventional culture of *Campylobacter* spp

Water specimens (400 ml) were initially filtered through a sterile polycarbonate membrane filter (43 mm diameter; pore size 0.20 μm) (Whatman Ltd., England) employing a sterile Millipore Water Filtration system (Millipore Inc., USA). Filters containing filtrate were removed and placed in Nutrient Broth no. 2 (Oxoid Ltd., England) supplemented with Preston Selective agents (Oxoid SR 117, Oxoid Ltd., England) and placed in universal containers (approximately 20 ml) with the minimum headspace volume allowed. Broths were incubated at 37°C for 24 hours followed by a further incubation at 42°C for 24 hours prior to streaking on to Preston Selective agar (Oxoid Ltd., England). All presumptive colonies were further characterised using phenotyping methods, as previously described.[5] The type strain *C. jejuni* NCTC 11351 was employed as a positive control for both extraction and characterization and sterile distilled water was employed as a suitable negative control.

Molecular confirmation of *Campylobacter* by 23S rRNA & flaA/flaB PCR

All isolates were further confirmed by PCR employing both the flagellin (*flaA/flaB*) gene [6] and the 23S rRNA gene,[7] as previously described.

Penner serology

Campylobacter isolates were serotyped according to the method of Penner and Hennessey, as previously described.[8]

ENUMERATION OF COLIFORM ORGANISMS FROM WATER SPECIMENS

Water specimens (100 ml) were initially filtered through a sterile polycarbonate membrane filter (43 mm diameter; pore size 0.45 μm) (Type HA, Whatman Ltd., England) employing a sterile Millipore Water Filtration system (Millipore Inc., USA). Filters containing filtrate were removed and placed in a sterile petri dish containing a petri pad soaked in Lauryl Sulphate Broth (Oxoid

TABLE

Occurrence of Campylobacter spp. in waters in Northern Ireland

Water Type	*No. of specimens examined*	*No. positive (% positive*	*Species*	*Penner serotype*	*Source*	*Coliform count (cfu/100 ml)* *
(i). *Drinking waters*						
Tap	367	0	–			
Spring	13	0	–			
Bore hole	9	0	–			
Well	11	1(9.1%)	*C. jejuni*-	ND [Preston biotype 6102]	Private Dwelling	ND
Bottled	2	0	–			
(ii) *Recreational waters*						
Swimming pool	345	0	–			
Lough	12	5 (41.7%)	*C. coli*	NT§	Lough Neagh	1.1×10^3
			C. coli	NT	Lough Neagh	1.4×10^3
			C. coli	NT	Lough Neagh	9.1×10^3
			C. coli	NT	Lough Neagh	5.4×10^3
			C. coli	11	Lough Neagh	1.6×10^3
River	8	7(87.5%)	*C. coli*	NT	River Lagan	3.5×10^3
			C. coli	11	River Lagan	9.1×10^4
			C. coli	NT	River Lagan	9.1×10^3
			C. coli	NT	River Lagan	$>10^5$
			C. coli	NT	Annesborough river	1.1×10^3
			UPTC †	NT	River Lagan	3.5×10^3
			C. jejuni	NT	River Lagan	3.4×10^3
Sea	1	0				

Notes: ND, not determined; §NT, non-typable; *cfu/100 ml, colony forming units/100 ml water; UPTC†, urease-positive thermophilic *Campylobacter*

MM615, Oxoid Ltd., England) and the inverted pads were incubated at 30°C for 4 hours, followed by further incubation at 37°C for 14 hours. Coliform organisms were confirmed by gas production in Brilliant Green Bile Broth (Oxoid CM31, Oxoid Ltd, England) and oxidase activity [oxidase negative]. Colony counts were expressed as colony forming units per 100 ml water examined [cfu/100 ml].

RESULTS

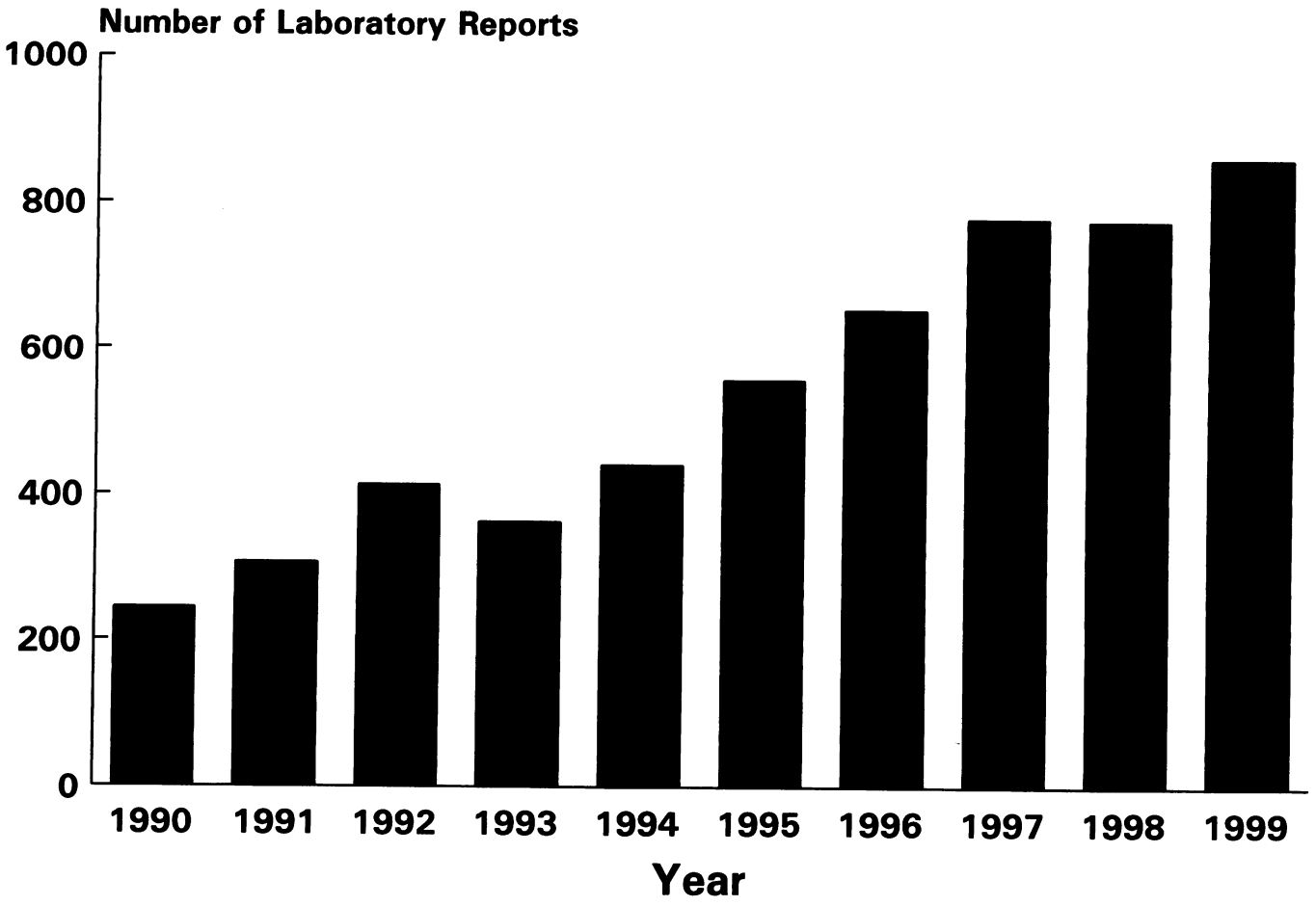
Viable *Campylobacter* spp. were only isolated from untreated well, lake and river waters, as detailed in Table. None of the chlorinated drinking water specimens were positive for this organism. The present study showed that all chlorinated swimming-pool waters were also free from viable campylobacters. Ninety seven percent of unchlorinated drinking-water specimens were negative, with one unchlorinated well-water supply yielding *C. jejuni* biotype 6102. In contrast to this, approximately 57% of untreated surface waters from loughs and rivers were positive for campylobacters. Of these, 83% were *C. coli*, 8.5% *C. jejuni* and the remainder urease-positive thermophilic *Campylobacter* (UPTC), as confirmed by both phenotypic and molecular (*fla*A/*fla*B PCR) analyses. The majority of campylobacters isolated from surface waters were untypable using the Penner serology scheme, with the exception of two isolates, which were Penner serotype 11. Coliforms were enumerated for *Campylobacter*-positive water specimens, as a marker of faecal contamination, and yielded mean counts of 3.72×10^3 cfu/100 ml and 1.86×10^4 cfu/100 ml for loughs and rivers respectively, indicating a moderate level of faecal pollution in these sources.

DISCUSSION

In Northern Ireland, *Campylobacter* spp. is the most common cause of acute bacterial gastroenteritis, exceeding other common faecal pathogens including *Salmonella, Shigella*, pathogenic *E. coli* (VTEC, EPEC, EHEC) and protozoa including *Cryptosporidium parvum*,

FIGURE

Annual laboratory reports of campylobacters isolated from faeces over the period 1990-1999.



with present annual laboratory reports of approximately 800-900 cases. The trend for this pathogen is demonstrating an annual rise, even in the present food safety climate. However, Northern Ireland infection rates for this pathogen are substantially lower than the rest of the UK, whereas the rates for England/Wales and Scotland are relatively similar. With the exception of the late Spring peak periods in 1997 and 1999, the rates of infection in Northern Ireland per 100,000 population has remained in the range 6-14, whereas the rate in England/Wales and Scotland has ranged from 15-40 persons per 100,000 population.[9] It has been postulated that this difference may be attributed to (i) a colder and wetter climate, curtailing summer picnics and barbeques, (ii) a higher rate of consumption of red meat than white meat, (iii) a social liking for "well-done" foods and (iv) a virtual absence of consumption of unpasteurised milk by the general public.

Campylobacters still remain the most common cause of acute bacterial food-poisoning in Northern Ireland, first exceeding gastrointestinal-related *Salmonella* isolation rates in 1991 and continuing to show an annual rise of approximately 21%, as shown in Figure 1.[9] Although the majority of diagnostic clinical laboratories locally do not characterise isolates to the species level, studies at the Northern Ireland Public Health Laboratory have demonstrated that approximately 90% of local infections relating to this genus are caused by *C. jejuni*, followed by 8% *C. coli* with the remaining 2% made up of *C. lari, C. upsaliensis* and other unusual species. Furthermore, as no local laboratories are carrying out non-selective differential filtration isolation, it is difficult to predict the prevalence and clinical significance of antibiotic-sensitive species in the Northern Ireland population.

The natural habitat of most *Campylobacter* spp. is the intestine of warm-blooded animals,

particularly poultry. Although the enteropathogenic campylobacters have been shown to cause disease in a wide variety of animals and man, certain species have been shown to have a preferred niche. *C. jejuni* have been shown to be most prevalent in poultry, whilst pigs appear to be the preferred niche of *C. coli.* Hence the ecological niche occupied by the *Campylobacter* spp may be of significant importance in relation to the epidemiology of the disease. Likewise, contamination of both recreational and drinking water with faeces from human and animal positive shedders represents a significant risk to the safety of such waters.

In the present study, it was reassuring to note the absence of campylobacters from a large sample population of chlorinated drinking water as well as from swimming pool water, indicating the maintenance of effective disinfection and quality control procedures. Swimming pool-associated outbreaks of human campylobacteriosis have not been reported in the literature indicating that this is not an established mode of transmission of this pathogen to man, unlike numerous outbreaks of cryptosporidiosis, which have been transmitted in this manner.[10]

All environmental samples were collected over a two month period in the winter time, when it would have been more likely to detect positive specimens by culture than in the summer time, as the rate of isolation has been previously shown to decline due increased ambient temperature, but also increased hours of daylight.[11] One untreated drinking water from a well in a private residence was positive for *C. jejuni* indicating the importance of proper control and disinfection through chlorination as an effective means of rendering water potable. In England and Wales there have been at least six outbreaks of human campylobacteriosis associated with the consumption of water from private supplies,[12] as well as an outbreak from unchlorinated well water in Canada due to contamination with meltwater.[13] Consequently, individuals consuming unchlorinated water from private supplies, including wells, bore holes and springs, should have their supply monitored microbiolgically at regular intervals to maintain a safe and potable supply and to discuss any irregularities with the Environmental Health Officer from their local council authority.

The most significant risk of human infection is from the accidental ingestion of contaminated untreated surface waters during recreational use, even in non-outbreak settings. A variety of such recreational activities including rowing, canoeing, water skiing, jet skiing, wind-surfing, angling and boating are popular at many sites (River Lagan and Lough Neagh). These are subject to contamination by campylobacters from point sources, including sewage releases, water sheds, run-off from agricultural and residential areas, faecal contamination from wildlife, as well as floods. In addition, positive waters may serve as a source of infection for domestic livestock as well as household pets.

In this study, three species of *Campylobacter* were isolated, i.e. *C. coli, C. jejuni* and the UPTC group. Both *C. coli* and *C. jejuni* are well-established human pathogens, whilst the latter group of campylobacters are atypical to other defined species within this genus, as these organisms have well marked urease activity, similar to their close phylogenetic neighbour, *Helicobacter pylori.*[14] As this group of organisms is not found in domestic animals or man, this suggests that these organisms may be endogenous to the acquatic environment, probably through introduction by water fowl and migratory birds.

Little is known about the survival and transmission of *Campylobacter* spp. in the environment or how domestic and wild animals which serve as a natural source become infected. Several epidemiological reports have implicated water as the source of campylobacters, although no *Campylobacter* spp. could be isolated from the suspected water. This has introduced the concept of the viable but non-culturable cell. Rollins and Colwell [15] reported on a viable but non-culturable *C. jejuni*, which changed form from a culturable spiral to an non-culturable coccoidal structure. These workers attempted to explain the dormant state of the *Campylobacter* spp. and the inability to culture these cells employing conventional techniques. McKay [16] reported on the significance of the viable but non-culturable form of *C. jejuni* and concluded that reliable detection methods must be available in order to allow detection of this form of the pathogen, as non-culturability cannot be equated with non-viability. Consequently the existence of a viable but non-culturable form of campylobacters has serious implications for both epidemiology and methods for detection, especially in the detection of enteropathogenic campylobacters in quality control situations in water microbiology. As a

result of such work, the "pseudosenescent" state was proposed, where bacteria lose the ability to multiply as a result of certain stresses, but remain completely functional as individuals – the so-called "viable but non-culturable" state. *C. jejuni* have been shown to have this viable but non-culturable form.[15] *C. jejuni* was shown to be viable in water samples by non-conventional culturing techniques, but could not be detected by conventional culture methods. These workers concluded that the inability to culture these cells was due a number of factors, including (i). survival of the organism in a viable but non-culturable state, (ii). persistence in a biofilm and adherence to surfaces – non-culturable by conventional methods, (iii). cells may be present in numbers below the threshold necessary to establish growth on laboratory media.

Consequently future studies should concentrate on the adoption of molecular detection systems employing molecular markers of viability such as detection of mRNA through RT-PCR, to account for physiological adaptation with this genus.

In conclusion, untreated surface waters may represent a source of contamination with campylobacters in Northern Ireland, where they have a recreational involvement or are used as a drinking source by either man or agricultural livestock. Therefore consideration of waterborne campylobacteriosis should be given to patients presenting with acute enteritis and a history of participation in water sports/activities. As faecal coliform organisms have been previously shown to be poor markers of water quality, especially for *Campylobacter* spp, new criteria should be established to assess the risk from campylobacter and to evaluate and monitor the quality of water used for recreational purposes.

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Electrocardiogram and rhythm strip interpretation by final year medical students

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SUMMARY

The pre-registration house officers (PRHO) is often called upon to interpret electrocardiograms ECG. We invited final-year medical students who had successfully completed their written final examinations, to interpret three rhythm-strip tracings, and three 12-lead ECG tracings. The rhythm-strips were of ventricular fibrillation (VF), ventricular tachycardia (VT), and complete heart block. Of the three 12-lead ECG tracings, one was an inferior myocardial infarction (MI), one was atrial fibrillation (AF), and one showed no abnormality. Forty-six medical students attended. Of these, 50% had received no formal training in ECG interpretation, although 89% had tried to learn ECG interpretation from books. Only 9% felt confident in their interpretation of ECG tracings. Of the rhythm-strips, 100% correctly identified VF, 96% recognised VT, and 67% identified complete heart block. Of the 12-lead ECG tracings, 61 % recognised the MI, 54% recognised AF, and only 46% successfully identified the normal ECG as such. The group were significantly worse at 12-lead ECG interpretation compared to rhythm-strips ($p<0.01$). The members of the group who had received formal training in ECG interpretation were significantly better at interpreting both rhythm-strips and 12-lead ECG tracings ($p<0.05$). It would appear that formal ECG training as an undergraduate improves PRHO interpretation of ECG tracings, and the PRHO should not interpret 12-lead ECG tracings without consulting more senior medical staff.

INTRODUCTION

Pre-registration house officers are the first-on-call doctors for the wards they cover. Frequently, house officers are called upon to perform an ECG and to interpret its findings. The House Officer is expected to be able to detect significant ECG abnormalities, and to show abnormal ECG tracings to more senior medical staff. The purpose of this study was to establish the level of training that medical students receive prior to qualification, the degree of confidence they had in their own ability, and how successful they were at detecting major rhythm and ECG abnormalities.

METHODS

Final-year medical students who had completed their written examinations attended a lecture two weeks prior to their clinical finals, and were invited to complete the ECG questionnaire. Regarding their training, they were asked (i) Had they ever received formal tuition from a Doctor regarding ECG interpretation, (ii) Had they tried to self-teach ECG interpretation, and (iii) Did they feel confident in their ECG interpreting skills. They were then shown three rhythm strips and three 12-lead ECG tracings, for one minute each. They were required to record their interpretation of the rhythm-strip or ECG. The rhythm strips were: ventricular fibrillation, ventricular tachycardia, and complete heart block. The 12-lead ECG tracings were: inferior myocardial infarction, atrial fibrillation, and a normal ECG. The completed questionnaires were then collected and marked by one author (B.L.)

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RESULTS

Forty-six final year medical students completed the questionnaire. Of these, only 23 (50%) of the group had received formal training from medical staff, but 41 (89%) had tried to teach themselves ECG interpretation by private study. Only 4 (9%) of the group regarded their own ECG interpretation skills with confidence.

Overall, 88% of rhythm-strips were correctly assigned, with 46 (100%) of the group identifying VF, 44 (96%) identifying VT, and 31 (67%) recognising complete heart block. The 12-lead ECG tracings were correctly assigned in 54%. The inferior myocardial infarct was the most recognised, with 28 (61 %) of the group detecting it. Atrial fibrillation was correctly diagnosed by 25 (54%), and the normal ECG was categorised as such by 21 (46%) of the group. Comparing the groups identification of rhythm-strips to their interpretation of 12-lead ECG tracings using a single-tailed T-test (paired sample, equal variance), rhythm strips were significantly more likely to be correctly interpreted ($p<O. 0 1$).

The subgroup that had previously received formal ECG instruction had correct rhythm-strip identification in 93% of cases, and correct 12-lead ECG interpretation in 64% of cases. The subgroup without previous formal instruction had lower rates of 83% and 43% respectively. The difference in correct interpretation rates was significant (T-Test, unpaired sample, unequal variance) for both rhythm-strips and for 12-lead ECG tracings ($p<0.05$). This suggests that previous formal teaching on the interpretation of ECG tracings produced a statistically significant improvement in ability.

DISCUSSION

Interpretation of ECG tracings can be difficult. In the setting of a casualty department, a study examining S-T segment elevation found that it was misinterpreted in 5.9% of cases of patients attending A&E with chest pain, however the clinical consequences of missed diagnosis were minimal [1]. A previous study had addressed the question of cardiology review of ECG tracings. After a review of 1,000 ECG tracings, thirty-eight patients had been discharged with 'abnormalities that could potentially alter case management'. Interestingly, after review by a panel of emergency physicians, only eight were felt to merit chart review, and no review altered case management. Cardiology review of all ECG tracings was not therefore commenced[2]. The provision of a correct history supplementing the ECG has improved accuracy of ECG interpretation by 4-12%, but a misleading history reduced accuracy by 5% for cardiologists, 25% for residents, and 19% for students[3]. In this study we omitted history, as the aim was solely to assess interpretation of ECG. Providing access to computer interpretation of the ECG tracing also has limitations, as it has a false positive reporting rate of 16.5%, and a false negative report rate of 10.5%. Computer interpretation is 18 times more likely to yield a false positive report than a trainee physician.[4]

The seniority of the doctor interpreting the ECG also has relevance. A recent study asked for interpretation of 30 ECG tracings, with respect to whether the interpreting individual would prescribe thrombolysis on the basis of it. All cardiology consultants correctly diagnosed all acute myocardial infarctions. Of acute MI tracings, house officers correctly identified only 76%, albeit in a small sample of 10 house officers[5].

In this study, interpretation of rhythm abnormalities was reasonably good, with 88% analysed correctly. However, the incorrect diagnosis rate for an acute inferior myocardial infarction was 39%. In addition, only 46% of the assessed group were able to successfully identify an ECG without abnormalities as such. This would suggest that house officers are not reliable in their interpretation of 12-lead ECG tracings, at the time of qualification, and only 9% are confident in their ECG interpreting ability. It may be necessary to incorporate formal ECG training and assessment into the undergraduate curriculum, as this improved diagnostic accuracy. It may also be necessary to require House Officers to show ECG tracings to a more senior doctor for the early part of their pre-registration year, until competence is demonstrated.

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Spironolactone prescribing in heart failure:

Comparison between general medical patients and those attending a specialist left ventricular dysfunction clinic

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SUMMARY

We compared the rate of prescription of low-dose spironolactone among patients with heart failure in a general medical inpatient setting and in a specialist left ventricular (LV) dysfunction clinic. 38% of general medical patients and 72% of patients attending the specialist clinic had been prescribed spironolactone. When contraindications were considered, 54% of patients in the general medical group and 77% of patients in the specialist clinic group were appropriately treated in respect of spironolactone prescribing. Patients attending a specialist LV dysfunction clinic are therefore more likely to be treated with low dose spironolactone, an accepted appropriate treatment for heart failure, than those admitted to general medical and acute geriatric units.Improvement in care for patients with CHF may be achieved either by increasing the use of specialist clinics or by better dissemination of evolving evidence.

