benefit are to get the new technology without undue delay. Jennett argues that two further steps are needed. He wants an economic appraisal that compares the technology with alternatives and also ranks it in competition with technologies for other conditions—coronary surgery versus dialysis, for example; and he recommends that hospital specialists whose decision making determines the use of technologies should be given up to date information on the balance between risks and benefits and encouraged to modify their practices accordingly.

So far, so good; in an ideal world all that would now be needed is agreement on the make up of the body to be created to make these assessments and enforce them. In practice, however, two very substantial problems remain.

The first is doctors' obsession with clinical freedom. Jennett describes the several occasions on which the American Medical Association has rejected proposals for independent assessment of diagnostic or therapeutic techniques on the grounds that "every doctor must remain free to choose whatever treatment or technique he thinks is best for his individual patients." Here in Britain Professor John Hampton has argued that such clinical freedom ought to be seen to be dead: it is an extravagance that we can no longer afford.⁶ Operating within the restraints of ever tighter financial controls NHS clinicians are, perhaps, now recognising that their budgets are finite and that ways have to be found of allocating the resources available among specialties and within them. So external forces, in the form of budgetary controls, may have helped doctors (in Britain at least) over the first hurdle—the recognition that the use of expensive techniques must be controlled and rationed on the basis of their relative worth. Tragically, with the recognition of that need has come the realisation that for most techniques far too few data are available for such assessments to be made.

The second big problem is that many expensive technologies are marketed—and that (just as with new drugs) doctors are remarkably simple minded in their recognition that science and marketing methods are incompatible bedfellows. Manufacturers of high technology equipment employ salesmen to promote its use; the sort of assessment system that Jennett and his supporters would like to see would obviously conflict with these commercial interests. Indeed, in the United States the National Center for Health Care Technology was killed because—in Jennett's words—"its promise of success so threatened certain vested interests that it became a target for abolition and Congress yielded to these lobbies."

The hope for the future may lie, however, in the recognition within industry as well as among clinicians that the new technologies of the 1980s can be introduced only by their replacing older, less efficient methods. Such a concept requires reliable data on all aspects of patient care—the sort of audit of process and outcome that the *BMJ* and others have been advocating for many years. Indeed, greater attention to the maintenance and analysis of good quality records might probably yield substantial savings—yet the NHS is still saddled with wasteful and labour intensive methods such as Hospital Activity Analysis, which have been documented time and again to be unreliable and unsatisfactory and yet about which nothing is done.

Does Britain, then, need an office of technology assessment? Jennett has no doubts: "Someone, somewhere has to face up to comparing hernias with hips and kidneys with hearts, making a value judgment that cannot be undertaken by computers or bureaucratic machinery." On balance he

favours a new institution (perhaps along the lines of an academy of medicine) rather than any of the existing ones; he sees such an institute as having a small staff and a larger advisory council and being independent of the established professional bodies and of the government. It would assess existing data and identify gaps in knowledge, making recommendations for research but not carrying out projects itself. The response of the medical community to such dispassionate advice should be apparent later this year after the first British consensus development conference (on coronary artery bypass surgery).⁷

If Britain does not set up such formal arrangements no doubt, says Jennett, "We shall continue to muddle through." Yet this is an opportunity we should not let slip. The close partnership between the NHS and academic medicine provides ideal circumstances for careful, objective evaluations. At the same time Britain would be foolish not to attempt some international sharing of the task. Just as most European countries have slowly but steadily moved towards a uniform approach to evaluating and regulating new drugs, so it should be possible for protocols to be agreed that would encourage as many countries as possible to regard each others' assessments of new technologies as scientifically and economically acceptable. In the past 20 years doctors have become progressively more sceptical of claims made for new drugs and have become better informed about the quality of the data they should demand before agreeing to use one. The same sort of informed scepticism needs to be encouraged among the users of high technology medicine—which may then be acquitted of its longstanding charges of extravagance and irrelevance.

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Osteogenesis imperfecta 1984

Within the past decade osteogenesis imperfecta has come of age.^{1,2} No longer a mere orthopaedic curiosity, its problems attract paediatricians, metabolic physicians, and orthopaedic surgeons, and its mysteries excite the dermatologist, geneticist, and molecular biologist. Osteogenesis imperfecta is a true inherited disorder of collagen which demands our attention not only because of the crippling it produces but because of the insight it provides into the biology of this structural protein. Recent advances have shown an ever widening clinical range, have modified the classification of the disorder, and have made genetic counselling less faulty; and prenatal diagnosis in the first trimester is now a real possibility.

