more often have little immediate impact. This may be partly because of the equivocal results of many small trials. When investigators conduct small trials these should preferably follow common multicentre protocols. Small independent studies should also make their results available for the combined meta-analyses that are increasingly being done—for example, on using β blockers after myocardial infarction and within the collection of over 3000 perinatal randomised trials catalogued in the Oxford Database of Perinatal Trials. Publication of meta-analyses and reports of major national and international trials will all enhance the impact of randomised trials on medical practice. New initiatives are also being taken by some professional societies, such as the Royal College of Obstetricians and Gynaecologists, for training their members in designing and conducting trials.

General practitioners need to participate in controlled trials of new treatments as well as in postmarketing surveillance. This would further educate them and the public in the importance and necessity of clinical trials. It is in all our interests that there is wider recognition of the need for medical care and research to go hand in hand and that doctors and patients become partners in this enterprise. As the Lugano conference concluded, the most effective argument in favour of randomised clinical trials is that the alternative, practising in complacent uncertainty, is worse.

MICHAEL B BRACKEN
Professor of Epidemiology, Obstetrics and Gynaecology,
Yale University,
New Haven,
Connecticut 06510,
USA


Kawasaki’s disease
An unusual febrile exanthematous illness swept Japan in the early 1960s and spread worldwide in the next decade. Kawasaki described the salient features in 1967, and further descriptions of arterial, and particularly coronary arterial, manifestations followed. The disease had been described sporadically before and called the mucocutaneous lymph node syndrome because of lymphadenopathy, the exfoliative cutaneous eruption, and the lesions in the mouth. The disease has no specific predilection for people of Japanese descent and occurs in all ethnic groups, though possibly the incidence of coronary arterial lesions may be higher in Japan.

Kawasaki’s disease affects young children; it has not been described in neonates and is rarely seen for the first time in those over 5. Although superficially the disease resembles mercury intoxication, the aetiology is unknown; it does not seem to be directly transmissible from an affected child. The onset is abrupt with high fever, a non-specific rash, and general malaise. Appreciable conjunctivitis, dry cracked lips, and a “strawberry” tongue appear early, and the child has generalised, often tender, but predominantly cervical lymphadenopathy. A striking feature is the plantar and palmar erythema with oedema and subsequent desquamation, particularly of the periungual area, after seven days. The acute symptoms may last for a week or more before improvement as the temperature subsides. The notable features in laboratory tests are a high erythrocyte sedimentation rate (often 80-120 mm in the first hour) and thrombocythaemia.

Coronary artery abnormalities are reported in up to a quarter of those affected and are usually silent, although severe episodic chest pain, angina, and myocardial infarction together with sudden death have been reported. Nodal and enlargement of other arteries, particularly the brachial arteries, because of fusiform dilatation may be detected by palpation. Pericardial effusion may be present. Routine serial electrocardiograms, even without chest pain, may show persistent abnormalities of the ST segment and T waves or even the pattern of frank infarction.

Cross sectional echocardiography may show the fusiform dilatation on the right, left, or anterior descending coronary artery (the circumflex branch of the left coronary artery is rarely affected). The stenotic lesions, however, which tend to be multiple and of varying severity (including complete occlusion), can be shown only angiographically. Repeat coronary arteriography has shown a considerable capacity for all types of coronary arterial lesions to evolve. The aneurysms may regress, leaving a patent coronary artery or less favourably segmental stenosis. Most stenotic lesions also regress, leaving normal patency, but a few progress or are effectively bypassed by new vessel formation. New coronary lesions are unlikely after two weeks, and, although most regress to some extent within two months, a year or more may pass without objective change.

Bed rest is desirable in the initial stages but is not mandatory. Aspirin and other antiplatelet drugs have been used to reduce the thrombotic complications associated with thrombocytopenia, and low aspirin dosage is recommended (3-5 mg/kg/day as a single dose). Natural prostacyclin concentrations are, however, high, and high aspirin concentrations would be counterproductive. Purified human gammaglobulin is held to reduce the incidence of coronary arterial lesions given in high but not low doses.

Relapse is rare, but the initial course is occasionally protracted for several weeks. Recovery of myocardial function even after frank infarction is usually complete. The relation of the coronary arterial lesions to later coronary atherosclerosis is conjectural.

J F N TAYLOR
Consultant Paediatric Cardiologist,
Hospital for Sick Children,
London WC1N 3JH

1112

BRITISH MEDICAL JOURNAL
VOLUME 294
2 MAY 1987

http://www.bmj.com
The different forms of neurofibromatosis

The classic form of neurofibromatosis, as described by von Recklinghausen in 1882, is one of the commonest autosomal dominant disorders, affecting at least 20 of every 100 000 of the population. Medical fascination with the disease was reflected in the many reports of apparent disease complications that followed von Recklinghausen’s description. Yet only in the 1950s, with the publication of two large surveys of patients with the disease, did an overall picture of the range of associated features begin to emerge. In the past decade techniques have been applied to the disease; it has emerged that there are at least two distinct forms of neurofibromatosis, and there is a real possibility that the genetic mechanisms underlying them will soon be elucidated.