INTRODUCTION

In September 1999, the findings of the Randomized Aldactone Evaluation Study[1] (RALES) were published. In this double-blind study, 1663 patients with left ventricular ejection fraction less than 35%, an(NYHA symptom class III-IV were randomised to receive either 25mg spironolactone or placebo. The study was discontinued prematurely after two years because interim analysis showed a 30% reduction in risk of death in the group receiving spironolactone. This is equivalent to a number needed to treat of nine to avoid one death during this two year period[2]. In addition, there was a 35% reduction in risk of hospitalisation for worsening heart failure (equivalent to a number needed to treat of eleven) and significant symptomatic improvement in this group. The low cost of spironolactone implied likely cost-effectiveness.

RALES therefore defined a standard in heart failure management having demonstrated an important contribution from low dose spironolactone in addition to conventional therapies. We appreciate the importance of applying evidence from clinical studies to practice, and it is therefore reasonable to aim to incorporate spironolactone into the medication of all patients with moderate to severe heart failure, except for the few in whom it is contraindicated. We accept that there is no evidence available at present to support its use in mild CHF.

We wished to assess the performance of the specialist left ventricular (LV) dysfunction clinic at the Belfast City Hospital with respect to spironolactone prescribing, comparing this against the prescribing rates for inpatients admitted to the general medical and acute elderly care units.

METHOD

The records of the last 50 patients whose hospital admission was coded with a primary diagnosis of heart failure were analysed prior to 20th February 2000. The 'final' chart related to an admission in December 1999. We also reviewed the records of all 75 patients who were attending the LV dysfunction clinic during the same period. The assumption was made that patients admitted to hospital on the emergency "take-in" due to heart failure and those referred to the specialist clinic

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would be unlikely to have mild CHF, and that almost all could be considered to have moderate-to-severe disease, meriting spironolactone therapy.

Data collected for the purpose of this study were:

1. Whether the patient was receiving spironolactone
2. If not, whether there was any contraindication. We identified three major contraindications, modelling these on those applied in the RALES[1]: serum creatinine >221umol/l, serum potassium >5.0mmol/l and hepatic failure.

RESULTS

Of the 50 general medical inpatients studied, 38% were on spironolactone. Of the remaining patients who were not receiving this drug 26% had at least one contraindication, while 74% were without clear contraindication (Tables I & II and Figure 1). It can therefore be concluded that 46% of these 50 patients were not receiving spironolactone without contraindication.

Of the 75 patients attending the LV dysfunction clinic, 72% were receiving spironolactone. Of those who were not, 19% had at least one contraindication, and 81% had no identifiable contraindication (Tables I & II and Figure 2). Therefore 23% of these 75 patients were not receiving spironolactone despite the absence of clear contraindication.

TABLE I:

Incidence of low dose spironolactone prescribing in heart failure patients in both settings.

	General Medical Inpatients	LV Dysfunction Clinic
Number of patients on spironolactone	19/50(38%)	54/75(72%)
Number of patients not on spironolactone	31/50(62%)	21/75 (28%)

TABLE II:

Proportion of patients with and without contraindication among those not receiving spirono actone in each setting.

	General Medical Inpatients	LV Dysfunction Clinic
Number not on spironolactone with contraindication	8/31 (26%)	4/21 (19%)
Number not on spironolactone without contraindication	23/31 (74%)	17/21 (81%)

DISCUSSION

The comparisons between the two sets of data are interesting but in some ways surprising. Patients who attended the LV dysfunction clinic were more likely to have been prescribed spironolactone; perhaps this is to be expected since physicians running a specialist clinic are probably more likely to be aware of recent evidence within their discipline. However, when the group which was not prescribed spironolactone in each case is examined, it becomes clear that there is little difference in the reason for its omission. One might have expected that the proportion of patients not receiving spironolactone due to contraindication (rather than oversight or lack of familiarity with current evidence) would have been greater among the LV dysfunction clinic patients; this was not the case. The absolute risk of 'oversight', however, was greater among the general medical patient population.

THE ROLE OF ALDOSTERONE ANTAGONISM IN HEART FAILURE

Aldosterone has an established role in the pathophysiology of left ventricular dysfunction. About 30% of patients with chronic heart failure (CHF) have diastolic dysfunction in the setting of normal or near normal systolic function.[3] In such patients, collagen matrix within the myocardium is felt to be the major culprit producing diastolic dysfunction by way of increasing myocardial stiffness. Such fibrotic infiltration also impairs systolic function and contributes to the development of conduction defects and associated arrhythmias.[4]

In addition to collagen, cardiac fibroblasts produce matrix metalloproteinase, an enzyme which

degrades interstitial collagen; these cells are under the influence of the renin-angiotensin-aldosterone system (RAAS).[3] Animal studies have demonstrated increased fibrosis in the setting of hyperaldosteronism and the absence of fibrosis when activation of the RAAS has been prevented. Furthermore, aldosterone stimulates collagen synthesis in cultured cardiac fibroblasts in a dose-dependent manner. In animal studies, in the setting of primary or secondary hyperaldosteronism, spironolactone has been shown to prevent myocardial fibrosis.

High serum aldosterone is a characteristic of CHF, with up to 40% of patients on Angiotensin Converting Enzyme (ACE) Inhibitors having persistently raised levels.[5] In addition to impairing cardiac function by way of causing fibrosis, aldosterone may further increase the arrhythmogenicity of this milieu via inhibition of cardiac noradrenaline reuptake, increased sympathetic activity, decreased parasympathetic tone and impairment of baroreceptor-mediated heart rate variability.[6]

Spironolactone has been found to decrease the amount of a key marker of vascular collagen turnover and also to bring about a decrease in heart rate.[4] Interestingly, this beneficial decrease in heart rate was most prominent in early morning when fatal cardiac events are known to be most common.

Spironolactone has also been shown to improve vascular endothelial dysfunction (characterised by improved responsiveness to vasoactive agents) and also to inhibit the conversion of angiotensin I to angiotensin 11.[7] Perhaps such effects may account at least in part for the mortality benefits of aldosterone antagonism identified in the RALES[1].

It is therefore well established that hyperaldosteronism has an adverse effect on cardiac function, one which may be avoided by the use of aldosterone antagonists. For many years it has been assumed that since ACE inhibitors block aldosterone production spironolactone is unnecessary[8]; however, the finding that it reduced mortality by 30% over a two-year period with concomitant reduction in morbidity must not be ignored. It should be noted that spironolactone is a useful adjunct to, but not substitution for, ACE inhibitor therapy. Indeed there is a feeling that the benefits of spironolactone are likely to be lost if a patient is not concomitantly receiving an ACE inhibitor.

In RALES[1], the major adverse effects of spironolactone in men were gynaecomastia and breast pain, occurring in 10% of the treatment group and in only 1% of the placebo group. Of note, serious hyperkalaemia was minimal in both groups. In support of this, another study found that adding spironolactone to conventional therapy resulted in no significant increase in serum urea, creatinine or potassium.[9] We might, therefore reasonably consider spironolactone to be a safe drug.

CHF is a major public health issue, with general prevalence estimated at 0.4-2.0% in the UK; among the elderly this rises to 10%.[10] It therefore carries significant implications for resource allocation and it is logical that interventions which reduce associated hospitalisations should be considered important.

The cost of a one-year supply of spironolactone is typically £32.85 per patient. Estimation of the total number of patients with CHF in Northern Ireland is fraught with difficulties. Based on extrapolation of Framingham data, the figure could be expected to be between 10000 and 11000. We attempted to corroborate this with an alternative method involving division of the annual number of defined daily doses (DDD) of loop diuretics prescribed by the number of days in the year. This proved unreliable, yielding a figure in excess of 30 000; it failed to exclude patients who would be receiving these agents for reasons other than CHF and it did not account for the many CHF patients who receive doses much greater than the DDD (40mg for frusemide and 1mg for bumetanide).

If we assume that at least 6000 patients in Northern Ireland have moderate-to-severe CHF and are without contraindication to spironolactone therapy, then the cost of treating such a group would be approximately £200000 per annum. Predicting cost-effectiveness is complex and data produced is unlikely to be very reliable, however, a guarded estimate can be made. If one applies the reduction in CHF-associated admissions observed by the RALES investigators (35%) and the estimate that 21.9% of patients with moderate-to-severe CHF require hospitalisation per annum as determined by the SOLVD investigators[11], then of a predicted 1300 admissions per year, around 450 could be avoided. Based on 1997

Belfast City Hospital figures, one such admission costs on average £2436. The potential saving is around £1.1million with an outlay of £200,000; the net saving could therefore be as much as £900,000. Even if these estimates are exaggerated, it seems likely that, with appropriate prescribing, savings on hospitalisation expenditure could negate the cost of any years of life saved.

Spironolactone is the latest addition to several advocated constituents of a CHF treatment regime; however, based on past performance it would seem likely that its widespread incorporation will be a slow process. Reluctance to move practice patterns in phase with new evidence has limited CHF management in the UK. Despite an abundance of evidence favouring outcome benefits and cost-effectiveness achievable by appropriate use of ACE inhibitors, there is a great deal of data to indicate that the 80-90% rates of tolerance estimated in the major mortality studies are poorly reflected in prescribing patterns. Davie and McMurray[12] reported ACE inhibitor prescribing rates of around 66% in hospital and data gathered in 1994 in a community setting in Northern Ireland estimated that perhaps as few as 18% of CHF patients were on such an agent.[10] In a survey of general practitioners' attitudes to CHF management[13], it became apparent that reluctance to prescribe ACE inhibitors was much more strongly related to fear of causing harm than ignorance of proven benefits (of which 98% were aware).

Interesting data are available suggesting that reluctance to prescribe in CHF is variable throughout Europe[14]. The UK typically display a lower rate of prescription, particularly with regard to digoxin and beta-adrenoceptor antagonists. One might expect, therefore, that the rate of prescription of spironolactone will also be lower than average in this country.

Our small study suggests that patients with heart failure who are managed at a specialist LV dysfunction clinic are more likely to receive spironolactone than those who are managed as inpatients in the general medical and acute elderly care units. It also highlights that even in the specialist clinic setting there is room for improvement. Admittedly, the study is not without flaw: there is imbalance in the number of patients in each group and in some cases, clinical decisions (such as to withhold a given treatment) may have been based on observations and measurements not documented. It is not appropriate to presumptively extrapolate these findings to other heart failure treatment interventions, nor to imply actual outcome differences between the two groups; however, our findings support in at least one facet the argument for having teams with a special interest in managing patients with heart failure. This is further supported by data from Chin *et al*[15] identifying an analogous situation relating to ACE inhibitor therapy, whereby general practitioners and general physicians were found to underuse these drugs when compared to cardiologists.

CONCLUSION

Low dose spironolactone has been identified as a safe and rational therapy which decreases mortality, improves symptoms and reduces hospitalisations (thus producing resource utilisation benefits) when added to conventional treatment in patients with moderate-to-severe CHF. When measured against this standard, the finding that we adequately treat only 54% of heart failure patients in a general medical inpatient setting and 77% of patients attending a specialist LV dysfunction clinic provides us with a point from which we might expect to improve; one might alternatively reason that this reflects surprisingly impressive receptiveness to new data over a relatively short time. We have a duty to raise the standard of care for patients with CHF, either by increasing the use of specialist clinics or by improving general physicians' awareness of evolving evidence.

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Can computed tomography identify patients with anaemia?

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Thirty-three in-patients attended for non-contrast enhanced computed tomography (CT) of chest and/or abdomen within a six-week period (11 M, 21 F). All had measurement of their full blood profile within the previous 72 hours. Patients with a blood dyscrasia or known history of active bleeding were excluded.

All patients were imaged using a Siemens Somatom Plus S scanner. The scanning parameters were standardised at 210mA, 120kV, 10mm slice thickness, pitch of 1. Following image review, circular regions of interest (ROI) were defined within the lumina of the aorta and inferior vena cava (IVC) at the level of the superior mesenteric artery origin. The mean attenuation value was calculated using on-board computer software, and recorded.

The mean patient age was 59.6 years (range 18-85 years). A non-parametric correlation analysis was performed and a linear regression plot obtained. A significant correlation was demonstrated between haemoglobin measurement and the aortic and IVC attenuation value. The correlation was stronger (r=0.64) for the aortic attenuation value than for the IVC attenuation values (r=0.57).

In addition, if anaemia is defined as less than 14g/l for a male and less than 12g/l for a female, then, in our study group, no male with an aortic attenuation value greater than 50HU and no female with an aortic attenuation greater than 45HU was found to be anaemic.

The results demonstrate a significant correlation between patients' haemoglobin measurement and the derived aortic attenuation value. We do not propose this as a method of accurately measuring the patient's haemoglobin; however, we feel that it may be possible for a radiologist at non-contrast enhanced CT examination to note the probable presence of anaemia.

INTRODUCTION

The measurement of an attenuation value of an anatomical region at CT examination is commonplace. The study aims to demonstrate a correlation between routine haematological assay of haemoglobin level and the attenuation value measured within the aorta or inferior vena cava (IVC) lumina at routine unenhanced CT examination.

The measured attenuation value is a reproducible physical density measurement, readily obtainable from a standard CT examination. A correlation between attenuation value and plasma haemoglobin may permit the identification of anaemia at CT examination.

MATERIALS AND METHODS

Thirty-three patients who attended for routine unenhanced CT of the chest and abdomen within a six-week period were evaluated. There were 12 male and 21 female patients. Patient age ranged from 18-85 years. Each patient had had a full blood profile performed within 72 hours of his or her CT examination. Haemoglobin was calculated using the standard hospital laboratory assay.

The CT examination was performed using a Siemens Somatom Plus S CT scanner (Siemens, Erhiangen, Germany). Ten millimetre axial sections were acquired at standardised imaging parameters (210mA and 12kV) and reviewed at a window width of 200HU and a window centre of 50HU Regions of interest (ROI) were then defined within the lumina of the aorta and IVC at the level of the superior mesenteric artery origin using the integrated software package on the scanner

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workstation. (Fig.1) Simple circular regions of interest were designated and interrogated.

The mean attenuation value, standard deviation, and region of interest area were recorded for both the aortic and IVC regions.

STATISTICAL METHODS

Correlation was calculated using the Spearman correlation coefficient.

RESULTS

The mean patient age was 59.6 years. Assayed haemoglobin values ranged from 8-16.6 g/dl with a mean of 12.8 g/dl. The ROI data set for the cohort was then subjected to statistical analysis using a non-parametric correlation analysis and a linear regression plot was also derived.

The Spearman correlation coefficient for the aortic attenuation value to haemoglobin level was 0.64. This compared to a value of 0.57 for IVC attenuation value to haemoglobin level and 0.33 for aortic attenuation to white blood cell count, which was measured as a control. These correlations for the aortic and IVC attenuations to haemoglobin level are significant, with the aortic correlation stronger. The linear regression plot obtained is displayed in Fig.2.

Anaemia was then defined as a haemoglobin value of less than 14 g/dl in a male and less than

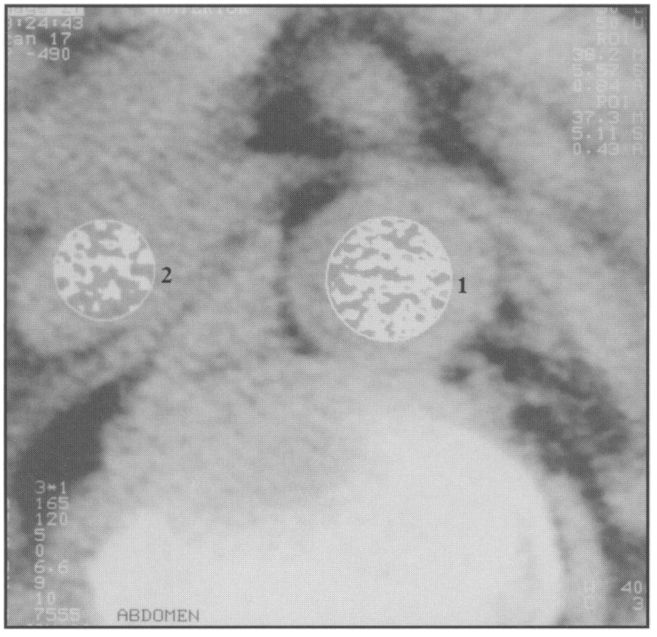

Fig 1. CT of the abdomen at the level of the superior mesenteric artery (SMA): Regions of Interest (ROI) defined within the lumina of the aorta (1) and the inferior vena cava (2).

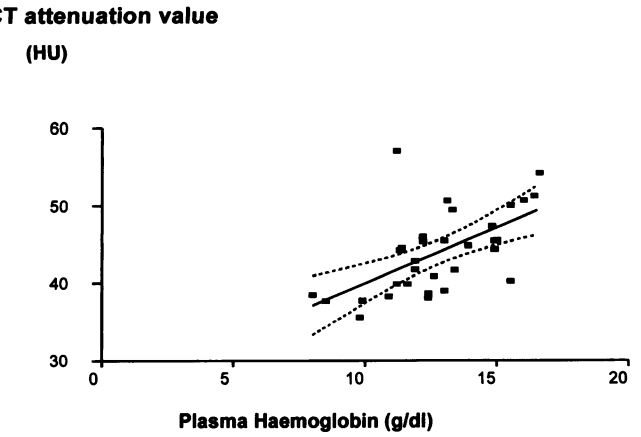

Fig 2. Regression plot of haemoglobin (g/dl) versus CT attenuation value (HU). (broken line reprsents 95% confidence limits).

12 g/dl in a female patient. Our study group was then divided into anaemic and non-anaemic sub-groups on the basis of this haemoglobin measurement. We found that no male patient with an aortic attenuation value greater than 50HU and no female patient with an aortic attenuation greater than 45HU was anaemic.

DISCUSSION

A correlation between plasma haemoglobin and the attenuation of ionising radiation has been shown in vitro and indeed is the basis for a previous method of measuring the haemoglobin level. However the use of abdominal CT examination to primarily measure haemoglobin is absurd.[1]

The data we have used to reach our conclusions is however freely available from the routine CT examinations performed in imaging centres. No additional radiation dose is incurred. There is a small time penalty in accessing and extracting the data but this is negligible.

Modern CT scanning systems are equipped with software to allow the extraction of highly accurate reproducible physical measurements from the routinely acquired data. This information has been used to assess and characterise lesions in many clinical settings. [2-3]

This study aimed to investigate the possibility of deriving a haemoglobin level from this readily available data. The degree of correlation we have demonstrated is not strong enough to give a highly accurate measurement of the plasma haemoglobin but is capable of providing a reliable indicator of the presence of anaemia. We have

shown that an averaged aortic attenuation value in excess of 50HU in a male and 45HU in a female is consistent with the absence of anaemia.

The amount of clinical information available to the radiologist at the time of reporting is variable and usually sparse. In this context the ability to note the presence of anaemia[4] may be a helpful adjunct in the process of interpreting the study – possibly altering or further limiting the differential diagnosis.

CONCLUSION

The results demonstrate a significant correlation between the haematological haemoglobin assay and the aortic attenuation value. In addition we have defined subgroups of anaemic and non-anaemic patients, and shown that measuring the averaged aortic attenuation value can differentiate these groups. This allows the accurate pin-pointing of anaemia at unenhanced CT examination, and we conclude that this readily available information may provide a valuable adjunct in the interpretation of such examinations.

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Maternal blood glucose and the baby. The origins of the Hyperglycaemia and Pregnancy Outcome study

The Scott-Heron Lecture at the Royal Victoria Hospital – 17 January 2001

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It is a great honour to be asked to give the Scott-Heron Lecture at the Royal Victoria Hospital. The list of lecturers since the first in 1957 comprises a formidable catalogue of distinguished medical names from all over the world. I remember as a medical student hearing the first lecture, on Smallpox in Ireland, by Sir William McArthur who was renowned for his remarkable visual memory and who gave his talk without notes. Little did I think that I might find myself in the same position over 40 years later. I am particularly honoured to be only the fifth serving member of the Royal Victoria Hospital staff to be invited to give this lecture.

The topic, Hyperglycaemia and Adverse Pregnancy Outcome, (HAPO) represents the story of my research interests over those 40 years, which range across a number of clinical boundaries including endocrinology, medical obstetrics, nutritional paediatrics and a great deal of epidemiology. The lecture was endowed by the generosity of Dr Francis Hugh Scott who died in 1946. He had practised as a family doctor in the district dispensary in Saintfield, County Down, where he was the predecessor of the present Dr James McKelvey's father. Dr James McKelvey himself remembers as a small boy meeting Dr Scott and being very impressed by his large motor-car. Dr Scott lived in a house in the Main Street in Saintfield as a bachelor, with a maid and a chauffeur who drove the big white car. The house is still there in the Main Street; now painted a rather dark brown colour, just opposite the parish church (Fig. 1). Dr Scott had a distinguished undergraduate career, winning the Malcolm Exhibition at the Belfast Royal Hospital and the gold medal at the Ulster Hospital for Children and Women. He qualified in 1891 by passing the

Fig 1. Saintfield Main Street, December 2000.

Scottish Triple Conjoint Diploma which was often taken by Belfast medical students at that time as the trip to Dublin to sit the MB BCh BAO examination of the Royal University of Ireland was considered more difficult and passing less assured. Also the triple qualification, although not a University degree, looked most impressive on a professional plate – LRCPEd, LRCSEd, LRFPS Glas. After general practice for a while in the south of England he was appointed to the district dispensary in Saintfield and worked there for the rest of his professional career. When he died in 1946, he left a legacy of £3,000 to the Royal Victoria Hospital for educational purposes. By careful investment this legacy has increased considerably in value and is maintained in both a capital and a revenue account under the supervision of the Chairman of the Medical Staff Committee. Dr Scott was buried in his mother's family mausoleum in Killyleagh Churchyard, the Heron family being long established in County Down. One of the early Herons was a joint founder

of the Ulster Bank, and a major donation to this hospital by another Heron enabled the top floor of 'A' Block to be built when it was known as the Heron Clinic for private patients. Major donations and legacies from wealthy families are still made to this hospital, but not any longer to the general funds of the hospital and often these donations are earmarked for a particular disease or specialty. This has made the continued funding of the Royal Victoria Hospital Clinical Research Fellowships increasingly difficult over the past number of years as these Fellowships have been funded from the general undefined Trust Funds of the hospital, and with the recent fall in financial interest rates the funds available for Clinical Research Fellowships have become severely limited.