Most physicians were taught that osteogenesis imperfecta is a single familial disorder, the hallmarks of which are

brittle bones, blue sclerae, and premature deafness. In the mid-1970s it became clear that the disorder showed considerable heterogeneity (hence "the brittle bone syndrome"), that normal coloured sclerae and severe bone disease were often associated, and that the traditional distinctions based on the presence or absence of fractures at birth could be misleading.³ The broad groups are now agreed but some details are still disputed, and the widely used classification of Silience and his colleagues suggests a precision that does not exist.⁴

Most patients (80%) have mild bone disease inherited as an autosomal dominant (type I), with a few arising as new mutations. In these patients fractures occur mainly in childhood, the deformity and scoliosis are minimal, and eventual stature is nearly normal. Extraskelatal tissues containing collagen are prominently affected, with blue sclerae, early onset deafness (distinct from otosclerosis), hypermobile joints, rupture of tendons, and thin aortic valves (occasionally incompetent).⁵ A few of these patients also have dentinogenesis imperfecta, and this has been used to define subgroups.⁶ By contrast, in an additional, rare, dominantly inherited form (type IV) the sclerae are of normal colour, the bone disease is more severe, the stature is considerably reduced, and dentinogenesis imperfecta is more common.⁷

Infants who are severely affected may be difficult to classify. Such cases are usually sporadic, but occasionally an affected sibling may suggest recessive inheritance. Those with a grossly abnormal skeleton die at or near birth—"perinatal lethal," type II. Typically, the structurally useless long bones are broad, short, deformed, and featureless, the skull is virtually unossified, and the ribs have innumerable fractures. In other forms that also cause perinatal death the bones are thin, bent, and fractured, giving a beaded appearance to the ribs, and countless wormian bones occupy the partly ossified skull.⁸ Neonates with many rib fractures occasionally survive for several months; during this time immobility can profoundly alter the appearance of the long bones.

Such rare survivors join other severely affected infants and children with progressive deformity (type III). Of this undoubtedly heterogeneous group, some are in residential care, most will never walk unaided, and nearly all have grossly limited growth. The expanded "cystic" or "popcorn" ends of the long bones contrast with the narrow, bent diaphyses, and there is progressive kyphoscoliosis, protruberance of the sternum, and a large asymmetric skull emphasising the small triangular face. The sclerae are often white or become so.

Children with the brittle bone syndrome require help from many quarters for their best management⁹; often a key decision is whether to embark on repeated surgery to straighten limbs or to accept a wheelchair existence. Death may occur in early childhood, often from respiratory infections. Within all groups of the brittle bone syndrome there are clinical puzzles. Why, if dentine and bone both contain the same type of collagen, are the teeth so often normal; why, if synthesis of collagen and osteoblast function is defective, do some patients make hyperplastic callus; and why, in some families, is the skull so abnormal in shape that occipital decompression is required?¹⁰

Parents will ask two important questions: what is the risk of an affected pregnancy, and what is the likely severity of the disease? The answers depend on the family history and type of disorder.¹¹ To predict the outcome of a pregnancy it is vital to know whether a parent has osteogenesis

imperfecta; when doubt exists family photographs (for head shape and facial appearance) and skull radiographs (for wormian bones) are useful. With a dominant family history and one brittle boned parent the chance of an affected infant is 50%; bone disease will be mild in type I, less so in type IV, but it nearly always follows the family pattern. With apparently normal parents the outcome of a second pregnancy may be predicted from that of the first. If a previous child had mild (type I) bone disease this is likely to represent a new dominant mutation with negligible risk of recurrence. If a previous infant had lethal osteogenesis imperfecta (type II) or survived with severe bone disease (type III) inheritance could have been recessive and the greatest risk of recurrence is 25%, but in practice it seems to be far less.

What is the outlook for an infant born with fractures when there is no family history of osteogenesis imperfecta and no previous pregnancies? Fractures at birth can occur in all types of osteogenesis imperfecta, so their presence need not indicate a bad prognosis; but when they are numerous, affect the ribs, and are associated with defective ossification of the skull the chances of survival are poor.⁸

In all such pregnancies at risk prenatal diagnosis by ultrasound is possible from the 16th week; deformity, fracture, or defective ossification may be confirmed or excluded by radiography at not later than 20 weeks.^{12,13}