Von Recklinghausen (peripheral) neurofibromatosis accounts for over 90% of all cases. Its major defining features are multiple café au lait spots, peripheral neurofibromas, and Lisch nodules (pigmented iris hamartomas). The first of these to develop, usually within the first year of life, are multiple café au lait spots (six or more); and in two thirds of patients freckling in the axilla will later develop. Cutaneous neurofibromas begin to appear around the onset of puberty and increase in number throughout life. Lisch nodules, which are best seen by slit lamp examination, begin to appear in early childhood and were present in all the adult patients in one series. In children with only multiple café au lait spots and unaffected parents Lisch nodules are useful to confirm the diagnosis.

About one third of patients with the disease will develop one or more complications, and as their occurrence cannot be predicted even within families this aspect of the disease is the most distressing. In a recent population survey in south Wales the commonest complications were plexiform neurofibromas (found in 30% of patients, causing severe cosmetic disfigurement in 3%) and intellectual handicap (10% of the patients were attending or had required education in a special school and 18% in a remedial class). The incidence of malignancy (including tumours of the central nervous system) related to the disease among all family members over 18 and their deceased relatives was 6%. The other important complications were: neurological problems 10% (epilepsy, aqueduct stenosis, and spinal neurofibromas), scoliosis 5%, pseudoarthrosis 3%, gastrointestinal neurofibromas 2%, endocrine tumours 2%, and renal artery stenosis 2%.

Bilateral acoustic (central) neurofibromatosis is the other best defined form of the disease. Its inheritance is also autosomal dominant, and the main features are bilateral acoustic neoplasms in patients who have few, if any, cutaneous manifestations but who often have other tumours of the central nervous system, particularly meningiomas. The largest series of patients has been reviewed by Kanter et al, who found that 42% had one or more café au lait spots (but none more than five) and 19% one or more dermal neurofibromas. Lisch nodules are not seen in this form of neurofibromatosis. In other words, more patients than expected had minor cutaneous manifestations but none would satisfy the now accepted diagnostic criteria for von Recklinghausen neurofibromatosis. Only recently has this form of neurofibromatosis been recognised as a distinct entity: most earlier reports classified patients or families with this condition as having “von Recklinghausen’s disease.” The recognition of bilateral acoustic neurofibromatosis as a separate disease is important: its clinical and genetic implications are quite different from those of von Recklinghausen neurofibromatosis.

The biggest problems facing people with von Recklinghausen neurofibromatosis are the uncertainties of their disease: how severe will be the cosmetic disfigurement from cutaneous neurofibromas, and will a complication develop? Because the disease complications are so varied specialists may be present to many different specialists during their life and yet find no one doctor taking a wide view of the disease. Several centres in the United States now run neurofibromatosis clinics to overcome this problem. Frustration at the lack of such clinics and information about the disease in Britain led two parents of children with von Recklinghausen neurofibromatosis to form in 1981 the British neurofibromatosis patients’ association LINK (“Let’s Increase Neurofibromatosis Knowledge”).

In February of this year LINK sponsored the first European symposium on neurofibromatosis, which brought together doctors and scientists researching neurofibromatosis from the United States and Europe. Perhaps the most exciting aspect of the meeting was the report of the progress towards the mapping of the genes responsible for the two forms of neurofibromatosis.

Martuza and Seizinger presented their recent work on acoustic neuromas. Prompted by the commonness of meningiomas in the disease and the loss of chromosome 22 previously reported in cytogenetic investigations of meningioma, they compared genomic DNA from tumour tissue and corresponding lymphocytes using polymorphic DNA markers localised to chromosome 22 from patients with both isolated unilateral acoustic tumours and bilateral acoustic neurofibromatosis. In both groups of patients they have shown loss of genes on chromosome 22 in the tumour tissue, suggesting the existence of a locus on chromosome 22 involved in the development of both sporadic and inherited acoustic neoplasms. The pathogenesis of acoustic neurotumours therefore appears to be similar to that of Wilms tumour and retinoblastoma.

To localise the gene for von Recklinghausen neurofibromatosis several groups are now carrying out family linkage studies using polymorphic DNA markers. The results presented were all negative, but the symposium gave an opportunity for pooling data; the gene has already been excluded from some 50% of the genome. In particular, von Recklinghausen neurofibromatosis is not linked to the chromosome 22 markers that were altered in acoustic neuroma tumour tissue, suggesting that the two forms of neurofibromatosis are not only phenotypically but also genotypically distinct. The mapping of the genes for the different forms of neurofibromatosis will be an important step towards understanding their pathogenesis.