WHERE ARE WE COMING FROM?

The HAPO Hypothesis states that

"hyperglycaemia in pregnancy less severe than overt diabetes mellitus is associated with increased risk of adverse maternal, fetal and neonatal outcomes that is independently related to the degree of metabolic disturbance".

The story begins with Dr Heinrich Bennewitz in 1823 at the Charité Hospital in Berlin[1] who was responsible for the delivery of a 12 lb baby to a patient who had developed thirst and polyuria in her pregnancy (Fig. 2). There was no measurement of blood glucose at that time, but he was able to demonstrate the presence of large quantities of sugar in her urine by the simple expedient of boiling this up in a saucepan and producing a treacle-like substance which he carefully weighed. The outcome of the pregnancy was not good. The baby died because of obstruction during delivery because it was so large. Dr Bennewitz wrote the case up as his thesis for the degree of doctor of medicine at the University of Berlin, but no further documentation either of his career or of

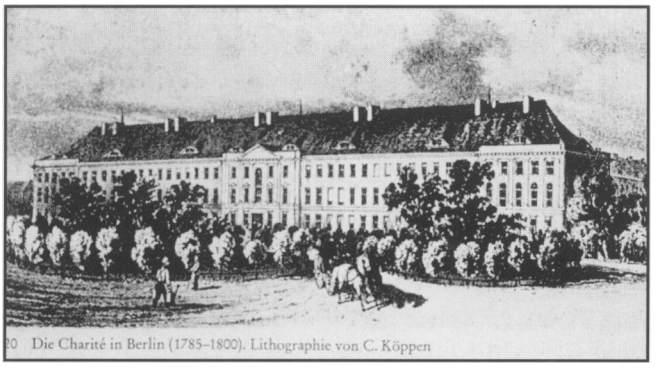

Fig 2. Charité Hospital, Berlin (1785-1800).

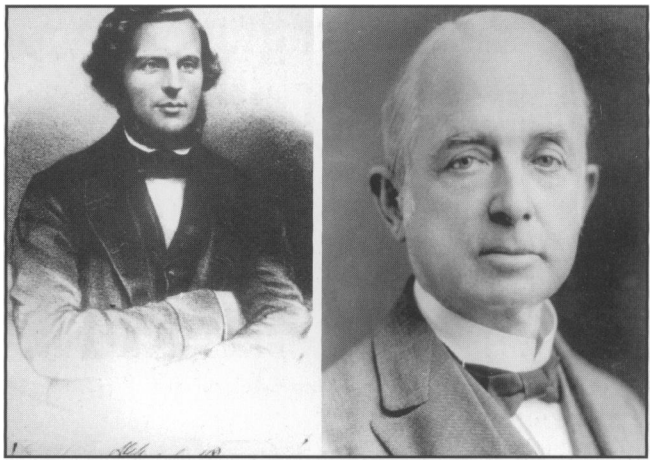

Fig 3. Dr Andrew Malcolm (1856)/Professor J A Lindsay (1923).

the future outcome of the mother has been found. The thesis, in Latin, was discovered in an archive in Germany in 1986, and was translated into English at the Department of Latin at the Queen's University of Belfast. Diabetes in those days was considered a relatively unusual diagnosis, and this was the first record of gestational diabetes.

Thirty years later, Dr Andrew Malcolm (Fig. 3), one of the brightest stars of the early Belfast Medical School, was in the process of writing a book which summarised his clinical lectures when he died suddenly of tuberculosis in 1856 at the age of 42. The book was published posthumously by his colleagues as "The interpretation of symptoms and signs".[2] In this he states "urine containing sugar is seen only in cases of diabetes . . . the characteristic taste of the urine is also an excellent test". Many years later, in 1923, the year that insulin first became available for clinical use, the academic interest in the diagnosis of diabetes in Belfast had changed somewhat. Professor James A Lindsay (Fig. 3) was more concerned in the possibility that the Belfast medical graduate might miss the diagnosis and pointed out a number of potential errors – "the urine may not be abundant, sugar may be temporarily absent, thirst and wasting may be unnoticed, the first symptoms may relate to eyes, skin or nervous system". Professor Lindsay's concern would not be inappropriate in the present era of clinical governance. He was well known to the medical students of his day for his small book "Medical axioms, aphorisms and clinical recommendations" which was published in 1923, and one of these aphorisms "for every mistake in medicine made by not knowing, there are ten mistakes made by not looking" is still very relevant

today.[3] There is a need for a Professor of Clinical Medicine to act as a focus for education as well as for research and it is everyone's hope at this time in the Belfast Medical School that a suitable person to fill that post will soon be identified.

Dr Jack Smyth was the first doctor in Belfast to specialise in diabetes mellitus. His background was originally in clinical biochemistry and this made it possible for him to obtain accurate blood glucose measurements through the clinical biochemical laboratory at this hospital.[4] In those days much of the clinical practice of physicians took place in their private consulting rooms and Dr Smyth lived at 23 University Square. I have found a letter from Dr Smyth to my father Dr Robert Hadden in Portadown dated 25 April 1944 giving an exact method of carrying out a 50 g oral glucose tolerance test at home. This shows that shared care for diabetes between family practice and hospital consulting practice was possible in those days, and it is also probable that this glucose tolerance test was actually carried out in early pregnancy on this particular patient. It was Dr Smyth who was responsible for encouraging his patient Sir George E Clark to leave a sum of £10,000 specifically to build a metabolic unit at the Royal Victoria Hospital. This unit was finally opened on 7 June 1957 by Professor Charles Best, one of the discoverers of insulin from Toronto (Fig. 4). The building was built by the old established firm of H & J Martin who are currently employed jointly in building the new Royal Victoria Hospital, which will open this year. It was then and probably still is the only purpose built unit for endocrinology and diabetes

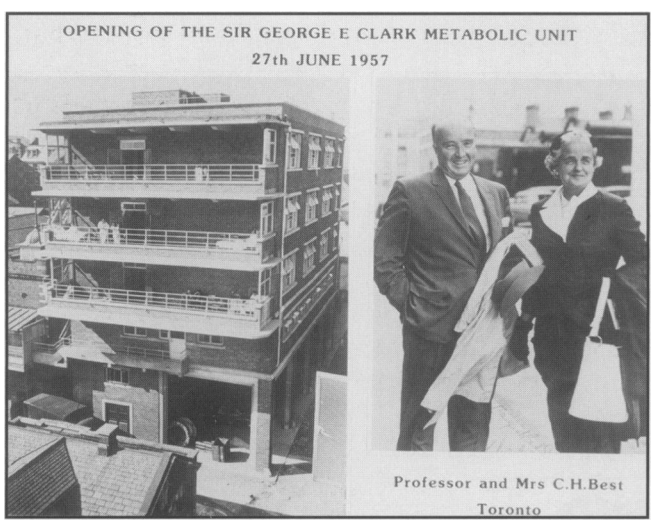

Fig 4. The opening of the Sir George E Clark Metabolic Unit, Royal Victoria Hospital – 27th June 1957.

in these islands containing the beds, the specialist and paramedical facilities, the education centre for diabetes and endocrinology, and the clinical and secretarial offices for the staff in the one building. Originally the metabolic outpatient clinics took place in this building but these were moved with the building of the new outpatient centre in 1967 to the other side of the hospital, which has always been an inconvenience for our medical and nursing staff as well as our patients. It has been my privilege to work in this building for the past 40 years. It opened while I was a medical student and it will close shortly before my retirement.[5]

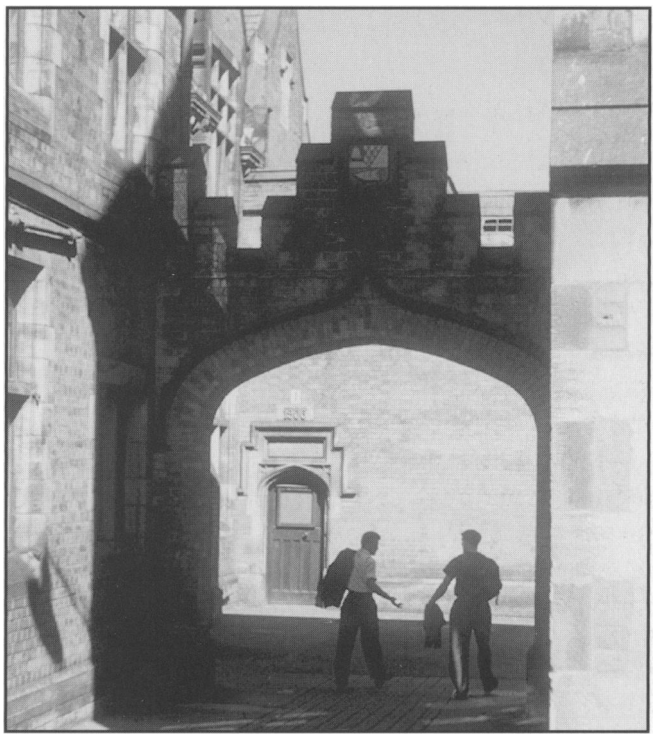

Fig 5. Biochemistry Department, the Queen's University of Belfast, 1956, seen through the archway (now replaced by the Administration Building).

Biochemistry in 1957 was taught entirely as an academic subject in the very small university department of biochemistry by Professor D C Harrison at the back of the quadrangle in the main campus of the university (Fig. 5). Theoretical biochemistry seemed distant and remote to most of us and the link between university and hospital was extremely tenuous.[6] Doctor Smyth was of the opinion that the only biochemical knowledge needed for a medical student was how to measure the blood glucose and the blood urea; he then added that the blood urea could be assessed by looking at the tongue – so we only learnt how to

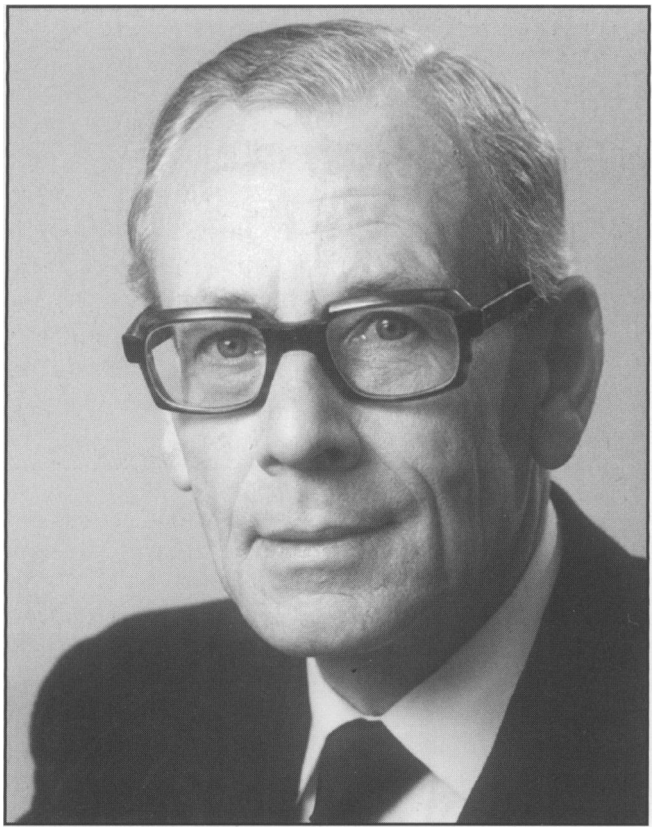

Fig 6. Professor D A D Montgomery.

measure blood glucose which was a tedious but exciting method involving Bunsen burners and test tubes, and various different coloured liquids. The ability for patients to self-monitor their own capillary blood glucose with a glucose oxidase strip has totally revolutionised the care of people with diabetes, in particular in pregnancy. In 1975, in the second edition of his textbook on Medical and Surgical Endocrinology, Professor DAD Montgomery stated "retrospective studies suggest there is an increased risk of perinatal death in children born to mothers who develop clinical diabetes later in life and that birth weights tend to be high. The characteristic features of the infant of the diabetic mother are well known. The baby is big for dates, owing mainly to excessive fat, but all organs, except the brain, are disproportionately large. The cause of the fetal "gigantism" is not known, but it may be that excess of glucose from the mother induces hyperplasia of the fetal islet cells, and this in turn causes fetal hyperinsulinism, excessive lipogenesis and neonatal hypoglycaemia. Effective control of the maternal blood sugar throughout pregnancy prevents these changes, and results in babies of average weight. An objection to this hypothesis is that many women with very mild diabetes, or those with potential diabetes and normal glucose tolerance, may have large babies years before their diabetes becomes manifest. The production of a large baby in a potential diabetic pregnancy may thus be genetically determined".[7] Professor Montgomery had established the academic basis of the metabolic unit which has continued to the present time, and he sends his apologies that he is unable to attend this lecture today (Fig. 6).

The knowledge that babies born to diabetic mothers could be either large or small had been identified by Dr Jorgen Pedersen in Copenhagen. He had been a physician interested in the outcome of pregnancy in the diabetic mother and wrote a famous book on this topic.[8] In this book is a photograph of two infants of diabetic women born on the same day at the Rijkshospital, Copenhagen (Fig. 7). One large fat baby weighing 4.7 kgs at 38 weeks gestation was born to a diabetic mother who had not attended the centre until two days before the baby was born. This mother's blood glucose was clearly much too high throughout the pregnancy. The other baby weighed only 2.05 kgs, born rather earlier at 36 weeks. The mother had attended regularly throughout the pregnancy but had more complicated diabetes with pre-eclampsia. Both large babies and small babies can happen in relation to diabetic pregnancy. These observations and others elsewhere sparked an ongoing interest in hyperglycaemia in pregnancy. In Belgium Dr J P Hoet, an obstetrician, had started doing 50 g

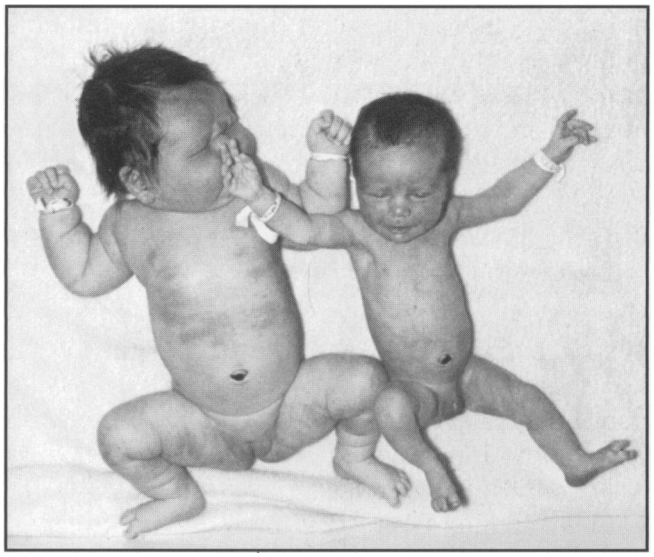

Fig 7. Two babies born to diabetic mothers in the Rijkshospital, Copenhagen, 1956 (reproduced from reference 8).

glucose tolerance tests in pregnancy after World War 2.[9] Following his visit to Boston, USA, a large prospective study of the effect of hyperglycaemia during pregnancy on the mother, and in particular on the chance of her developing permanent diabetes, was established by Dr John O'Sullivan at the Boston Lying-in Hospital and published in 1964.[10] This produced the major US criteria for the diagnosis of gestational diabetes which still stand to the present day, based on a 50 g glucose load for screening plus a second 100 g load for diagnosis. In Belfast, Dr Graham Harley and I had started glucose tolerance testing in pregnancy in 1962 as part of my MD thesis. My hypothesis at that time was that the big baby of the diabetic mother was in some way attributable to excess growth hormone secretion in response to hyperglycaemia in pregnancy. This was not a particularly robust hypothesis and I was never able to prove it, but I did learn a great deal about glucose tolerance tests in pregnancy, which interest has continued to the present day.[11]

I was awarded an RVH Research Fellowship of about £1,000 per annum (there were never more than two or three research fellows at the same time in those years). I was able to collect human pituitary glands from autopsies carried out by the Department of Pathology and to extract human pituitary growth hormone from them. Ultimately it was possible to obtain further human pituitary growth hormone from the combined UK collection of pituitaries and to use this for treatment of growth hormone deficient children with very encouraging results in over 40 cases. The possibility that even one of these human pituitary glands might have been carrying the then unrecognised Creutzfeld-Jakob disease prion did not become apparent until about 20 years later. I am glad to say that none of these patients treated in Belfast for growth hormone deficiency have thus far developed this fatal condition and they remain under counselling and long-term endocrine supervision.[12]

With this incomplete knowledge about growth hormone and its immunoassay, and some continued interest in glucose tolerance tests in pregnancy I proceeded to the Johns Hopkins Hospital, Baltimore, Maryland, USA, to work with Dr Samuel P Asper who was at that time the senior endocrinologist (Fig. 8). Dr and Mrs Asper were most kind to me and took me into their home for some time in much the same tradition as Dr and Mrs Osler had offered the latchkey of their

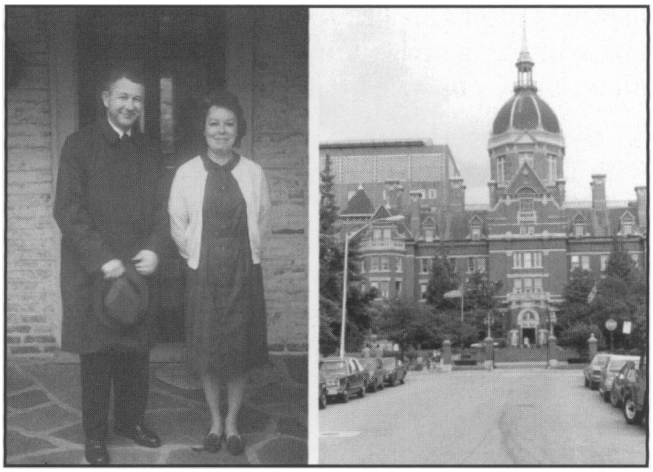

Fig 8. Dr and Mrs Samuel P Asper, Baltimore, 1964 and the Johns Hopkins Hospital, Baltimore, USA.

Baltimore house to the young Dr Harvey Cushing in 1920. Dr Asper was an expert in thyroid disorders and subsequently became Visiting Professor at the American University of Beirut in the Lebanon where he was in charge of the hospital during the civil strife and riots in that city. He gave the Scott-Heron Lecture at the Royal Victoria Hospital in 1977 and related his experiences in Beirut, which were much more alarming and dangerous than any of us had been exposed to during the Belfast troubles. While at the Johns Hopkins Hospital I was asked to attend a meeting for Fulbright Fellows to meet President John F Kennedy in the Rose Garden at the White House, shortly before his assassination. I remember President Kennedy's address to the visiting fellows. He most politely thanked us for coming to his country and for bringing our knowledge so

Fig 9. President John F Kennedy addressing Fulbright Fellows at the White House, Washington, USA, in September 1964 (DRH in the front row).

that they might benefit. I am sure we all felt that the knowledge was travelling in the reverse direction to our own benefit (Fig. 9).

At the Johns Hopkins Hospital I collaborated with Dr Thaddeus Prout who had developed an ingenious method of demonstrating binding proteins in normal human serum using radioiodinated hormones and jointly we demonstrated for the first time that there was a growth hormone binding protein in normal human serum. I presented this to the Annual Meeting of the Endocrine Society at Atlantic City, New Jersey, and met with considerable opposition from a member of the audience, who mounted the platform and pronounced that my work was wrong. I only found out later that this was Dr Solomon Berson who at that time with Dr Rosalyn Yalow had developed a radioimmunoassay for human growth hormone, which would have been under some theoretical suspicion if a growth hormone binding protein actually existed in normal human serum.[13] It has taken over 30 years for this argument to be resolved. It is now clear that growth hormone can be measured in normal human serum using an additional strongly binding gamma globulin antibody, but that there is also a less strongly bound normal serum binding protein. This was finally demonstrated by Dr Gerard Baumann at Northwestern University, Chicago in 1986.[14] It is interesting and perhaps salutory that as the Medline computerised database on the Internet does not extend backwards in time before 1966 no mention is currently made of the original discovery of the binding protein in 1964 (Fig. 10).

When I returned to Belfast I found that the original protocol for 50 g glucose tolerance tests in pregnancy had been continued under Dr Graham Harley's supervision at the Royal Maternity

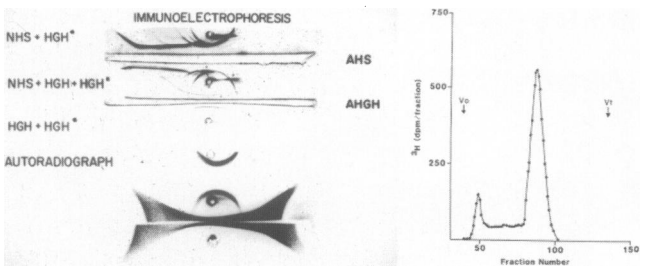

Fig 10. The growth hormone binding protein in human serum identified by radioimmuno-electrophoresis in 1964, and again by selective chromatography in 1986 (reproduced from references 13 and 14).

Hospital and soon there were a very large number of glucose tolerance tests which we analysed in many ways to assess the relation of maternal hyperglycaemia to the fetal result.[15] Several papers were published but the matter remained uncertain and we were not able to demonstrate strong relationships between the size of the baby and the maternal blood glucose. It eventually became clear that this is because the prevalence of gestational diabetes in Belfast is much less than in other parts of the world. Further developments of the glucose tolerance test including a standard breakfast test have been subsequently used but none have been predictive in Belfast in terms of outcome of the pregnancy.[16]

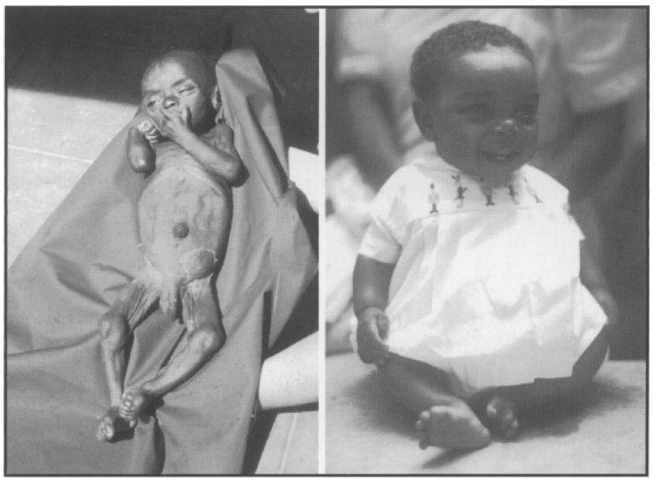

Fig 11. A severely malnourished marasmic infant at the MRC Infantile Malnutrition Research Unit, Kampala, Uganda – on admission and after refeeding (1966).