To this clinical account an exciting biochemical chapter is now being written (the details find space elsewhere^{14,15}). Tissue analysis and culture of fibroblasts have localised the defects to type 1 collagen (the only collagen of adult bone) and often to its $\alpha 1(I)$ chain.^{16,17} With the development of specific probes for the collagen genes, and with the model of haemoglobin to work on,¹⁸ early prenatal diagnosis may now be attempted, either by establishing linkage of the disease to known restriction fragment length polymorphisms or by the direct demonstration of deletions within the gene.²⁰ Except in one family²¹ no such linkages or deletions have been described in non-lethal osteogenesis imperfecta; and the importance of the recently described 300 base pairs deletion in lethal osteogenesis imperfecta, using the $\alpha 1(I)$ -like collagen gene,²² is controversial.^{23,24}

When it becomes available diagnosis in the first trimester will not eliminate the brittle bone syndrome, as in many first affected pregnancies the disorder will be unsuspected; and when lives (and reputations) are at stake we have a duty to interpret the results of gene probing with caution.

The early supposition that in the brittle bone syndrome we are seeing the "thalassaemia of collagen" is being amply confirmed,²⁵ but the number and size of the collagen genes make the problems infinitely more complex than those of haemoglobin.²⁶ Nature is unlikely to yield her collagen secrets easily; but the burgeoning interest in osteogenesis imperfecta can do nothing but good.

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Familial hypercholesterolaemia: renewed interest in an old problem

Familial hypercholesterolaemia is an autosomal dominant disorder which was first described more than 100 years ago. It is distinguished from other causes of hyperlipidaemia by the typical cutaneous manifestations (xanthomas), a particularly high risk of premature cardiovascular disease, and a distribution in families compatible with the mode of inheritance. The xanthomas, nodules filled with cholesterol, are most classically seen in the extensor tendons at the back of the hands and in thickened Achilles tendons. The presence of xanthelasma and premature corneal arcus are suggestive but not diagnostic of the condition.¹

Untreated, the outlook is poor: half of all men suffering from familial hypercholesterolaemia may expect to die from coronary heart disease by the age of 60.² In the rare homozygous form symptoms of coronary heart disease may occur in childhood.

The condition results from a genetic deficiency of specific cell surface receptors normally responsible for removing cholesterol rich low density lipoprotein, and blood lipid analysis will usually show a substantially raised concentration of total cholesterol as a result of increased levels of low density lipoprotein cholesterol (in adults usually greater than 5 mmol/l) with other lipid and lipoprotein concentrations relatively normal.³ Familial hypercholesterolaemia may be diagnosed from cord blood at birth. On the basis of the number of known homozygotes, Slack has estimated a frequency of one in 500 in Britain, but in some other countries (for example, South Africans of Dutch origin) rates are believed to be substantially higher.⁴

In view of the fairly high frequency, the ominous prognosis in untreated sufferers, and the relative ease of diagnosis it is surprising that the condition has not aroused greater interest. This probably results from a failure by clinicians to appreciate how common the condition is and the lack of

evidence that treatment improves the outlook. Effective lowering of cholesterol by dietary modification and drug treatment can certainly reduce the size of the xanthomas. Recently the Lipid Research Clinics' much publicised trial of patients treated with cholestyramine (which included some with familial hypercholesterolaemia) has confirmed the circumstantial evidence suggesting that adequate lowering of cholesterol can produce an appreciable reduction in morbidity and mortality from cardiovascular disease.^{5,6} As a result of the trial cholestyramine is widely regarded as the drug of choice in patients resistant to dietary treatment (most of those with familial hypercholesterolaemia), but probucol, nicotinic acid, and bezafibrate have been used in the few patients not able to tolerate cholestyramine. These drugs have also been used in conjunction with cholestyramine when it alone has not produced adequate lowering of cholesterol. Ileal bypass surgery has been used with some success in a few specialist centres in patients resistant to drug treatment. Management of the rare homozygous form presents special problems reviewed in detail elsewhere.⁷ Against this background patients with familial hypercholesterolaemia have formed a new self help organisation—the Familial Hypercholesterolaemia Association—which aims to make the public and medical profession more aware of the condition, to inform and support those found to have familial hypercholesterolaemia, and to encourage further research into the cause and treatment of the condition. Its address is PO Box 612, London W2 2EE.

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Medical education and manpower in the European Economic Community

Without having anything quite like a common medical policy the European Economic Community has achieved a doctor mountain. What to do with it is a headache for all of those concerned, and that must potentially include Britain. We can scarcely plough doctors back into the ground or sell them cheap to the Russians. Nobody doubts that they could be helpful in the world, given the right opportunities for their use. So could butter and eggs and milk and, some might say, even wine. Cutting down their production will not make doctors go away; their very imperishability, as well as their social and economic value, intensifies the embarrassment of their overproduction.

While we are trying to decide whether Britain is itself training too many doctors (and our problem, if it exists at all,