After a year or so back in Belfast I was met one morning on the RVH main corridor by the then Professor of Medicine, Professor G M Bull, who asked me what I was doing. I told him I was interested in hyperglycaemia in pregnancy and in hypoglycaemia in the infants of diabetic mothers. He replied that I should go at once to Uganda where the Medical Research Council were looking for a clinical investigator to study the hypoglycaemia that was thought to occur in the malnourished children with marasmus and kwashiorkor in that country. As Professor Bull was a member of the Tropical Medicine Board of the Medical Research Council it was a matter of only a few weeks before I found myself called for interview at Park Crescent in London, the headquarters of the Medical Research Council, and very rapidly dispatched to the Medical

Research Council Infantile Malnutrition Research Unit at Mulago Hospital, Makerere University, Kampala, Uganda. I have discussed my findings there elsewhere, suffice to say that there was evidence of insulin resistance in the protein deficient children with high serum insulin and low serum growth hormone levels which did relate to the degree of fat retention (Fig. 11). This was entirely related to their protein deficient diet, in the face of a relative sufficiency of carbohydrate coming from the banana staple in that country.[17, 18] The MRC unit in Kampala was technically under the control of Professor R A McCance, the Professor of Experimental Medicine in Cambridge at that time. He encouraged me to return to Cambridge bringing blood specimens for measurement of insulin and growth hormone with me from the babies. Professor McCance had been undertaking parallel experiments with a group of undernourished pigs at a farm outside Cambridge and the picture of the three pigs of the same age is now famous – one pig, very small, being severely energy restricted, one pig of medium size but pale, puffy and lethargic, having had sufficient carbohydrate but insufficient protein it its diet, and the third pig having had normal mash and having grown to normal size. These animal studies, which were backed up by further studies on smaller animals such as rats and guinea pigs, confirmed that nutritional status had a profound effect on growth in early life, and it is now clear that growth in the fetal period is equally dependent on a proper nutritional balance.[19, 20] At that time I was the senior registrar in endocrinology at the old Addenbrooke's Hospital in Cambridge. I think I had only one patient and most of my time was spent hearing about the Professor's pigs and other animal interests, to say nothing of his well known racing bicycle (Fig. 12).

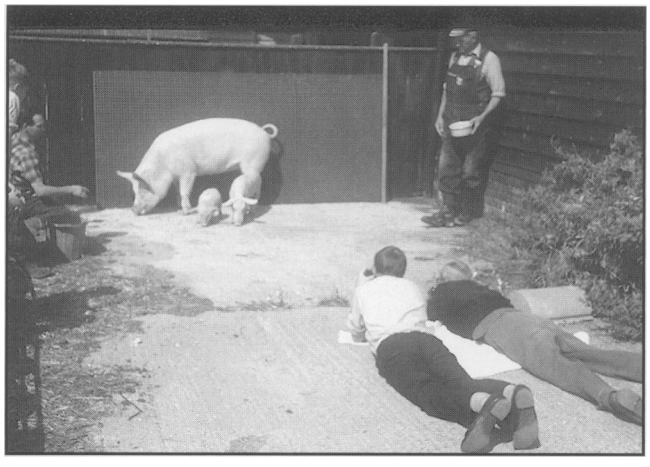

Fig 12. Professor R A McCance (lying on right) photographing three pigs aged one year old, the two smaller pigs having been undernourished to mimic marasmus and kwashiorkor (Cambridge 1965).

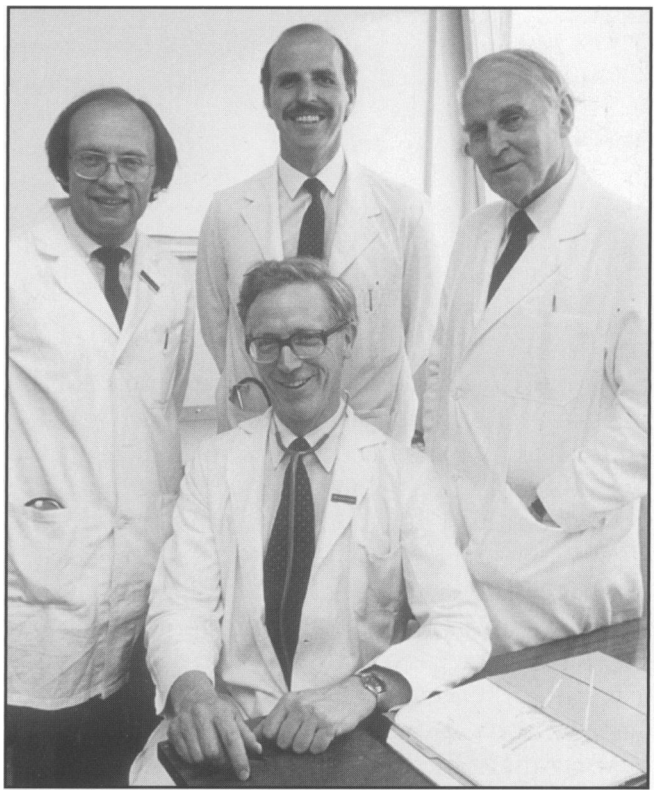

Fig 13. Dr A B Atkinson, Dr A L Kennedy, Dr J A Weaver and DRH in the Metabolic Outpatient Clinic (1983).

After Professor Montgomery's retirement in 1980, Dr Weaver and I were joined on the staff of the metabolic unit by Dr Laurence Kennedy and Dr Brew Atkinson (Fig. 13). At that time a main interest in the metabolic unit was the epidemiological study of patients with Type 2 diabetes. After a number of retrospective studies we had embarked on a prospective natural history study of the long-term survival of patients with this type of diabetes which became known as the Belfast Diet Study.[21, 22] This has achieved a considerable degree of international recognition by the demonstration that with careful and even rigorous dietetic advice and follow-up under the supervision of Miss Anne Wilson and her dietetic colleagues it was possible for a large group of newly diagnosed patients with Type 2 diabetes mellitus to be controlled by diet only (Fig. 14). The graph shows that after a period of weight loss over the first year the group of 172 patients

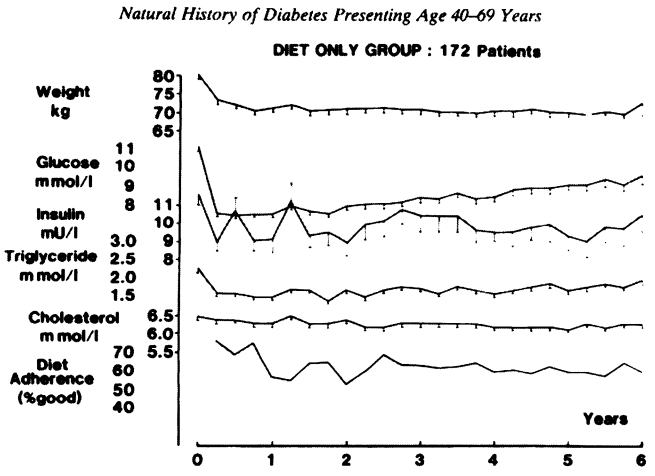

Fig 14. Six year analysis of the Belfast Diet Study (Reference 22).

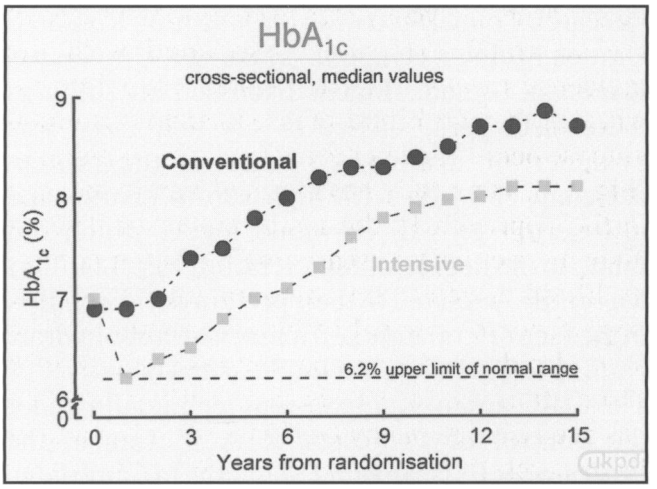

Fig 15. Fifteen year analysis of the UK Prospective Diabetes Study (Reference 24).

remained exactly the same average weight for the following six years. The fasting blood glucose which had fallen in the first three months from the initial diagnostic mean level of 11 mmols/l to about 8 mmols/l did not, however, show the same steady level of longterm control and there was a slow inexorable rise during the following years. There was no change in serum cholesterol and our simple measurement of dietary adherence also did not reveal any significant alteration. This study and its subsequent extension to 10 years has become known as "The Belfast Blood Glucose Phenomenon". The fasting plasma glucose in Type 2 diabetes mellitus treated on diet only rises steadily, in spite of good control of weight and good dietetic adherence, by 0.3 mmols/1 per year. This means that over 10 years it will rise by 3.0 mmols/1. Further studies in the Metabolic Unit suggested that this was largely due to the gradual failure of the beta cells of the pancreas although there is still reasonable debate that it is also due to increasing insulin resistance with the passage of time.[23]

After completing this study we joined the much larger United Kingdom Prospective Diabetes Study which had been initiated by Dr Robert Turner at Oxford. This study enrolled over 5,000 newly diagnosed Type 2 diabetic patients and followed their progress for 15 years. It subsequently became clear that these patients also showed the initial fall of blood glucose on intensive control but that there was a steady inexorable rise at about 0.3 mmol/1 per year over the next 15 years. This is demonstrated by the HbA1c data which shows that both on conventional and on intensive treatment this progressive rise in blood glucose took place [24] (Fig. 15). There is further evidence that this is due to a combination of both beta cell failure and insulin resistance. Sadly Dr Turner died in 1999 shortly after the important results of the study had been published.[24] We in Belfast recognise that 10% of the patients in this large study came from Belfast, both at the Royal Victoria Hospital and the Belfast City Hospital, and the further follow-up of the surviving patients will continue for some years to come. A further important outcome of the United Kingdom Prospective Diabetes Study was the recognition that blood pressure is just as important as blood glucose in the long-term survival of these patients. Both the updated mean systolic blood pressure and the

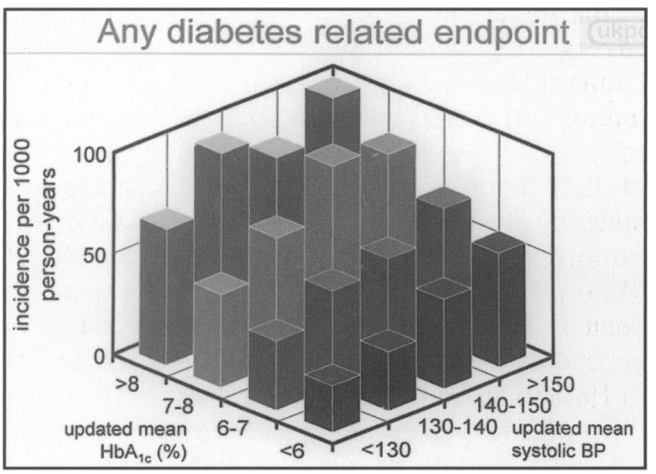

Fig 16. Relation of updated mean HbA1c and of updated mean systolic blood pressure to incidence of any diabetes related endpoint (Reference 25).

updated mean glycosylated haemoglobin (HbA1c) are separately stepwise associated with the incidence of any diabetes related endpoint, but when both high blood pressure and high blood glucose occur together the effects are cumulative (Fig. 16). This study has initiated a major change in the approach to the management of Type 2 diabetes, not only in searching for better control of blood glucose but also in clarifying the importance of control of blood pressure and of blood lipids. Further important research into the association of insulin resistance and hypertension has been carried out by Dr P M Bell and a number of research fellows at the Metabolic Unit using the glucose clamp technique. The United Kingdom Prospective Diabetes Study was one of the first in which nursing research played an important independent role and the pioneer work of Nurse Netta Webb and her nursing colleagues has been widely respected throughout the study.[25]

These studies in the genesis of insulin resistance and beta-cell failure in Type 2 diabetes were taking place at the same time as the ongoing studies of glucose tolerance in pregnancy. Dr Ralph Roberts at the Royal Maternity Hospital had initiated investigation of the association of insulin sensitivity with pregnancy induced hypertension, using a different "minimal model" technique for assessing insulin response to glucose stimulation and had suggested that pregnancy induced hypertension was in many ways analogous to pregnancy induced hyperglycaemia.[26] The close proximity of the Metabolic Unit to the Royal Maternity Hospital facilitated these studies, and provided a suitable background to the development of the hyperglycaemia and adverse pregnancy outcome concept. Professor Graham Harley had continued to encourage our interests in the obstetrical aspects of carbohydrate metabolism and his place as obstetrician in charge of diabetic pregnancy at the regional centre was taken by Dr A I Traub. The outstanding record of improvement in perinatal mortality at the Royal Maternity Hospital over the past 60 years has been internationally recognised, with a fall in perinatal mortality from over 30% of pregnancies in 1940 to about 6% in the year 2000.[27] However this still is greater than the overall hospital mortality, and the present day diabetic mother is still faced with a fourfold greater risk to her baby than a nondiabetic mother. Perinatal mortality over the past 10 years in the whole of Northern Ireland was 37/1000 for diabetic pregnancies compared to only 9/1000 overall.[28] It is our aim further to reduce this risk of pregnancy to the diabetic mother. A recent pregnancy outcome for a diabetic mother who had difficulty in obtaining good blood glucose control in early pregnancy will illustrate the point. Her baby was born with only two chambers in the heart, one ventricle and one atrium, but after cardiac surgery has survived to the age of five or more. He was also unfortunate enough to be affected by another complication of maternal hyperglycaemia known as sacral dysgenesis which meant that his sacrum and bladder did not develop properly at the right embryological time and he had to remain in nappies up to the age of four years (Fig. 17). Similar congenital abnormalities can be produced in experimental rats where the mother is exposed to a high blood sugar for a relatively short time in the early stages of pregnancy and there seems to be a window in time when the teratological effects of a high blood glucose are expressed.[29]

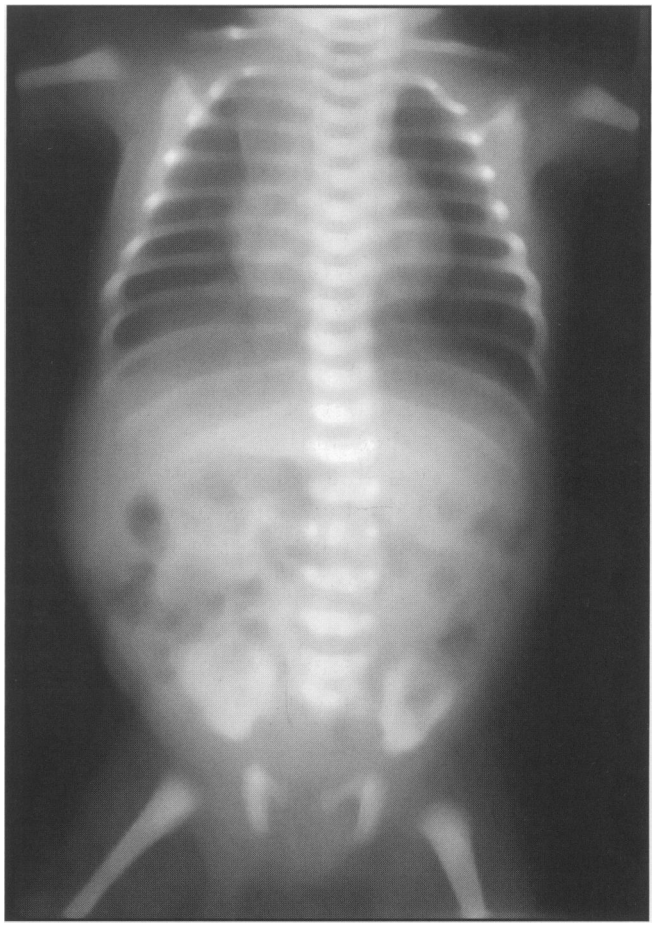

Fig 17. X-ray of new-born baby of Type I diabetic mother showing cardiomegaly due to congenital maldevelopment producing only one atrium and one ventricle, and also sacral dysgenesis.

WHERE ARE WE NOW?

The Pedersen hypothesis has now been amply established, with the demonstration that decreased maternal insulin sensitivity produces impaired maternal glucose metabolism resulting in maternal hyperglycaemia, which passes directly across the placenta to cause fetal hyperglycaemia; the fetus however is not diabetic and has normal pancreatic beta cells after 20 weeks and therefore is able to produce increased insulin in response to the high blood glucose (Fig. 18). This increased insulin in association with normal nutrition results in increased fetal fat deposition and macrosomia. This hypothesis has been proved to be true in a number of experimental models and is now widely accepted as the explanation for the occurrence of at least some cases of macrosomia in diabetic pregnancy. However, large babies continue to be born even when the blood glucose appears to be relatively normal.

The concept of gestational diabetes has now been defined as "glucose intolerance with onset or first recognition during pregnaney".[30] There is good evidence that the prevalence of gestational diabetes varies very considerably in different parts of the world with a 100-fold difference demonstrated in studies between Newcastle-on-Tyne and Belfast where the prevalence is low, and in cities like Los Angeles and San Antonio, USA, which are both close to the Mexican border and to which many Mexican-Latino mothers come during their pregnancy, where the prevalence is one in ten pregnancies or more.[31] The reasons for this enormous difference in the prevalence of gestational diabetes has not been fully explained, neither has the increasing incidence in different ethnic groups coming from different parts of the world to live in the same place, such as the increasing prevalence shown in studies in St Mary's Hospital, London, or in Melbourne, Australia over a relatively short time. There are a number of reasons why gestational diabetes is different in different parts of the world including different prevalences of Type 2 diabetes, different diagnostic criteria, different screening methods for hyperglycaemia in pregnancy and different genetic backgrounds in different ethnic groups. The reason for the apparently dramatic increase in prevalence over relatively short periods of time is widely thought to be related to changes in the food which is eaten amongst the population in rapidly developing countries. There is intriguing evidence that the prevalence of diabetes was very low in Ireland before the potato famine in 1840 but that there was a rapid increase associated with the increasing living standards of the general population following the famine, although that was associated with a change from the previous very healthy diet which had consisted of up to 10 pounds of potatoes and a pint of milk per day for a working man (90% of the energy carbohydrate, 5% protein and 5% fat).[32] Whether dietary changes explain all of the rise in gestational diabetes remains uncertain but it is undoubtedly a major public health problem in the developing as well as the developed world.[33, 34]

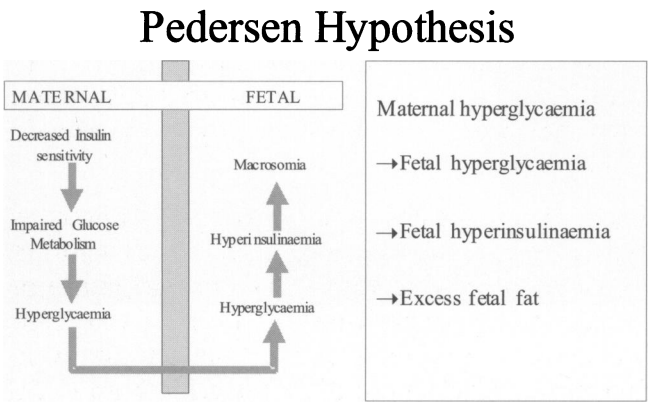

Fig 18. The Pedersen Hypothesis.

The careful studies of O'Sullivan in Boston have proved that gestational diabetes predicts subsequent Type 2 diabetes in the mother.[35] A further question, however, is whether gestational diabetes poses a risk to the baby. O'Sullivan's studies had suggested an increased perinatal mortality in babies born to mothers with gestational diabetes (6.4% versus 1.5% in a control group). His definition of gestational diabetes was related to the original 100g three hour glucose tolerance test which has long been used by American obstetricians.[36] More recent studies by the group at the US National Institute of Health in Phoenix, Arizona, studying the Pima Indians, showed similar results related to a 75 g glucose tolerance test which has been much more widely used in other parts of the world including Europe.[37, 38] In Australia the large experience of Beischer was conducted in relation to a 50 g oral glucose tolerance test which he had learnt to use when working as an obstetric registrar in Belfast in the late 1950's.[39] For many years the Australian continent continued to use the 50 g GTT. There were thus considerable difficulties in comparing the results from one country to another.

This difficulty and other concerns about the long-term outcome of the infants of gestationally diabetic mothers led a group of interested physicians, obstetricians and paediatricians to meet at the invitation of both the US National Institute of Child Health and Human Development and the US National Institute of Diabetes, Digestive and Kidney Diseases, at an international workshop on Adverse Perinatal Outcomes of Gestational Diabetes in 1992, at the National Institute of Health, Bethesda, Maryland, USA. At that meeting we determined to make a joint application for a study of the outcome of pregnancy in the milder hyperglycaemic mother, and this eventually developed into the HAPO hypothesis (Hyperglycaernia and Adverse Pregnancy Outcome). It was recognised that there was considerable controversy in the field, with concern that the results of blood glucose measurements were confounded by maternal obesity, increasing maternal age and maternal hypertension,[40,41] and also that there might be bias expressed by the care giver in relation to suspected but unproven risk associated with alleged hyperglycaemia that might still be within a normal range.[42,41,44] At the same time there was increasing concern from parts of the world where gestational diabetes was common that even lesser degrees of hyperglycaemia than those currently recognised as gestational diabetes were causing effects on the baby which were being passed on to the next generation. There was thus conflicting advice on the one hand to increase screening procedures and to lower diagnostic criteria and on the other hand to stop all efforts to identify maternal hyper-glycaemia unless more data on morbidity in the offspring of glucose intolerant mothers was available.[41,46]

At about that time the studies of Professor David Barker and his colleagues in Southampton University, which have become known as the Barker hypothesis, were being published. These studies initially comprised long-term retrospective follow-up of populations of babies born in several well described parts of England where it was possible to identify those same babies 50 or more years later. It was found that babies who were small at birth were very much more likely to have developed Type 2 diabetes and hypertension 50 or 60 years later and that the diabetes and hypertension were associated with insulin resistance.[47,48] The Barker hypothesis was that these small babies were due to placental

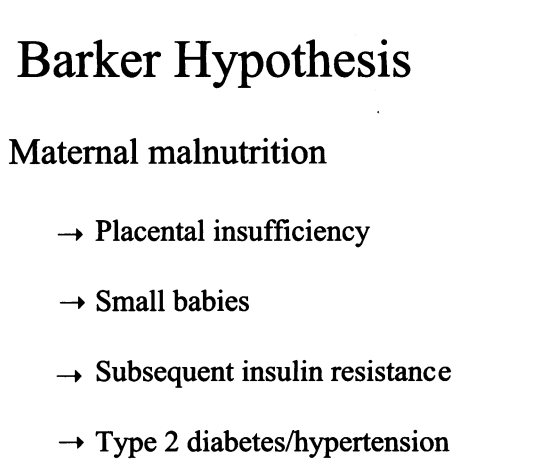

Fig 19. The Barker Hypothesis.

insufficiency related to some form of maternal malnutrition. This has led to a debate on the merits of the so-called "thrifty genotype" hypothesis and the "thrifty phenotype" hypothesis. The former had been proposed 30 years ago,[47] based on the concept that a hypothetical diabetes gene would endow an ability to survive in time of famine, as the blood glucose would be maintained for longer at a level to allow normal physiological function of muscle and brain, rather than suffering from hypoglycaemia. This idea had some credence in the unusually high recent prevalence of diabetes in some native American tribes who had survived in apparent good health without diabetes during successive generations of presumptive nutritional deficiency when they were actively defending their territory, only to show a dramatic increase in the incidence of diabetes when they became sedentary and were exposed to nutritional excess under a U.S. government settlement in the safety of an Indian Reservation. The thrifty phenotype hypothesis, on the other hand, emphasised that Type 2 diabetic adult had achieved a physiological adaptation involving insulin resistance in a number of metabolic processes, following on an early period of nutritional deficiency which could be both intrauterine and early postnatal: this adaptation led to obesity, hyperglycaemia, hyperlipidaemia and hypertension.[48]

The very extensive epidemiological database available on the Pima Indian population in Arizona, USA, allowed further investigation of these transgenerational effects. Dr David McCance and colleagues were able to show in that population where diabetes affects up to 50 per cent of adults, that there was a greater, prevalence of adult diabetes when the individuals

birth weight had been either smaller than average (less than 2.5 kg) or greater than average (more than 4.5 kg), than when birth weight was between these figures.[49] This "U-shaped" curve of diabetes prevalence held for adults aged 20-39, and led to a third concept of the "surviving small baby genotype". Was the small-for-dates baby which had been identified in the Barker hypothesis carrying a gene for diabetes or diabetes susceptibility which both accounted for its small size at birth and its later diabetes? This would not necessarily be the same pathophysiological process which accounted for the increased diabetes risk of the large-for-dates baby, where the previous Pedersen hypothesis seemed to give an adequate explanation (Fig. 20).

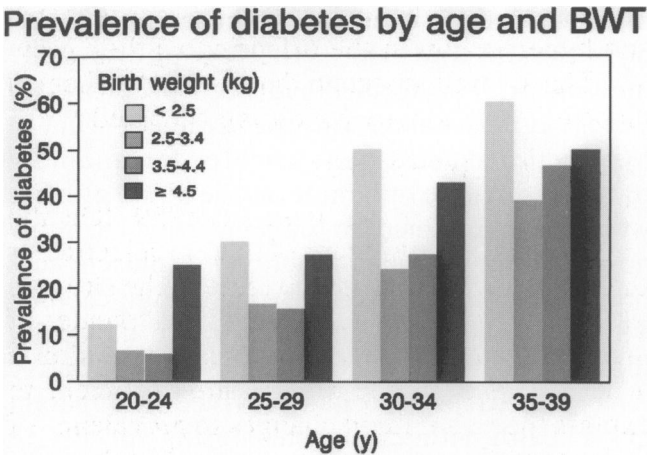

Fig 20. The "surviving small baby" genotype (reference 49). The diagrams show that the prevalence of diabetes in adults in four age groups from 20 to 35 years, each showed a U shaped curve with more becoming diabetic for birth weights less than 2.5 kg and more than 4.5 kg than for the intervening birth weights.

An extension of this third hypothesis was offered by Hattersley and Tooke[50] in an elegant demonstration of the birth weight distribution in a small number[58] of off-spring born to mothers known to have an unusual form of Type 2 diabetes due to a recognised genetic mutation affecting the glucokinase enzyme. When neither mother nor fetus had the mutation the birth weight was normal, as it was when both mother and baby were affected. When the mother was affected (and hyperglycaemic) but the baby was normal (did not have the mutation) the birth weight was high, presumably due to fetal hyperglycaemia leading to fetal hyperinsulinaemia as in the Pedersen hypothesis. When the mother was normal, but the baby had the defective glucokinase

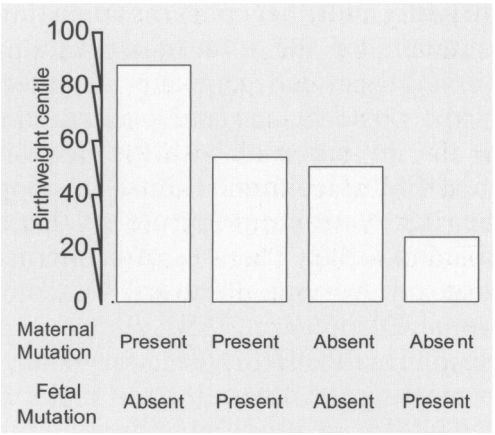

Figure 3: Birthweight centile distribution in 58 offspring of parents with glucokinase mutations according to maternal and fetal genotype

Fig 21. Birth weight centles in MODY families with glucokinase mutations, according to maternal and fetal genotype (Reference 50).

gene the birth weight was low, presumably because the developing fetus could not metabolise even the normal glucose available to it (Fig. 21). Hattersley has indicated the two alternative explanations for the association of small thin babies with insulin resistance, Type 2 diabetes and ischaemic heart disease - either an effect of poor intrauterine environment, or of a gene influencing insulin resistance. Each of these mechanisms would result in small thin babies, and each would account for insulin resistance which would ultimately lead to the long-term problems of the adult.

There had been careful studies of fetal pancreatic beta cell function in gestational diabetes in a number of centres, and there is no doubt that in this condition the fetal insulin is high enough to affect the outcome. Mean amniotic fluid insulin in 52 gestational diabetic pregnancies was 15.0 mU/l compared to 7.4 mU/l in 27 control pregnancies, and similar differences were found in umbilical cord c-peptide levels at birth.[51] There is also evidence that both childhood[52] and adult obesity[13] in the offspring is related to gestational diabetes in the mother.

These concepts have also been confirmed in studies of the development of adult diabetes in the next generation. The role of the intrauterine environment has been demonstrated in producing congenital susceptibility to Type 2 diabetes in the Pima Indians[54] and in adolescent offspring of gestational diabetic mothers in Chicago.[55]

The development of a large-for-dates or macrosomic baby related to increased maternal blood glucose has been recognised from the early studies of diabetes in pregnancy. More extensive epidemiological reports from the Pima Indians,[37] Italy[56] and the Latino population of Los Angeles[57] have confirmed this concept in mothers with gestational diabetes. There is also evidence that treatment of the mother with insulin during pregnancy will prevent this macrosomia. In an early randomised clinical trial of prophylactic insulin in 1966 O'Sullivan showed that whereas 13.1% of babies born to 306 gestational diabetic mothers weighed more than 9 lb at birth, compared to 3.7% of 324 control normoglycaemic mothers, administration of a standard dose of 10 units of isophane insulin in later pregnancy significantly reduced the number of babies weighing more than 9 lb to 4.3% of 305 pregnancies.[58] Subsequent clinical studies have supported this study, although there is still considerable uncertainty as to when and how best to use insulin in this situation.[59]

The present concept of transgenerational diabetes, which is related in part to intrauterine malnutrition and in part to overnutrition, with or without the expression of a gene promoting hyperglycaemia, and resulting in either a small baby or a large baby which has resistance to insulin action, is reasonably well accepted (Fig. 22). These theoretical concepts of the effects of carbohydrate intolerance on maternal fetal outcome will only be of public health importance if they represent an increasing problem even at lower levels of blood glucose than those currently diagnosed as gestational diabetes. The Toronto tri-hospital project (which used the standard North American 100 g OGTT) studied 3,600 women who were known not to have gestational diabetes and showed that even a relatively mild degree of increasing carbohydrate intolerance within the normal range was associated with macrosomia, pre-eclampsia, increased Caesarean section rate and a longer hospital stay.[61] The stage has thus been set for the HAPO study to investigate this matter by a larger study using a standardised 75 g glucose tolerance test in many parts of the world. This will allow further assessment of the relative roles of the Pedersen hypothesis of fetal overnutrition and the Barker hypothesis of fetal undernutrition on the subsequent development of insulin resistance in the baby, and the longerterm risks of diabetes and hypertension in the offspring as they grow up. The overall concept that "diabetes begets diabetes" is gradually becoming accepted.[61]

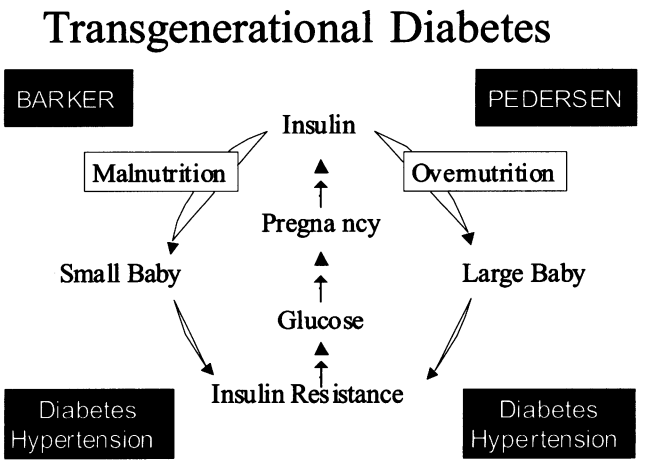

Fig 22. Transgenerational diabetes: the possible roles of under-nutrition and over-nutrition in producing a small or a large baby, related to insulin resistance and subsequent diabetes and hypertension.

WHERE ARE WE GOING?

Charles Darwin in his work in 1859 "On the origin of species by means of natural selection or the preservation of favoured races in the struggle for life" is generally accepted as the founder of the concept of genetics as the means of evolution.[62] Whether genetic mechanisms are sufficient to explain the rather rapid changes in prevalence of diabetes mellitus remains uncertain. The previous and largely discredited theories of Lamarck (1801) on the inheritance of acquired characteristics might be thought to be applicable to the transplacental passage of hyperglycaemia from mother to baby but that concept would not be sufficient to explain the famous problem of why the giraffe has a long neck.[63] Both the philosophical and practical aspects of mild disturbances in maternal carbohydrate tolerance were initially emphasised by Dr Norbert Freinkel, at that time in charge of the research group at Northwestern University, Chicago, and he would certainly have approved of the subsequent application for a major international grant to study this problem.[64] The first application was made by the Steering Committee in 1995 and after very considerable work and the utilisation of a very large amount of paper in many parts of the world, was finally successful at the third attempt in 1999. The organisational details of the study are now available on the Internet.[65] The Steering Committee met again in Chicago in 1999 to finalise the very detailed manual of

operations which has undergone further refinement with the passage of time. The total grants awarded to date include $8.8 million from the National Institutes of Health supplemented by $1.5 million from the American Diabetes Association and £102,000 from Diabetes UK. A smaller grant of 36,000 Ecu's had been awarded by the European Community for portions of the work judged to show the principle of subsidiaity within Europe but unfortunately even that small grant was withdrawn because of our failure to start the study within their strict time limit. We hope that some further generosity from the European Community will still be available.

The aim of the HAPO study is to examine glucose tolerance in a large multinational multi-cultural ethnically diverse cohort of women in the third trimester of pregnancy with medical caregivers "blinded" to blood glucose data (except when predefined criteria are met). There will be 16 centres with a common protocol and data collection, a uniform training of personnel and a central laboratory. This will derive internationally acceptable criteria for gestational diabetes mellitus. The field centres are at Bangkok, Barbados, Beersheba, Belfast, Bellflower (Los Angeles), Brisbane, Chicago, Cleveland, Hong Kong, Manchester (UK), Newcastle (Australia), Petah-Tiqva (Israel), Providence (USA), Singapore, Toronto and Utrecht. Other centres were considered by the Steering Committee and it was with considerable reluctance that we had to reduce to the final 16 in order to satisfy the very strict obstetrical criteria laid down by the US National Institutes of Health. This is not to say that the findings of the HAPO study will not be of equal importance in all parts of the world and in all obstetrical communities.

The central laboratory for the whole study will be at the Royal Victoria Hospital under the supervision of Professor Elizabeth Trimble, with blood samples from 25,000 women coming in over the next two years for measurement of glucose (Mr Selby Nesbitt and Mr Mike Smye), C-peptide and insulin (Mr Brian Sheridan and Mr Colin Burgess) and glycosylated haemoglobin (HbA1c) (Professor T Lappin and Miss Geraldine Savage). The laboratory has been inspected to a very high degree by the US National Institutes of Health and found to be satisfactory in every respect. There will be a very considerable amount of work to complete the measurement of all these samples within the time line. The clinical co-ordination centre and data interpretation centre will be at Northwestern University in Chicago and data from the central laboratory will be transferred instantaneously by e-mail to the computer suite in Chicago for statistical analysis.

An important ethical issue is the blinding of the obstetricians and midwives (caregivers) to the results of the glucose tolerance test, unless these exceeded those levels which are currently diagnostic of gestational diabetes. This is in order to provide unbiased information, without intervention following the GTT, on any relationship between the outcome of pregnancy and the maternal blood glucose. The whole study including this aspect is carefully explained to all mothers at time of enrolment and detailed informed consent is obtained by the HAPO midwives. We have already found very many mothers attending the Royal Maternity and Jubilee maternity service to be enthusiastic about joining this study and they show considerable interest in what happens, both to themselves and to the study as a whole.

The primary outcomes will be the occurrence of a Caesarean section, of fetal macrosomia or obesity measured by skin fold callipers, of neonatal hypoglycaemia measured one to two hours after birth by heel prick analysis, and of fetal hyperinsulinaemia measured by a cord blood C-peptide assay. Secondary outcomes will include neonatal polycythaemia, hyperbilirubinaemia, respiratory distress and the occurrence of shoulder dystocia or any birth injury. One initial study was necessary to document the effect of early feeding on the neonatal blood glucose level at one hour of age.[66] This has already been published indicating that early breast feeding as sometimes practised at the present time does not affect the baby's capillary blood glucose level between one to two hours, and is therefore acceptable if it is the wish of the mother within the study protocol. A number of other ancillary studies have now been approved by the Steering Committee. These include a further study of matemal blood pressure and insulin responses which will allow assessment of the role of insulin resistance in both pre-eclampsia and gestational hypertension in this large group of pregnancies. At the same time, and after specific informed consent, blood specimens from mother and baby will be kept for DNA analysis allowing further investigation of possible genetic determinants of Type 2 diabetes and of fetal weight. A specific study in the Asia and Pacific

region will investigate further possible causes of neonatal hypoglycaemia unrelated to hyperinsulinism. The Hong Kong group will undertake a study of maternal oxidative stress and its effect on fetal outcome. The Cleveland Ohio group hope to study a number of more detailed and more accurate markers of neonatal total body fat in relation to maternal nutrition. The Belfast group will study a number of factors including maternal thyroid status at the 28 week time of the oral glucose tolerance test, the genetic control of haemoglobin synthesis, maternal nutritional status by dietary questionnaire, and a more detailed genetic study including DNA sampling from the father as well as the mother and baby which should allow a more searching assessment of the fetal insulin genetic theories which have been discussed previously. The HAPO study has already commenced in most of the centres, after careful inspection and accreditation by the US National Institutes of Health to ensure consistent standards both of obstetrical practice and neonatal care. The considerable grant income associated with this study has had a beneficial effect on the research ratings of the endocrinological, biochemical and obstetrical groups at the Royal Group of Hospitals and also with the Queen's University of Belfast.

Charles Darwin stated "without hypothesis there is no useful observation". The HAPO hypothesis that hyperglycaemia in pregnancy less severe than overt diabetes mellitus is associated with increased risk of adverse maternal fetal and neonatal outcome that is independently related to the degree of metabolic disturbance remains to be proved, but we expect very considerable interest in the outcome of the study when it is finally published in the year 2004. There has traditionally been an interest in the birth of a big baby and concern at the birth of a small baby. The relation of both of these events to the consumption of 75 g of a glucose drink by the mother at 28 weeks gestation, and whether the mother's glucose levels are connected to the weight of the baby by a nutritional or by a genetic mechanism, or by both acting in concert, remains uncertain.

ACKNOWLEDGEMENTS

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Case Report

Salter Harris Type I Fracture of the Proximal Tibial Epiphysis

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Accepted 1 June 2001

INTRODUCTION

Injuries of the proximal tibial epiphysis are rare. They predominantly occur in adolescent males following, signfficant trauma. They usually involve a Salter Harris Type II, III or IV injury, and are associated with a high level of growth disturbance. We present the case of a twelve year old boy, who suffered a Type I proximal tibial epiphyseal injury. The mechanism of injury has not been previously described.

CLINICAL COURSE

A twelve year old boy presented to the accident and emergency department having sustained a twisting injury to his right knee whilst racing on a scrambler bike. He described that his right foot became lodged into the ground, with his knee in the extended position, as the motorcycle turned sharply to the right. Clinically he had a swollen and bruised right knee. There was an obvious internal rotation deformity, with the foot internally rotated with respect to the knee and thigh. Knee motion was grossly restricted and the patient could not straight leg raise. There was localised tenderness over the proximal tibia. It was not possible to accurately assess the status of the collateral and cruiciate ligaments. There was no evidence of neurological or vascular compromise, although the calf was very swollen.

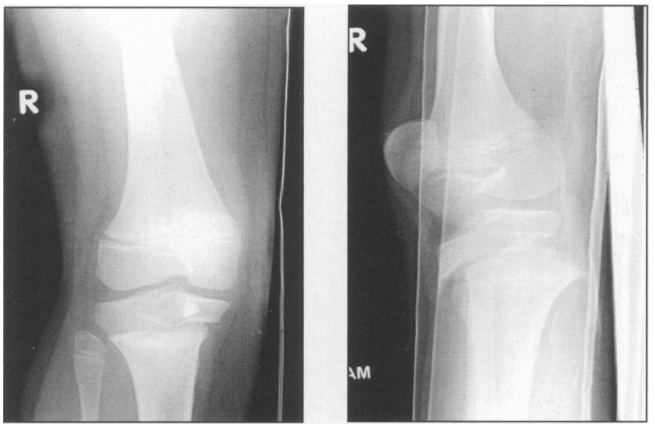

Fig 1: Salter Harris Type I fracture of proximal right tibial epiphysis with associated non-displaced fracture of proximal fibula.

Radiographs demonstrated a Salter Harris Type I injury of the proximal right tibial epiphysis (Figure 1). It was treated by closed reduction and K-wiring, with plaster immobilisation (Figure 2). Post-operatively the tight lower limb remained neurovascularly intact and radiographs were satisfactory. He remained in cast for six weeks and the pinswere removed in the fracture clinic. He was reviewed after six months, and found to have healed in anatomical position with a full range of knee movements and ligamentous

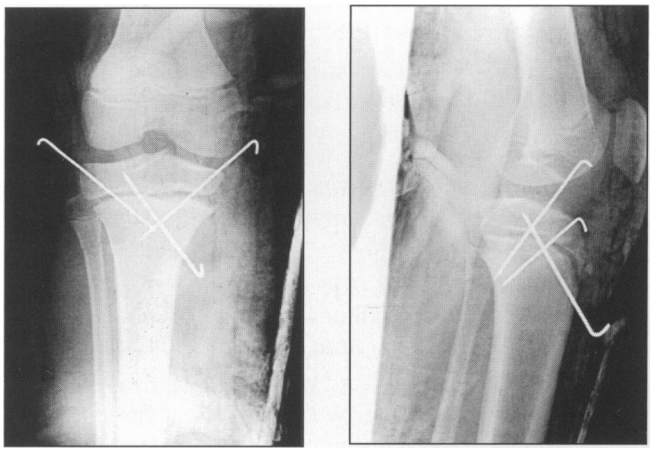

Fig 2: Fracture following closed reduction and K-wiring.

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stability. There was no evidence of premature physeal arrest as the Harris growth lines remained parallel to the growth plate.

REVIEW OF THE LITERATURE

Epiphyseal injuries of the upper tibia are rare. It has been estimated that fractures of the upper tibial epiphysis account for 0.5 % to 3. 1 % of all epiphyseal injuries [1, 2].

There are a number of anatomical factors which may account for this relatively low incidence. The proximal tibial epiphysis does not receive attachments from the medial or lateral collateral ligaments. Hence varus and valgus forces are transmitted not directly to the epiphysis, but to the metaphysis. This is in contrast to the lower femoral epiphysis which does receive attachments of these ligaments, and which has a higher incidence of injury[1]. Laterally, the proximal tibial epiphysis is buttressed by J the upper end of the fibula, and anteriorly the tubercle projects inferiorly to overhang the metaphysis. The epiphyseal attachment to the shaft is irregular, hence any fracture at this level will shear across different levels within the physeal plate. This fact may, explain the high association of proximal tibial physeal fractures and growth disturbance. Additionally, the insertion of the semi-membranosus tendon extends into the metaphysis and the patellar tendon inserts into a separate centre of ossification, protecting the epiphysis from avulsion strains[3].

The peak incidence of injuty is twelve to fourteen years of age being more common in males. This probably reflects a greater exposure to trauma and the relative skeletal maturity found in females, rather than to any intrinsic physeal difference. Analysis of five series of these types of injuries, published by Burkhart and Peterson[2], Poulsen *et al.* [4], Rhenirev *et al.*[5], Wozasek *et al.*[6] and Gautier *et al.*[7], gives a total of eighty-four patients of whom sixty-three were males and twenty-one were females.

There were fifteen Salter Harris Type I injuries, nineteen Type II injuries, twenty-four Type III injuries, twenty-two V injuries (one case was bilateral Type IV fractures[2]), four Type V injuries and one fracture described as "recurvatum and valgus"[6].

Most of these injuries are sustained in either sports-related activity or road traffic accidents[2,4,5]. The various types of trauma have been described as shearing, avulsing, splitting, or crushing. In the case presented, the mechanism of injury was twisting with the foot fixed and the twisting force applied to the leg. The knee capsule and cruciate ligaments withstood the force and the physeal plate failed first. This would correspond to the adult dislocated knee where the ligaments fail before the bone.

Clinical features include the inability to lift the leg because of pain and because of hamstring spasm. There may be a haemarthrosis present with soft tissue swelling of the leg and tenderness ness at the level of the growth plate 1 to 1. 5 cm. distal to the joint line. Wozasek *et al.*[6] in a series of 30 patients found a 40 % incidence of ipsilateral lower limb injuries.

Radiographs may be difficult to interpret, and when an epiphyseal injury is suspected, stress views and -views of the unaffected leg may be required[5,8]. Hyper extension of the knee should be avoided because of the possibility of popliteal artery injury.

Anatomical reduction may be achieved by closed reduction and cast immobilisation, K-wiring, or open reduction with screw fixation[4,5].

Associated problems include ligamentous injuries[4], vascular complications[6] including compartment syndrome, knee instability, and growth disturbance[4,7]. Growth disturbance, as defined by deformities of more than 25 mm in length, or more than 5° of angulation, has been reported to occur in more than 25% of cases of proximal tibial injuries in children, when a meta-analysis of published series was performed[7]. Gautier *et al,* in a study of six children with proximal tibial injuries reports that the most consistent clinical deformity was recurvatum, with a resultant effect on the range of motion of the knee[7].

CONCLUSION

The mechanism of injury in this case has not been previously described. Given the forces involved i.e. the momentum due to the combined mass of the patient and the scrambler effectively pivoting at high velocity on the long axis of his lower linib, this should be regarded as a high energy injury. This high energy rotational force has resulted in a fracture through the growth plate, as opposed to ligamentous injury. This may be because with the patient's body weight acting through the extended knee, the proximal tibial epiphysis becomes the

focus through which the rotational force acts. In the adult population the resulting injury would probably have been knee dislocation. Clinically there was an internal rotation deformity evident, and this is in contrast to the expected appearance of the knee when the mechanism of injury has been the more cornmonly described shearing, avulsing splitting, or crushing.

The treatment consisted of accurate closed reduction and stabilisation with heavy K wires and cast. The physeal plate appeared widened probably because of periosteal interposition, but given the nature of the injury open reduction was felt not to offer any benefit. Had the fracture extended into the joint surface (Salter Harris Types III or IV), open reduction to gain articular congruity would have been carried out.

This case illustrates that Salter Harris Type I and II injuries of the proximal tibial physis can be managed adequately with accurate closed reduction and stabilisation. The patient has regained full knee motion with no evidence of growth disturbance at six months from fracture. Careful initial assessment and documentation of the vascular status of the limb is required because of the association with compartment syndrome and popliteal artery injury.

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Case Report

Synovial chondromatosis of the pisotriquetral joint

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CASE REPORT A 45 year old right-handed male presented with a soft-tissue mass arising on the volar aspect of the right wrist at the distal end of the ulna. The mass had been present for one year and had been slowly enlarging. He gave no history of preceding trauma, and had no mechanical problems arising from the mass. He had no significant medical history of note and had no symptoms with any other joints.

On examination he had a 5 cm x 4 cm mass which was soft, non-tender and fluctuant. He had full range of wrist and hand function. He had some irritability of the ulnar nerve at the elbow but no other significant clinical findings. The initial presumptive diagnosis was of a wrist ganglion

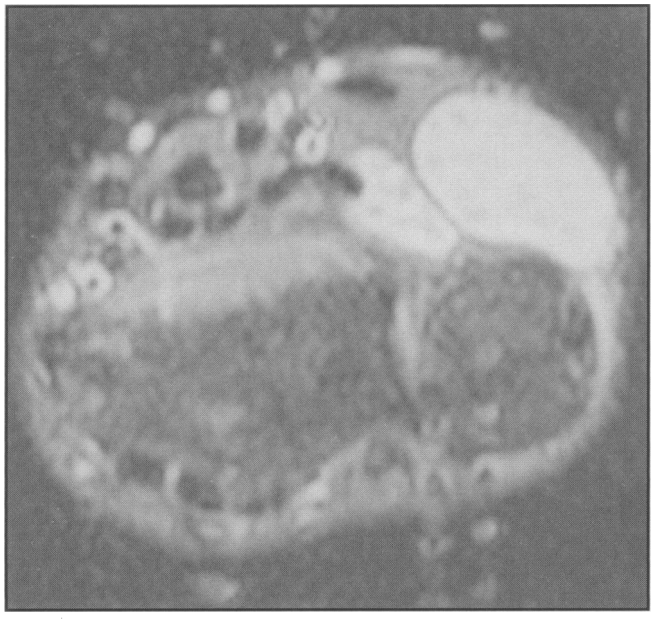


Fig 1

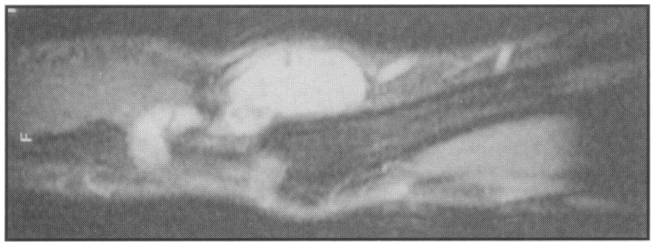


Fig 2

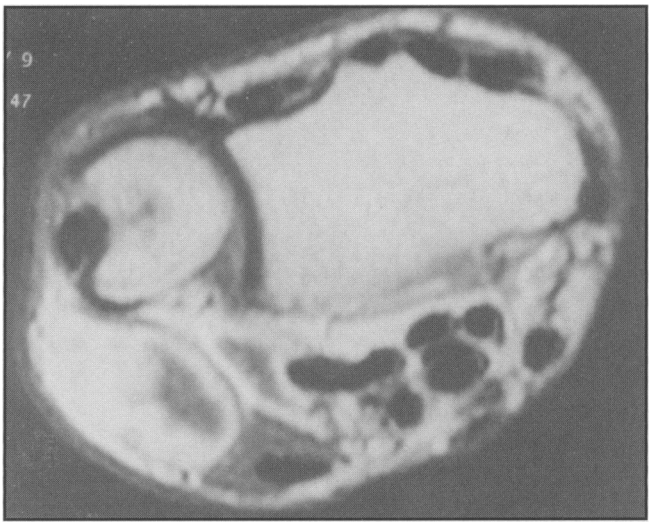
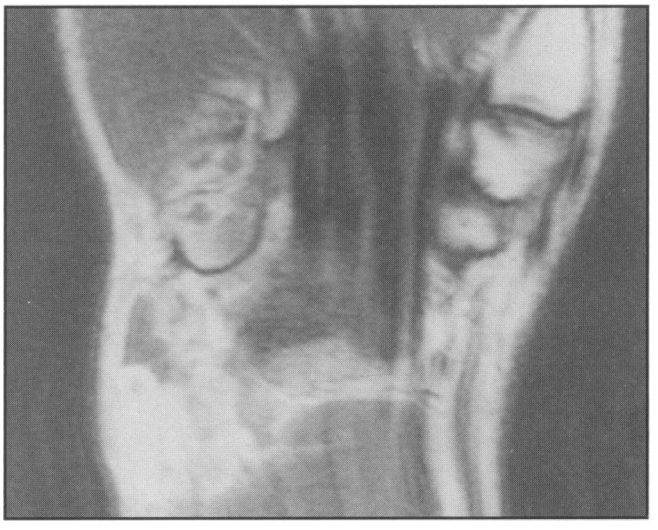


Fig 3



Figures 1,2,3,4. Gadolinium enhanced MRI scans of the right wrist showing 'lucent' synovial based tumour arising from piso-triquetral joint in cross-section, coronal and saggital planes.

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but there was concern regarding the size and location.

Standard radiographs were reported as normal. A MRI scan revealed a lesion 4 cm long extending from the region of the pisiform proximally and medially and spreading distally to the hook of the hamate. There was marked displacement of the neurovascular bundle laterally. The features were thought to be in keeping with a synovial-based tumour, and probably synovial chondromatosis.

At operation the mass was exposed through a volar approach to the distal forearm and palm. The tumour was found to be bifurcated deep to flexor carpi ulnaris and was dissected out bluntly from the main branches of the ulnar neurovascular bundle. The sac extended into the pisotriquetral joint. The pisiform was excised with the mass to ensure complete excision of the tumor. A further extension of the tumor was excised from around the hook of the hamate. The wound was closed and the wrist splinted for 18 days.

Wound healing was uneventful and wrist function returned satisfactorily post-operative. Histological analysis revealed synovial chondromatosis with no evidence of malignancy.

DISCUSSION

Synovial chondromatosis is an uncommon monoarticular condition of the large joints (knee, hip, elbow, shoulder and ankle) originally described by Laennac in 1813. It is rare (fewer than 100 cases reported) in the joints of the wrist and hand. Of these it is most commonly reported in the distal radioulnar joint, radiocarpal joint, metacarpophalangeal joints and proximal interphalangeal joints. It has been postulated that most of the wrist cases actually arise from the piso-triquetral joint but as Milgram(1977) reported only one case arising in the pisotriquetral joint in his study of 30 cases, there is no strong evidence for this. It can also arise from the tendon sheaths or bursae.

The aetiology of synovial chondromatosis is largely unknown. It is described as a metaplastic condition of the synovium and related tissues. A pleuripotent synovioblast reverts to either a fibroblast, a chondroblast or an osteoblast. These cells then undergo metaplastic change to connective tissue, cartilage or bone. These represent the components found in the nodules of synovial chondromatosis. The condition affects males slightly more frequently than females. There is a wide variation in age-range with a peak in the 3rd and 4th decades. There is an association with trauma in cases arising from the tenosynovium, but no such link in cases arising from joints. Milgram described three stages of the disease: 1 active synovial disease with no free or loose bodies; 2 a transitional stage where there is active synovial disease with osteochondral bodies in the synovial tissue and loose in the joint cavity or bursa; and 3 a dormant stage in which there are multiple osteochondral loose bodies but no active synovial disease.

Clinical features of the condition include pain, presence of a mass, loss of movement and joint crepitus. Functional features such as triggering and locking have also been reported as have features related to nerve compression. Many cases however remain asymptomatic.

X-ray appearance of multiple peri-articular radio-dense bodies often with an indiscrete outline is suggestive, but not specific to the condition. These often have the stippled appearance of a cartilaginous lesion. With larger lesions peripheral linear densities with radiolucent centres develop and bony trabeculation may be seen in mature areas of the nodules. The differential diagnosis include degenerative joint disease, rheumatoid disease, osteochondritis dessicans, tuberculous arthritis, crystal arthropathy, psoriatic arthropathy and pigmented villonodular synovitis. In the present case radiographic examination had been unhelpful. The size of the swelling clinically was suggestive of neoplasia. MRI scanning accurately identified the size and extent of the lesion as well as strongly suggesting the actual diagnosis. The characteristic findings are on T-1 weighted images an intraarticular lobulated homogeneous appearance isointense with the surrounding soft tissues and on T-2 weighted images a hyperintense signal. Some nodules have foci of signal void on all pulse sequences (calcification) and others have a halo of low intensity around the central soft-tissue like signal (ossification). This pre-operative information allowed the surgical approach to be more conservative than might have otherwise been with a swelling of this size in this location.

Macroscopic appearance is of multiple pearly grey/white osteochondral nodules from 3 to 10 mm in size sometimes as large as 50 mm, normal articular cartilage and hyperaemic synovium. Histological analysis reveals cartilaginous and osseous pockets within a fibrous-tissue envelope.

The only treatment is surgical, as spontaneous regression is rare. Localised disease is best excised completely. Removal of loose bodies either by open surgery or arthroscopically is effective for mechanical symptoms while pain and swelling are best dealt with by open synovectomy.

CONCLUSION

Synovial chondromatosis is a rare condition of the wrist. It may cause confusion with clinical diagnosis of common tumours such as giant cell tumours or ganglions arising in unusual sites. Radiographs may not be diagnostic. MRI scanning is appropriate in the investigation of any swelling of the wrist in an unusual site.

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Case Report

Augmentation of phantom limb pain by normal visceral function

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Following major nerve injury or amputation, a number of changes occur both peripherally and centrally within the nervous system due to the deafferentation process. The occurrence of phantom-type sensations are extremely common after this type of injury. These sensations are painful in many cases, especially if there was pain immediately before deafferentation. Two cases are described which are unusual, since in addition to pain within the distribution of deafferentation, there is visceral involvement.

Case 1 A twenty-three year old male involved in a motor cycle accident sustained major trauma to his left buttock, including deep lacerations, a fracture of his left greater trochanter and shredding of the sciatic nerve. He described the pain in his leg as a shooting, stinging and stretching sensation especially around his left foot. He also had pain in his left buttock while sitting, with reduced sensation of his lower leg and the posterior aspect of his thigh. Defaecation and micturition intensified the pain and he had difficulty sleeping.

On examination foot drop was present, together with, muscle wasting of lower left leg and foot, in keeping with an S2-S3 lesion. He was treated with co-dydramol, amitriptyline. 50mg nocte and ibuprofen. Later carbamazepine 800mg per day together with transcutaneous nerve stimulation was also used. It was only possible to achieve minimal relief of his pain with the above therapy and gradually each of these therapies were withdrawn.

Case 2 A forty-five year old male was injured in an explosion. His injuries required amputation of some of his right upper-limb digits together with a left above knee amputation. He also had vascular and bony injuries to his right leg. He was first seen by the pain team twenty days after the incident. His symptoms were sleep disturbance and pain in both legs, including a phantom left leg pain. His initial treatment was with celecoxib 200mg for the soft tissue injury and slow release oxycodone 20mg bd for the multiple aching pains. An escalating dose of an anticonvulsant active at the calcium channel site, (gabapentin to1800mg per day) was added for the phantom pain. Nine days after starting the above treatment, he had no aching pain so oxycodone was reduced to 10 bd. The phantom limb pain and sleep disturbance were less troublesome so gabapentin was continued at the previous dose.

Twelve days later his left phantom pain became much more intense than before, but only on micturition. On further questioning it became clear that the exacerbation of his phantom limb pain occurred only after his urinary catheter was removed. The dose of gabapentin was increased to 2400mg per day and an anticonvulsant active at the gamma-amino-butyric acid (GABA) receptor site, was added (baclofen 10mg qds). Since the pain on micturition did not improve on this combination of anticonvulsants after three days, his baclofen was discontinued and an anticonvulsant active at the sodium channel (carbamazepine in a rapidly escalating dose) was added to the gabapentin.

Three weeks later there was no improvement in his micturition induced phantom limb and on discharge for rehabilitation his medications were gabapentin 1800mg per day together with carbamazepine retard 400mg bd on a declining dose, with a view to using gabapentin alone since it controlled the phantom limb pain at rest and he could now tolerate the pain associated with micturition.

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DISCUSSION

Phantom limb pain occurs among most amputees and is difficult to treat[1]. Similar sensations and problems occur following nerve trunk injury. In the early part of the last century it was thought that phantom limb pain was a psychiatric problem due to unresolved grief for the missing limb. In the last few decades, phantom limb pain has been recognised as a distinct pain syndrome, in which a sensation is perceived in the denervated or missing limb. Both peripheral and central factors cause phantom limb pain[2].

Stress magnifies the pain as in most chronic pain states. Phantom limb pain is frequently described as a burning, cramping, shocking or shooting sensation. Peripheral factors include muscle spasm in the residual limb and this can lead to the tight, cramping sensations often experienced. Phantom "exercises" can be carried out to alter the muscle tension in the residual limb and this has been found to reduce this quality of pain. Surface blood flow around the stump is often altered in association with the nerve injury, due to the cross-coupling of sensory with sympathetic fibres, resulting in a burning sensation. These burning sensations often respond to interventions that increase blood flow to the residual limb, for example, beta blockers by reducing the sympathetic activity within the vasculature of the limb. Ectopic discharges from the neuroma within the stump, together with those within the dorsal root ganglion and the dorsal horn of the spinal cord are respondible for the intermittent sharp, shooting pains. These sensations are due to central factors such as reorganisation of the amputation zone within the somatosensory cortex where a sensory memory map exists[3]. Indeed it has been shown that suppression of afferent input from the amputation stump by brachial plexus anaesthesia eliminates both cortical reorganisation and phantom limb pain in approximately 50% of subjects[4]. In some amputees, cortical reorganisation and phantom limb pain are maintained by a peripheral input, whereas in others intra-cortical changes are more important.

In 1988 Bach *et al* carried out a controlled study of lumbar epidural blocks prior to amputation[5] and concluded that pre-emptive analgesia resulted in less phantom pain but recent studies have been equivocal about the value of this technique. Loss of a limb or major nerve injury pain management revolve around the use of N-methyl D-aspartate (NMDA) antagonists and GABA agonists, as these are directed at modifying the progression of spinal sensitization and cortical reorganization respectively. In the second of the two cases described, the patient experienced phantom limb pain which was successfully treated with gabapentin. This drug is an alpha-2-delta calcium channel blocker which has a therapeutic range similar to that used in the management of epilepsy.

The further development of micturition related phantom pain can be explained by the physiology of sympathetic-coupling to somatic nerves. Nerve laceration triggers a massive sprouting of sympathetic fibres at the injury site and increased activity within the dorsal root ganglia. This is associated with an upregulation of alpha-adrenergic receptors in the primary afferent neurons. These receptors mediate the excitatory effects of postganglionic sympathetic efferent[6]. It has been shown that there is considerable cross-talk within neuromas, between efferent sympathetic nerves and afferent nociceptors[4]. Therefore any stimuli in the body which increases sympathetic tone will also increase the likelihood of phantom limb pain or nerve injury pain. The use of alpha-adrenergic antagonists can be effective in managing this aspect of the pain.

With an understanding of the factors involved in phantom limb pain treatment can be more effectively orientated towards altering these unpleasant perceptions:

- Educating patients about phantom sensations, to alleviate stress.
- Anticonvulsants to reduce spontaneous neuronal firing of deafferent nerves
- Alpha-adrenergic antagonists to reduce sensory-sympathetic coupling
- Beta blockers to improve circulation to the stump

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Case Report

Hereditary Hemorrhagic Telangiectasia in association with Generalised Juvenile Polyposis

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CASE REPORT

A 22-year-old lady was referred to the respirology department of a tertiary referral hospital for further assessment of newly diagnosed pulmonary arteriovenous; malformations (AVMs) She had initially presented to a paediatric department at the age of 8 years for investigation of recurrent epistaxis and iron deficiency anaemia. Her stool was identified as being positive for faecal occult blood and following further gastrointestinal investigation, multiple polyps were discovered throughout her gastrointestinal tract (Fig. 1). Histological examination determined the polyps to be hamartomas and she was diagnosed as having generalised juvenile polyposis. She had a subtotal colectomy aged 9 years and a panproctocolectomy with subsequent fashioning of an ileal pouch anastomosis aged 19 years. During this period of time she continued to suffer from recurrent epistaxis and had numerous embolisation and surgical procedures carried out in an attempt to alleviate this problem. Within the last 2 years, multiple telangiectasias were identified on the vermillion border of her lips and underlying Hereditary Haemorrhagic Telangiectasia (HHT) or Osler-Weber-Rendu Syndrome was suspected. She had no documented family history of this or juvenile polyposis, however her father had been rejected several times from being a blood donor because of anaernia. A magnetic resonance imaging (MRI) scan of the brain did not show any evidence of an intracranial AVM. Computed tomography (CT) scan of her chest did however identify multiple pulmonary AVMs, thus prompting her referral to respirology.

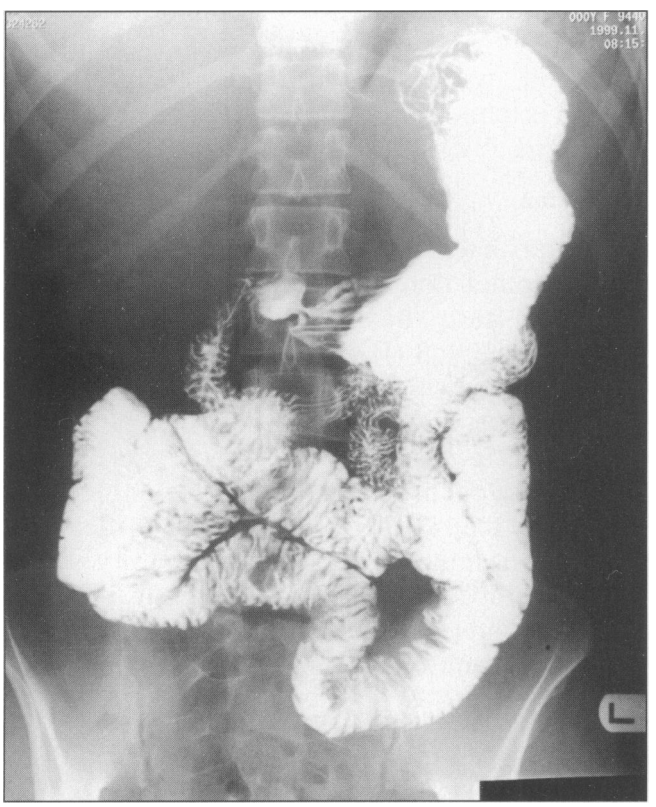

Fig 1. Small bowel series demonstrating several filling defects consistent with polyps in the jejunum. The patient was post colectomy at this stage.

At this presentation there was no history of dyspnoea, cough, haemoptysis or blackouts. On physical examination she had facial telangiectasia, which was most marked adjacent to her bottom lip. There was no evidence of anaernia or central cyanosis. Respiratory rate was normal and there was no finger clubbing. Apart from scars from her previous abdominal surgery, physical examination was otherwise unremarkable.

Haematological investigations revealed a haemoglobin of 122 g/L and normal electrolytes. Oxygen saturation was 86% on room air. An arterial blood gas revealed pH 7.40, pCO_2 40

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mmHg, pO2 52 mmHg, HC03 25 mmol/L and BE 0. Pulmonary function tests showed mildly impaired diffusion capacity at 71% predicted, but was otherwise within normal limits. A repeat spiral CT scan of chest (Fig.2) using a high resolution protocol was performed to accurately

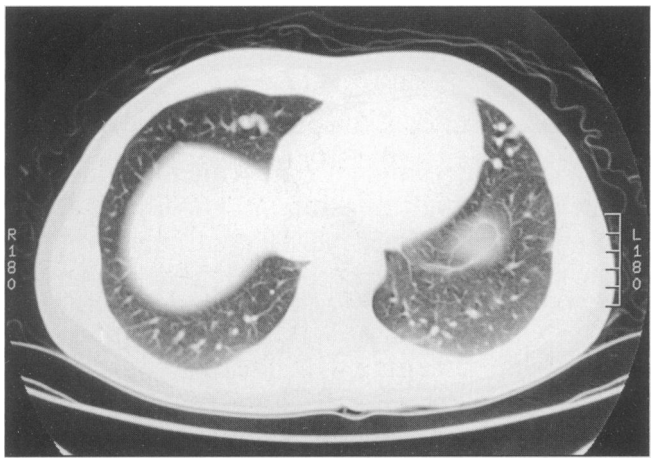

Fig 2. CT scan of chest showing the typical serpiginous characteristic of AVMs within the lingula and right middle lobe.

determine the size and distribution of the pulmonary AVMs. This identified multiple pulmonary AVMs in the right middle lobe, lingula and left lower lobe. These were later confirmed by a pulmonary angiogram (Fig.3). Coil

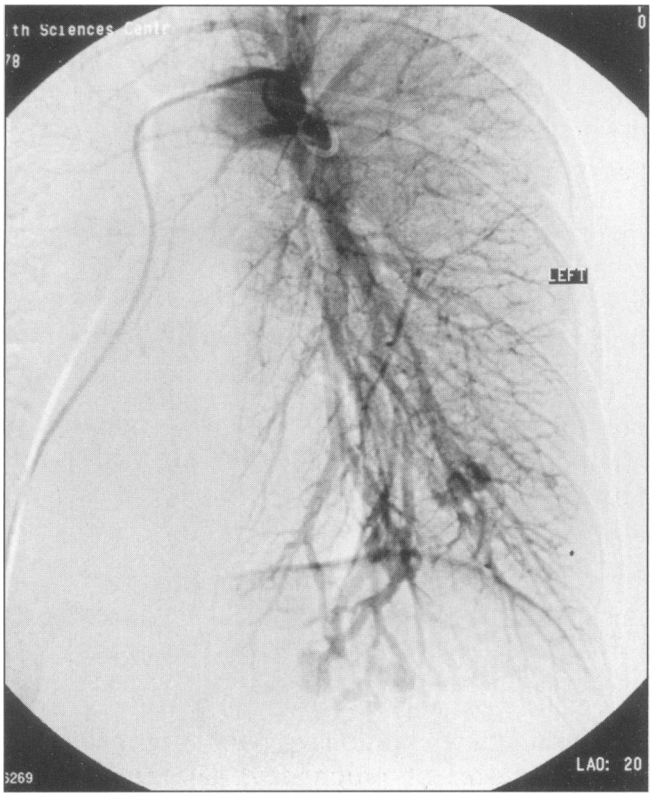

Fig 3. Pulmonary arteriogram confirming the nature of the AVM in the lingula prior to embolisation.

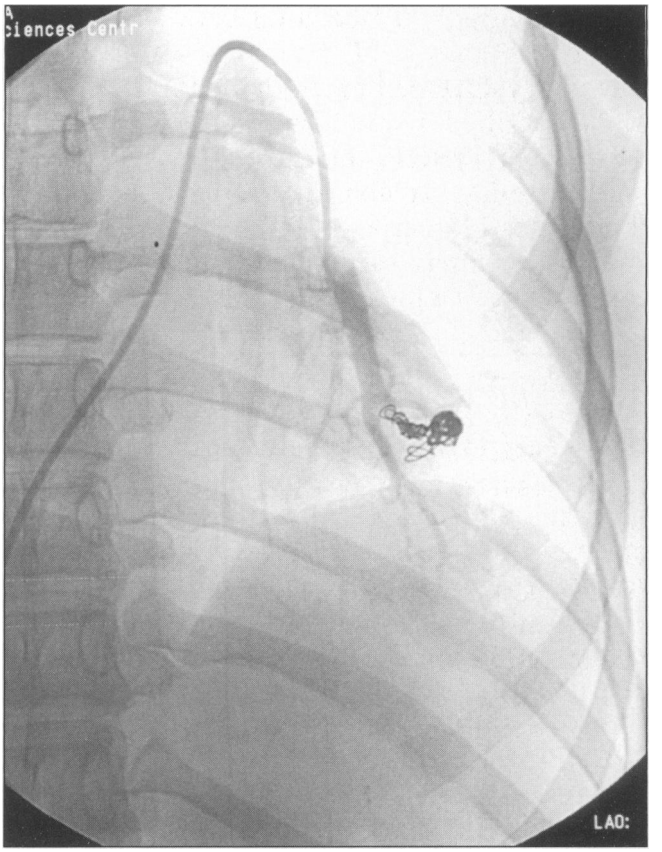

Fig 4. Post successful coil embolisation of the lingular AVM.

embolisation of the AVMs was attempted and the largest AVM in the lingula was successfully occluded, without complication (Fig.4). The patient is to return for further embolisation of her remaining AVMs.

Discussion

Hereditary haemorrhagic telangiectasia is a group of autosomal dominant disorders with genetic linkages that have been established to chromosome 9q3 (HHT 1) and 12q 13 (HHT2), although it is possible that genes on other chromosomes may also be involved[1]. The clinical diagnosis is made with two or moreof the following: recurrent epistaxis, telangiectasis elsewhere than in the nasal mucosa, evidence of autosomal dominant inheritance or visceral involvement. Visceral involvement includes AVMs found in the pulmonary, gastrointestinal, hepatic or central nervous system circulations.

Juvenile polyposis is also an autosomal dominant condition featuring the development of multiple hamartomatous polyps, most commonly in the colon, but which can also occur in the stomach or small intestine[2]. It usually presents in the first or second decade with the onset of rectal bleeding

and anaemia. An association between juvenile polyposis and HHT has only rarely been previously documented. Initially in 1982, Cox et al[3] described a mother and daughter with generalised juvenile polyposis, pulmonary AVMs and severe digital clubbing. Both patients fulfilled the diagnostic criteria for HHT. Since then further cases have intermittently been identified[2],[4-8], culminating in a short series of cases by Ballauff and Koletzko in 1999[9].

In HHTI, the genetic mutation at chromosome 9q3 has been identified as involving endoglin. This encodes an integral membrane glycoprotein that binds transforming growth factor ß (TGFß). In HHT2, the abnormal gene on chromosome 12q13 encodes activin receptor-like kinase 1 (ALK-1), a cell surface receptor for the TGFß superfamily of ligands[8]. When undergoing investigation for HHT, our patient had normal endoglin levels, making it likely she had either HHT2 or a mutation in a previously unidentified gene.

In juvenile polyposis, although the exact genetic abnormality is not known, it ha been proposed that mutations in the tumour suppressor gene PTEN on chromosome 10q may be responsible in certain cases[2]. Juvenile polyposis has also been described in association with other genetic syndromes including Gorlin Syndrome and Bannayan-Riley-Ruvalcaba Syndrome, as well as HHT, suggesting a certain genetic heterogeneity in its aetiology[2]. It is likely that the genetic abnormality associating HHT and juvenil polyposis is linked, and although this link has not yet been identified, it is statistically more likely than both these rare diseases existing as a coincidence[3].

The importance of diagnosing juvenile polyposis is that although the polyps are hamartomas, there is an overall increased risk of gastrointestinal malignancy in these patients when compared to the general population[10]. Colectomy is often required with continued surveillance of the upper gastrointestinal tract.

It is important to highlight that an association can occur between these two conditions. Early recognition of this association allows the pertinent management problems of each syndrome to be addressed. With regard to HHT, pulmonary and intracranial AVMs are of particular concern, as they may be clinically silent lesions, which can result in sudden morbidity or death[1]. Patients with pulmonary AVMs are much more common and at risk of stroke or cerebral abscess secondary to the pulmonary systemic shunt, Antibiotic prophylaxis is thus mandatory in these patients undergoing dental procedures and during endoscopy. Endoscopy may be performed for the investigation of gastrointestinal haemorrhage, either secondary to mucosal telangiectasia or hamartomatous polyps.

Screening protocols for pulmonary AVMs have been suggested to identify persons whose risk of pulmonary AVMs is sufficient for diagnostic imaging to be warranted. It is most indicated in patients with a low $P0_2$ or family history of AVM, but should be considered in all patients with HHT. A recent report from a Canadian group showed that screening with chest radiograph and pulse oximetry was insufficient[11]. They reported that initial screening by clinical examination followed by measurement of PaO_2 while breathing 100% oxygen is warranted[11]. This same group recently showed the added advantage of agitated saline contrast echocardiography as a useful adjunctive test. In their prospective study it was the only positive screening test in 31 % of patients[12]. This group have also reported their experience with diffuse pulmonary AVMs and reported that transcatheter embolectomy reduced the risk of neurologic complications[13]. They reported that the patients can live for many years and lead productive lives but they do not recommend lung transplantation as survival with the disease is difficult to predict and they had a perioperative transplant death[13].

In our hands screening for pulmonary AVMs is easily performed with spiral computed tomography. Screening for intracranial AVM is achieved with magnetic resonance imaging, although the indication for this is less well defined in the absence of headache or a family history of intracranial AVM[1]. It is advised that persons affected by, or at risk for, HHT who have a family history of pulmonary or cerebral AVMs should undergo pulmonary screening at puberty, or sooner if the family history includes prepubertal AVMs, and again at the end of adolescence. For persons from families without such a history, pulmonary screening should be considered but is less clearly indicated. As there have been cases of life threatening pulmonary haemorrhage in the third trimester of pregnancy, affected women should have pulmonary screening before conception. Anyone in whom a pulmonary AVM

is found should undergo helical computer tomography every five years to rule out the possible growth of residual malformations in the intervening period.

Particular care maybe needed to ensure appropriate screening investigations are preformed as the need for these particularly arises at a time when transition is being made from paediatric to adult clinics.

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Case Report

Paraganglioma of the nasal cavity

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INTRODUCTION

Paragangliomata of the head and neck, although a recognised entity, are extremely rare tumours and will be encountered by only a few clinicians. Furthermore, the nasal cavity and nasopharynx are among the least common sites in which this neoplasm may arise. We describe a case of a paraganglioma of the nasal cavity mucosa and draw attention to the difficulties encountered in predicting the biological behaviour of these uncommon tumours.

CASE HISTORY

A twenty-four year-old caucasian male was referred to the ENT outpatient department complaining of left-sided nasal obstruction and recurrent epistaxis of a few weeks' duration. Anterior rhinoscopy revealed the presence of a polypoid lesion in the posterosuperior aspect of the left nasal cavity, the appearance of which was suggestive of an angiofibroma. The patient was also noted to be mildly hypertensive. Computed tomography confirmed the presence of a lobular soft tissue mass in the left side of the nasal cavity extending posteriorly into the nasopharynx with associated thinning and lateral displacement of the nasal septum but there was no evidence of lateral extension into the pterygopalatine fossa.

Histological examination of a small incisional biopsy specimen showed features of a neuroendocrine tumour, most likely a paraganglioma. A lateral rhinotomy was performed; at operation, a pink pulsatile exophytic tuniour measuring five cm in diameter was seen arising from the mucosa of the posterosuperior nasal cavity and extending into the ethmoid sinus. Of interest is the fact that the patient's blood pressure fluctuated more than would have been expected during the procedure. The lesion was completely excised and the patient remains well fifteen months after surgery.

HISTOLOGICAL FEATURES

The surgical specimen consisted of multiple fragments of firm pale grey tissue weighing 39g in total. Histological examination of haematoxylin- and eosin-stained material showed an ulcerated and highly vascularised turnour consisting of mildly pleomorphic polygonal "chief" cells with eosinophilic cytoplasm and a granular nuclear chromatin distribution. The tumour cells were arranged in infiltrative trabeculae and nests with a vague *zellballen* pattern (Fig. 1); occasional mitotic figures were noted. Histochemical reticulin staining demonstrated a fine connective tissue network between the trabeculae and *zellballen* of tumour cells (Fig. 2). Neuroendocrine differentiation was confirmed by strongly-positive immunohistochemical staining for chromogranin

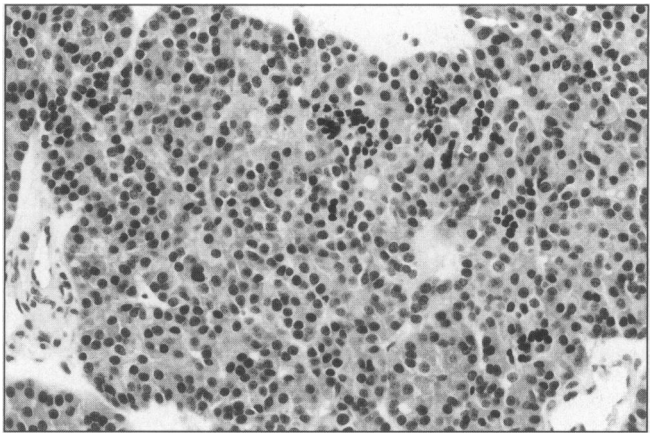

Fig 1. *Zellballen* architecture in paraganglioma (H&E, x100).

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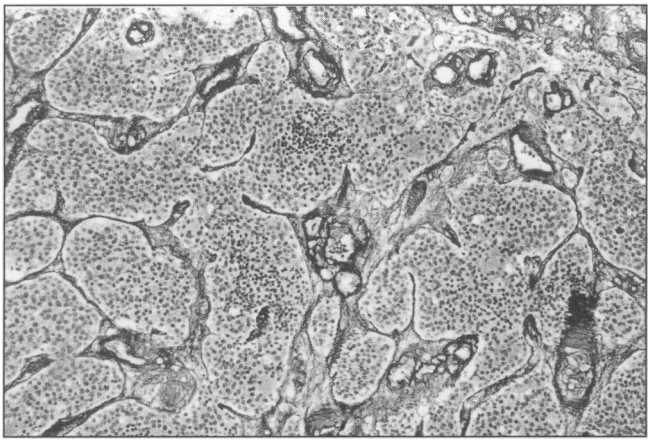

Fig 2. Fibrous stroma imparting *zellballen* pattern (reticulin, x40).

A and neuron-specific enolase. Antibodies directed against S-100 protein, a neural crest-derived antigen, identified sustentacular cells at the periphery of tumour nests, thus confirming the diagnosis of paraganglioma (Fig. 3). Electron microscopy demonstrated abundant dense-core neurosecretory granules within the polygonal chief cells and confirmed the presence of sustentacular cells surrounding the *zellballen.*

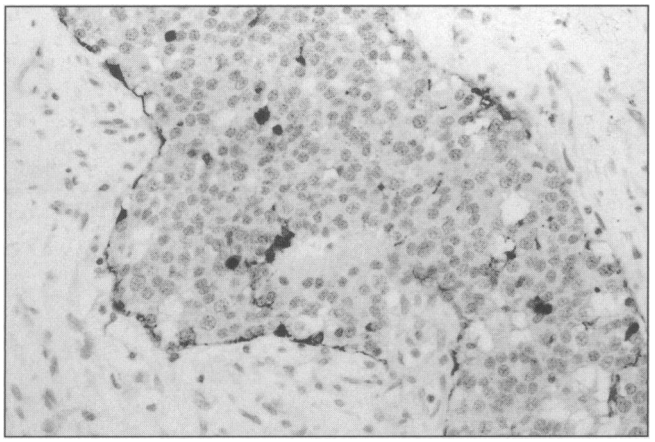

Fig 3. S100-positive sustentacular cells surrounding *zellballen* (immunoperoxidase, x100).

DISCUSSION

The extra-adrenal paraganglion system consists of focal collections of neuroepithelial chief cells arranged in *zellballen* nests encircled by a layer of Schwann-like S-100-positive sustentacular cells. Paraganglia. (and their neoplastic progeny) have been found in various locations within the head and neck, the most notable of which are the carotid bodies (giving rise to the classical chemodectoma). Paragangliomata of the nose and paranasal sinuses are extremely rare – a recent review identified twenty-five cases worldwide, only twelve of which arose from the nasal cavity mucosa[1]. It is generally accepted that these nasal neoplasms should be divided into two distinct groups based on their presumed anatomical origin; paragangliomata arising from the mucosa of the nasal cavity must be separated from tuniours which develop within extranasal paraganglia. (the most common sites of origin being the jugulotympanic, vagal and ciliary ganglia[2]) and invade the nasal cavity by direct growth. A different surgical approach is often required according to the site of origin of the tumour[3].

As with all neuroendocrine tuniours, it is frequently impossible to accurately predict the biological behaviour of individual cases; paragangliomata may exhibit a variable degree of cellular atypia and mitotic activity but the vast majority are clinically benign. Many authors maintain that morphological features cannot be used as the only criteria by which to diagnose malignancy. Invasion of bone or distant metastasis is the *sine qua non*[1].

Immunohistochemistry can be of help not only in diagnosis but may also assist with regard to prognosis[4] - Achilles et ar assessed the value of immunohistochernical staining for S-100 protein in the diagnosis and prognosis of paragangliomata and observed that malignant paragangliomata. were completely devoid of S-100-positive sustentacular cells; however, a small proportion of benign turnours were also lacking in sustentacular cells, thus making it difficult to reach an unequivocal conclusion about the reliability of this finding. Nonetheless, sustentacular cells were well represented throughout the turnour in the present case. It is also reassuring to note that only four of the reported nasal and paranasal paragangliomata have proven to be overtly malignant[1].

Ki-67, a nuclear antigen ubiquitously expressed by dividing cells during all active parts of the cell cycle, may well prove to be of diagnostic and prognostic significance. Karamitopoulou *et al*[6] studied Ki-67 immunoreactivity in central nervous system turnours (including three paragangliomata) for assessment of cell proliferation. They observed increased reactivity in each of the paragangliomata studied, a characteristic which contrasted with their benign morphological features. In the present case, over 18% of the tumour cells stained positive for Ki-67 using the M113-1 monoclonal antibody; this

reflected a much greater degree of cellular proliferation than one would have expected from the histological appearance and correlated with a Ki-67 labelling index of 18.7, considerably higher than the mean of 2.19 previously described. This intriguing finding warrants finther investigation to determine the ultimate value of Ki67 immunohistochemistry in predicting tumour behaviour, particularly in cases in which there is significant doubt regarding the adequacy of surgical excision. Local recurrence is an important complication of these turnours and should be viewed with deep suspicion and treated appropriately. Although the turnour in this case contained numerous sustentacular cells, the degree of cellular proliferation is worrying and suggests a high potential for local recurrence. The patient has since been closely reviewed every three months and remains well with no clinical or radiological evidence of recurrent disease fifteen months after surgery.

CONCLUSION

Nasal paragangliomata are exceedingly rare tumours but are an entity of which clinicians should be aware, particularly when they meet with a case of unilateral nasal obstruction or recurrent epistaxis. Although paragangliomata can provide diagnostic and prognostic difficulties, immunohistochemistry is proving to be a useful adjunct to routine histological examination. When dealing with neuroendocrine tumours of the head and neck, a thorough approach to surgery is obligatory as is vigilant follow-up[7].

ACKNOWLEDGMENTS

We are indebted to Mr R Creighton for kind assistance with histological photography.

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Case Report

Churg-Strauss syndrome associated with leukotriene receptor antagonists

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Accepted 10 June 2001

CASE REPORT A 46-year-old man presented with a three-year history of rhinitis treated with intranasal corticosteroids. In July 1998 he attended his general practitioner with wheeze and was diagnosed as suffering from asthma. Treatment with inhaled salbutamol and beclomethasone 200 mcg twice daily was commenced in September 1998 and he improved. In January 1999 he presented with recurrent wheeze and non-productive cough; chest examination showed bilateral rhonchi. Chest radiograph showed obvious airspace consolidation in the left midzone, with a smaller area in the right midzone and possibly a further area at the right apex (Figure 1). He was commenced on zafirlukast 20 mg twice daily. Although he had improved at review 8 weeks later, it was noted he had developed a petechial rash over the lower pretibial area of both legs. He was changed from zafirlukast to montelukast. Chest radiograph two weeks following this review showed resolution of the previous areas of consolidation but new consolidation was noted at the left base and right mid zone (Figure 2). Eosinophil count was noted to be elevated at 16.9 x 10^9/1 (72% eosinophilia). The platelet count was normal. There had been no reduction in the dose of inhaled corticosteroids over this period. He was thought to have pulmonary eosinophilia and was commenced on prednisolone 40 mg daily for one week with symptomatic improvement including resolution of the petechial rash. At review two weeks following completion of prednisolone, he was again noted to have a petechial rash, again in a similar distribution. He complained of diarrhoea five days later and montelukast was stopped. He continued to complain of dyspnoea, wheeze and non-productive cough. At review two weeks later, he complained of increasing exertional dyspnoea and he was commenced on prednisolone 30 mg daily for one week. Again he symptomatically improved and the petechial rash resolved. Again, one week following completion of prednisolone, he continued to complain of dyspnoea, wheeze and cough and was commenced on prednisolone 30 mg daily for five days.

He was initially seen at the Chest clinic six weeks later, two days after completing a further five-day course of prednisolone 30 mg for increasing dyspnoea. He still complained of dyspnoea and non-productive cough. There was no other significant history and in particular there was no history of any inhaled allergens. Chest radiograph was normal. He was commenced on fluticasone 1000 mcg twice daily. At review, four weeks later, his symptoms had improved, but he complained of recurrence of the rash over both lower limbs. On examination he was thin. He had a purpuric rash, which was more extensive than previously, over both lower limbs and particularly pretibially. The nasal mucosa was reddened and inflamed and nasal polyps were noted. Respiratory rate was 15. Chest examination was normal. There was no other abnormality on examination. Spirometry showed an FEV1 of 3.941 (108% predicted) and a FVC of 4.731 (104% predicted). Residual volume was 126% predicted; total lung capacity was 108% predicted and residual volume/total lung capacity ratio was 110% predicted. Transfer factor was 72% predicted.

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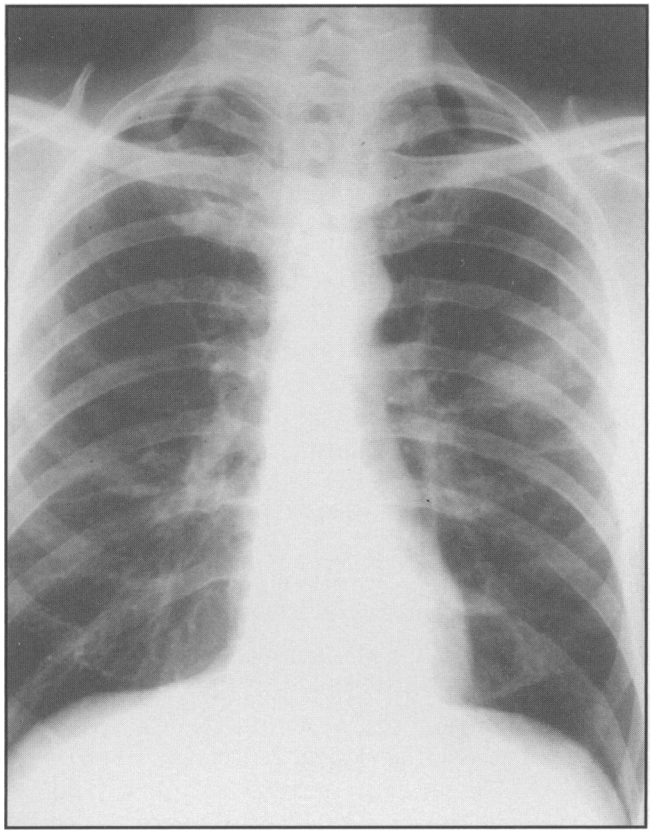

Fig 1. Chest radiograph showing obvious airspace consolidation in the left midzone, with a smaller area in the right midzone and possibly at the right apex.

Chest radiograph showed peripheral ill-defined streaky infiltrates with septal thickening. CT chest showed bilateral peripheral pulmonary infiltrates, more prominent on the right. C reactive protein was 31. Eosinophil count was 15.0 x 10^9/l (69% eosinophilia). Platelet count was normal. IgE was 1003 IU/1. pANCA was 1:20 however myeloperoxidase (MPO) was negative indicating this was a false positive and not significant. The remainder of the vasculitic and autoimmune screen was normal. Skin biopsy showed evidence of necrotising small vessel vasculitis with eosinophilic infiltration.

Nerve conduction studies showed that peripheral nerve conduction was within normal limits. Transthoracic echocardiographic examination was normal. Direct urine microscopy showed an inactive sediment. Renal function was normal. Churg-Strauss syndrome was diagnosed and the patient was commenced on prednisolone 60 mg daily. Within one week he was clinically well, his symptoms and the vasculitic rash had resolved completely. C reactive protein was 5, eosinophil count was 0.1 x 10^9/l (1% eosinophilia) and chest radiograph was normal.

DISCUSSION

Churg-Strauss syndrome is an eosinophilic necrotising vasculitis. The presence of four of six defined criteria (asthma, paranasal sinus abnormalities, mononeuropathy or polyneuropathy, non-fixed radiographic pulmonary infiltrates, eosinophilia > 10% and biopsy containing blood vessels with extravascular eosinophils) establishes the diagnosis with a sensitivity of 85% and a specificity of 99.7%.[1] The differential diagnosis of hypereosinophilia and systemic vasculitis is beyond the scope of this case report; however this has previously been comprehensively reviewed.[2] Recent reports have described Churg-Strauss syndrome in asthma patients being treated with leukotriene receptor antagonists. The Committee on Safety of Medicines has received 63 reports of Churg-Strauss syndrome since 1963, 59 since the start of 1998. Of these, 90% were associated with drugs used to treat asthma, mainly leukotriene receptor antagonists.[3] It has been suggested that these patients had formes fruste Churg-Strauss syndrome which was unmasked following

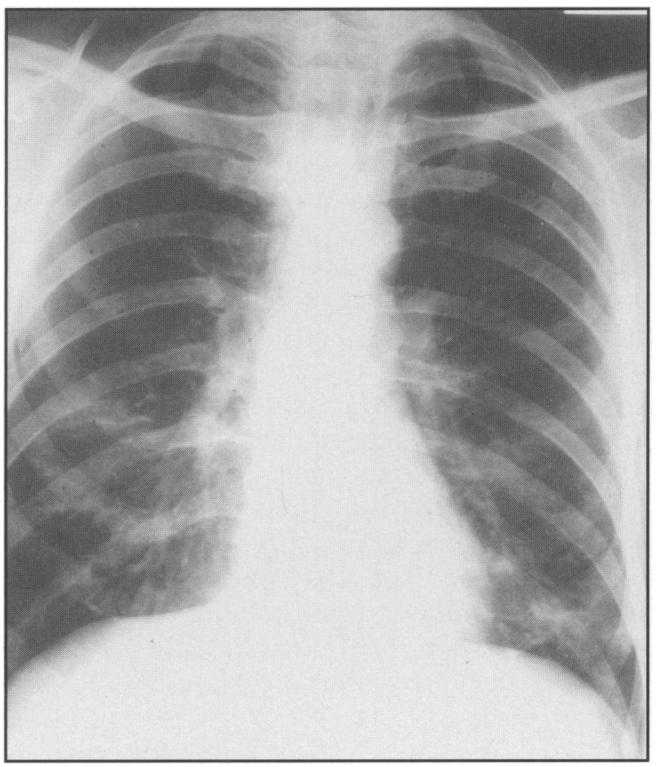

Fig 2. Chest radiograph showing resolution of the previous areas of consolidation but new consolidation at the left base and right mid zone.

corticosteroid withdrawal facilitated by the use of the leukotriene receptor antagonists .[4] Churg-Strauss syndrome has also been reported in patients who have not received maintenance systemic corticosteroids.[4-9] However in all but one of these reports the patients had received recent intermittent systemic corticosteroids.[9]

It is likely that this patient already had Churg-Strauss syndrome at the time of initial presentation. At that stage three of the four required American College of Rheumatology criteria for the diagnosis of Churg-Strauss syndrome were present (rhinitis, asthma and pulmonary infiltrates) but the eosinophil count was not measured. The skin vasculitis appeared following the introduction of zafirlukast. Whilst the onset of the skin vasculitis could have been coincidental, the clear temporal relationship would also be consistent with the hypothesis that leukotriene receptor antagonists accelerated the disease process. This patient had not previously received any systemic corticosteroids. Furthermore the dose of inhaled and intranasal corticosteroid used is lower than that recognised to have a systemic effect. The mechanism by which leukotriene receptor antagonists cause Churg-Strauss syndrome is uncertain. It has been postulated that leukotriene receptor blockade which does not inhibit the eosinophilic chemotactant, leukotriene B4, may result in a state of eosinophilic activation leading to the development of Churg-Strauss syndrome. However, the fact that Churg-Strauss syndrome has been reported with the 5-lipoxygtrase inhibitors, which also block leukotriene B4, makes this possibility less likely. Alternatively it is possible Churg-Strauss syndrome may represent an idiosyncratic or hypersensitivity reaction to leukotriene receptor antagonist exposure. In conclusion this report provides evidence that the use of leukotriene receptor antagonists may play a part in accelerating Churg-Strauss syndrome. This case report illustrates that leukotriene receptor antagonists may trigger Churg-Strauss syndrome, and that this condition should be suspected in patients with asthma who develop marked eosinophilia or other vasculitic features following the introduction of leukotriene receptor antagonists.

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Case Report

Coexistence of supravalvular aortic stenosis and osteogenesis imperfecta

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Accepted 27 September 2001

CASE REPORT

A 54 year old woman was admitted for cardiac catheterisation. She had been attending the outpatient clinic since 1975, with regular review. She had diagnoses of type I osteogenesis imperfecta, and of supravalvular aortic stenosis. Osteogenesis imperfecta was diagnosed in early life on clinical grounds including the presence of blue sclerae and the occurrence of several bone fractures secondary to minimal trauma. A number of family members have been diagnosed with the same condition (figure 1-family pedigree).

The supravalvular aortic stenosis was not diagnosed until later. She was initially referred to the cardiology clinic for further evaluation following the discovery of a systolic murmur during routine examination at an antenatal clinic. Echocardiography revealed a morphologically normal aortic valve and confirmed the presence of supravalvular aortic stenosis, with an estimated peak systolic gradient of 20 mmHg.

Examination of her family history has also revealed several members with a diagnosis of supravalvular aortic stenosis (Figure). Neither of her parents was known to have had the disease, but her mother had died prematurely at the age of 42 years supposedly due to asthma. There are three family members diagnosed with both osteogenesis imperfecta and supravalvular aortic stenosis. Therefore, some members of this family have either supravalvular aortic stenosis or osteogenesis imperfecta, some have both diseases and some have neither.

Cardiac catheterisation (SVAS) revealed normal coronary arteries and left ventricular function. There was narrowing of the ascending aorta immediately above the aortic valve with poststenotic dilatation of the aorta, giving the typical "hourglass" appearance seen in SVAS. There was a peak-to-peak gradient of 40 mmHg across the lesion on catheter pull-back.

Karyotyping revealed a normal XX pattern with no deletion evident. The mutation causing SVAS in this family has been mapped to the elastin gene on chromosome 7. This family has not yet been investigated with regard to the molecular basis for theirosteogenesis imperfecta.

DISCUSSION

Supravalvular aortic stenosis is defined as an obstructive vascular disease due to severe narrowing of large elastic arteries, particularly the ascending aorta, and including the pulmonary, coronary and carotid arteries. The incidence of the disease is estimated at I in 20,000 births. The large majority of cases are familial, with transmission of the disease in an autosomal dominant manner[1]. The disease is caused by mutation in the elastin gene (ELN), located at chromosome 7q11.23[2]. Supravalvular aortic stenosis is also a common feature of Williams' syndrome, a congenital multisystem disorder caused by contiguous gene deletion that may include the elastin gene[3].

Osteogenesis imperfecta is an inherited connective tissue disorder, characterized by skeletal, ocular, otologic and dental abnormalities with an incidence of around one in 28,500 live

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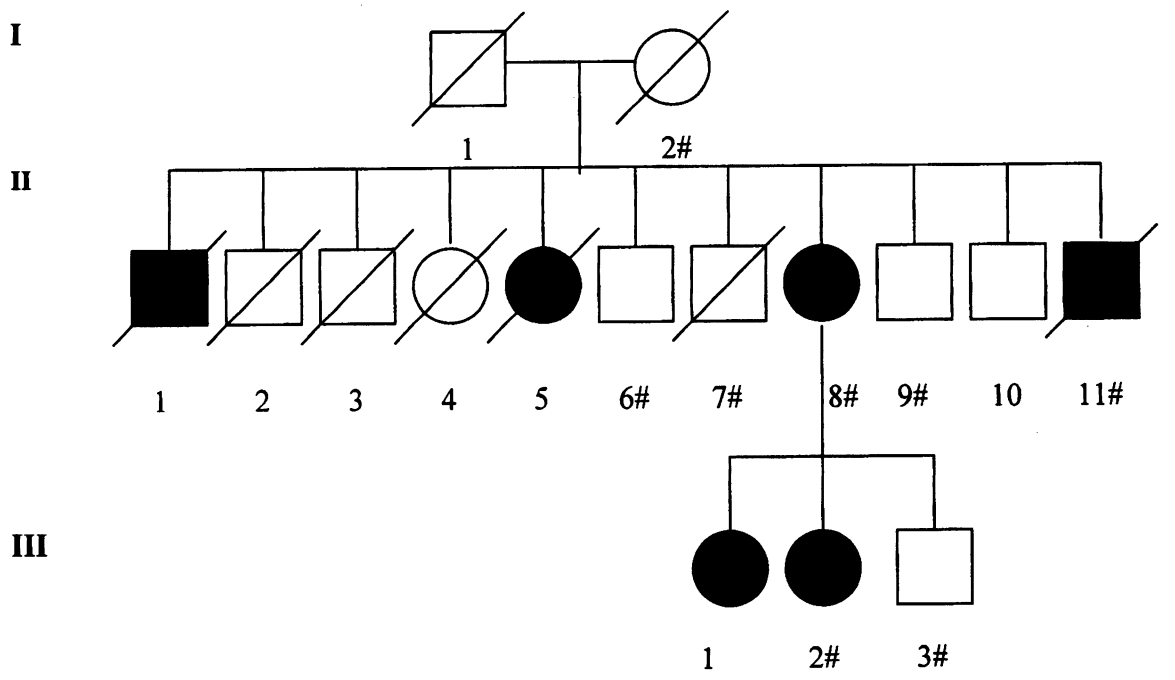
FIGURE

Family Pedigree



■ = Affected SVAS
\# = Affected OI
Individual II8 is the person described in this paper.

births. Sillence *et al* specified four basic types of the disease, based on age-of-onset, severity and mode of transmission[4]. The family described meet the criteria for type I osteogenesis imperfecta. Cardiovascular involvement in osteogenesis imperfecta type I was described in one study and includes mitral valve prolapse in 18% with rare progression to mitral regurgitation, and slight but significant increase in aortic root diameter associated with aortic regurgitation in 1 to 2%[5]. Over 70 mutations have been associated with osteogenesis imperfecta, all affecting type I procollagen synthesis. The osteogenesis imperfecta type I phenotype can be produced by mutation in either the COL1A1 gene on chromosome 17 (17q21.3 1-q22) or the COL1A2 gene on chromosome 7 (7q22.1), and possibly in other genes[6]. The presence or absence of presenile hearing loss was the best predictor of the mutant locus in osteogenesis imperfecta type I families with 13 of the 17 COL1A1 segregants and none of the COL1A2 segregants demonstrating this feature[7].

The estimated incidence of both osteogenesis imperfecta and supravalvular aortic stenosis occurring together by chance in an individual is over one in five hundred million. Although the ELN and COL1A2 genes are both present on chromosome 7, it is highly unlikely that the coexistence in the individuals discussed is due to expression of one genetic defect for a number of reasons. Firstly, the ELN and COL1A2 genes are not closely linked on chromosome 7, and in the knowledge that the individual discussed has a normal karyotype, a large deletion cannot explain coexistence of the diseases. Secondly, the family described have had presenile hearing loss as a feature of osteogenesis imperfecta, which has not been a feature of mutation in the COL1A2 gene; therefore it can be postulated that the mutation in this case is linked to the COL1A1 gene on chromosome 17. Finally, the diseases have not segregated together in this family, so there have been some members with both osteogenesis imperfecta and supravalvular aortic stenosis, some with only one disease and some with neither disorder.

In conclusion, we present a case with coexisting supravalvular aortic stenosis and osteogenesis imperfecta, the first documentation in the literature. Both diseases have a single gene basis, autosomal dominant transmission, altered

production of structural proteins and manifestation in the cardiovascular system. The likelyhood of pure chance association is low.

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Case Report

Prolonged asystole following direct-current cardioversion for atrial flutter

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We describe the case of a 64-year old lady with multiple established cardiovascular risk factors including non insulin-dependent diabetes mellitus, hypertension and previous history of stroke, with known to have atrial fibrillation, who presented for emergency admission with acute dyspnoea due to the onset of a fast ventricular response. Satisfactory rate control was achieved with digoxin. The cause of atrial fibrillation in this patient was presumed to be mild-to moderate regurgitation at the mitral valve, as evidenced by echocardiographic examination, in the absence of alternative positive findings.

CASE REPORT

The patient was admitted as an elective day-case two months later for direct-current cardioversion (DCC) following four weeks of adequate anticoagulation with warfarin, having discontinued digoxin three days previously. Other medications were: carbamazepine and thyroxine. The electrocardiograph at this time revealed atrial flutter with variable block, a ventricular rate of 108 per min, QRS axis of 15° and a T-wave axis of - 90°. She was sedated with 500 micrograms of alfentanil and 4mg of midazolam intravenously according to standard hospital practice. Flutter persisted despite 1x50Joule and 2x100Joule DC synchronised shocks. Following a further 200Joule shock the patient became asystolic. Percussion pacing was required to maintain cardiac output. The patient continued to breathe spontaneously and remained conscious, though heavily sedated, the rhythm being assessed every minute for three minutes until sinus rhythm developed at a rate of 56 ventricular beats per min. At this time she was normotensive and was monitored in hospital for 24 hours during which sinus node dysfunction, manifest as Tachycardia-Bradycardia Syndrome, was revealed. Serum electrolytes and thyroid function tests were found to be within normal reference ranges.

A permanent pacemaker was implanted three weeks later after which the patient has been generally well; although she relapsed into atrial fibrillation once.

Discussion

DCC, originally described for treating atrial fibrillation and flutter in 1963 by Lown *et al*, is a common procedure and is considered to be a simple and safe technique for restoring sinus rhythm[1]. A Medline and PubMed search revealed only one similar case of prolonged asystole following DCC. Hansen *et al*[2] described asystole preceded by a few seconds of atrial flutter and followed by severe nodal arrhythmia following DCC for atrial flutter. The authors postulated that while the precipitant may have been the direct current energy, this effect was facilitated by the adverse effects of pharmacological agents used which included sertraline, sotalol, digoxin and thiopental.

Kabutan *et al*[3] described cardiac arrest at induction of general anaesthesia with isoflurane in a patient who, as in the case we have described, had sick sinus syndrome. In one study of post-DCC arrhythmias[4] asystole was noted to be a transient

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characteristic, almost always lasting for less than two seconds. While several post DCC arrhythmias have been recorded in such studies, we were unable to establish any incidence of prolonged asystole[1,4,5].

It is difficult to confidently propose a mechanism for this complication since the salient characteristics of the reported case previously mentioned as well as the case we describe, are shared with all elective DCCs: sedation and DC shock against a backdrop of concomitant medical therapy often accompanied by underlying cardiac pathology. Synchronised DC shocks are known to have arrhythmogenic effects, however, these typically induce ventricular tachyarrhythmias. Perhaps the outcome of asystole rather than a slow nodal or ventricular rhythm may suggest generalised conducting system dysfunction; while ischaemia would seem the most likely basis for this, particularly in view of cardiac risk factors, there was no direct evidence of coronary artery disease. Carbamazepine has been reported to have effects on conducting tissue and indeed alfentanil is known to be a cause of asystole; unfortunately we do not know what the serum digoxin level was at the time of the procedure. It is possible to postulate that in this case the combined action of drugs, DC shocks and a susceptible substrate of sinus node dysfunction may have collectively led to the asystolic event; the contribution of each, however, cannot be confidently concluded.

Since DCC is a procedure which is commonly carried out in district general hospitals in a general medical day-patient setting by relatively junior medical staff, while the outcome we report is uncommon, we feel that its potential gravity justifies its consideration. It is therefore of critical importance that those who carry out this procedure should be aware of the possibility of asystole and be adequately trained and experienced so as to feel capable of managing this as well as other more common complications. The trend towards developing nurse-led elective DCC[6] adds further weight to such a position.

Sinus node dysfunction may be a prerequisite for prolonged post DCC asystole. Clinicians should be alert to this as it may be unmasked by DCC itself.

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Book Reviews

Ask Dr Ian About Sex. Ian Banks. The Blackstaff Press. 1999. ISBN O 85640 570.

"Ask Dr Ian About Sex" is unique as a book. It is not a text book, it is not a novel, it is not a history or a political book. It is a book about sex. It is not prudish, pornographic or distasteful in any way. Dr Banks uses mirth to write this book. This is a very common method used in our society to talk or discuss sexual matters and is used in a cultural, social and clinical settings. The content page is baffling to say the least and not for the faint hearted, for instance "Pick a number, any number" gives 5 pages on group sex and "Greener Grass" deals with gender conflicts and dysphoria. The index is more straight forward. It lists clearly group sex and gender conflicts. Page 214 gives a useful list of addresses and phone numbers where those in need may find help. Relevant addresses in Northern Ireland are indented and could be very helpful to those reading the book in Northern Ireland, not so if one is in Southern Ireland or in any other area of the world. It is skilfully illustrated by cartoons, which again uses mirth to illustrate intimate parts of human sexual behaviour.

The longest chapter is on orgasm. There is a chapter on libido, masturbation, gender conflicts, sexual abuse, sexually transmitted diseases, contraception, the breast, the cervix, the menopause, the testes, the penis, the prostate and erectile failure. There are chapters which deal with pseudo-masochism, group sex, anal intercourse, fetishes, sexual aids and the loss of a sexual partner. A very comprehensive list but maybe over ambitious in 221 pages.

Each chapter begins with a very short introduction on the topic to be discussed. There is then a short problem vignette, followed by a suggested solution. This is a very superficial look at the problems and their solution. This could be misleading as the reader could generalise from the presented problems to problems that appear to be similar, but are clinically and otherwise very different.

A very large part of this book deals in a straight forward friendly way with topics which are only dealt with by the pornography industry. It will find many interested readers as the topics covered in the book are very widespread among the general population. One word of caution; I think it would have been helpful to advise the readers if they identify with some of the problems described in the letters to consult a medical practitioner for confirmation of the self-diagnosis, which they are highly likely to make. In terms of sex therapy this book should be read by most sex therapists. It is a book readily available to their patient population so the patient may come with certain expectations for solutions to their problems, which the book suggests are readily manageable and that each problem has its own solution. This may not necessary be the case in real life medicine.

Reference is made in the text to many eminent authors such as Freud & Grafenberg. A Reference list would be useful to many of its readers.

E O'GORMAN