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Cure and survival in childhood cancer

Survival for five years after the diagnosis and treatment of malignant disease in childhood is often thought of as synonymous with cure. This was probably the case with the early successes, when the survivors were mostly confined to patients whose disease was localised at diagnosis and completely removed surgically, or whose residual disease was eradicated by radiotherapy or short courses of chemotherapy. What is the outcome with longer follow-up?

Li *et al*[1] have recently reported on the course of five-year survivors of childhood cancer in two large series, one from a group of co-operating institutions in the United States, and the other from patients treated at the Sidney Farber Cancer Institute. In the first study, 1807 patients from a total of 6153 diagnosed between 1950 and 1969 were alive five years later and in the second 425 out of 3631 (the lower proportion in the second series was due to excluding patients from analysis if they had not been referred to the institution within two months of diagnosis). In both groups roughly a further 10% died in the next five years, and the life table analyses showed projected survival of 83% and 79% respectively at 25 years—compared with an expected 97% in the general population. Clearly survival falls off after five years and continues to do so for a considerable time, and in these series the survival curve had not joined that of the general population at 25 years. Most of the deaths occurred in patients who had already suffered one relapse before entry to the study, and the chance of survival to 15 years in this group was only 54%, compared with 92% in those who were in their first remission. One-third of the patients who subsequently died had leukaemia. Five deaths were due to second primary neoplasms, and seven to the effects of anti-cancer treatment.

Throughout the 1970s the trend has been to use more intensive chemotherapy programmes and to combine them with radiation. More effective treatment has led to many more children being free of disease five years after diagnosis. We cannot yet ascertain whether these children are really cured or whether the time of relapse has merely been delayed. The data of Li and colleagues suggest that the risk of late recurrence is maximal between five and nine years, and if intensification of treatment is simply delaying relapse it seems likely to occur at that stage. Beyond ten years from diagnosis the more important causes of morbidity and mortality are second primary neoplasms and the effects of treatment.[2,3] The size of the problem of second primary tumours, both benign and malignant, is still unknown. One specific association is that with osteogenic sarcoma, both within and remote from the radiation field, in survivors of retinoblastoma; tumours of other types may also be commoner in these patients and their relatives, suggesting a genetic predisposition to the development of malignancy. The second largest group of long-term survivors in the series described by Li *et al* was made up of children with nephroblastoma—the most common primary tumour in children who developed second tumours in Meadows's report.[2]

The frequency of second primary tumours in retinoblastoma and nephroblastoma may reflect the higher rates of survival in these groups, genetic predisposition, or the direct effects of treatment. Clearly data on long-term survivors must be based on treatments that are to some extent outdated. Nevertheless, the findings by Li *et al* show the need for careful follow-up of all long-term survivors of malignant disease in childhood.

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Poisoning and enuresis

"He still wets the bed, doctor." Too often this afterthought, produced as the mother is leaving the consulting room, induces a reflex stretching of the hand to the prescription pad for a tricyclic antidepressant. Use of the word *enuresis* has raised bed-wetting to the status of a disease that requires a drug to cure it—when in fact in most cases the child is normal.

About half of children are dry at night by the age of 2, 75% by 3, and 90% by 5 years. The annual spontaneous cure rate after five years is 14%.[1] If the child is less than 5 years old excluding physical disease by examination of the urine for sugar, albumin, and infection and explaining the range of normality should be enough to satisfy the parents, and often is. Treatment is indicated only in older children, and the choice lies between incentive schemes using tokens such as coloured paper stars, a buzzer-and-pad waking device, or a tricyclic antidepressant. The waking device produces a long-term cure in 80% of children,[2] but an antidepressant will suppress wetting completely in only about 30%,[3] and within three months of stopping treatment many will be wet again.[3] This high relapse rate is acknowledged by one of the manufacturers of antidepressants, who provides free books of stars for use with its drugs.

Why are buzzers not used more frequently? Large numbers are available for loan in paediatric outpatient clinics, and many school clinics have a supply. District supplies officers can be persuaded to hold a stock, but doctors find it easier to write a prescription for an antidepressant than to persuade an administrator to buy, supply, and service the equipment. If antidepressants were completely safe their low success rate

might be acceptable. On page 722 a report shows that these drugs are potentially lethal: they are now the commonest cause of fatal poisoning in children under the age of 5 years. Young children should not, we believe, be given antidepressant treatment for enuresis. If such treatment is prescribed the child should be old enough to take tablets—reducing the risks of his developing an irrepressible liking for the tasty elixir and so taking an overdose. When antidepressants are prescribed for adults with depression they are used for treating a potentially fatal disease, as the mortality rate from suicide is high. Every year a score of doctors probably regret writing a lethal paediatric prescription for a benign condition which usually resolves spontaneously.

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Back pain—what can we offer?

Low back pain is a major cause of disability, and the second most common cause of loss of work (after chronic bronchitis).

Broadly, the causes of pain in the back can be classified as structural, inflammatory, neoplastic, metabolic, and referred from abdominal or pelvic lesions. Usually the first line of inquiry is into the structural causes, and a definitive diagnosis is often possible—such as a prolapsed intervertebral disc, spondylolisthesis, or a fracture. Frequently, however, radiographs show degenerative changes, and the symptoms can rarely be ascribed to these lesions with any certainty. In three population surveys[1] covering a total of 1702 men and women low back pain was found in 59% of those with radiological evidence of degeneration of the lumbar disc and in 47% of those without. Clearly, therefore, in many individual patients no structural abnormality can be defined as being responsible for the symptoms. These patients are better labelled as having "non-specific back pain" rather than being given pathologically unfounded diagnoses such as "sacroiliac strain."

Suspicion that the cause of back pain is something other than a structural lesion usually arises after taking a careful history and physical examination. For example, ankylosing spondylitis should be suspected in any younger patient with an insidious onset of persistent low back pain, appreciable morning stiffness, and relief by exercise. A forme fruste of ankylosing spondylitis, in which there is no radiological sacroiliitis, is far more common than has been appreciated. This increased awareness is based on recognition of the association of ankylosing spondylitis with tissue type HLA-B27, which occurs in about 7% of the normal population. Surveys have shown that as many as one-fifth of individuals with HLA-B27 develop at least mild forms of the disease.[2] Clearly, however, at least 80% of persons with HLA-B27 will not develop ankylosing spondylitis, so that the test by itself is of more value for excluding rather than making the diagnosis. Other inflammatory causes of pain in the back include rheumatoid arthritis affecting the lumbar spine[3] and infective lesions. Neoplasms, including the reticuloses, may cause an insidious and progressive increase in symptoms and eventually neurological signs. Referred pains are usually associated with appropriate abdominal or pelvic symptoms and signs and do not cause limitation of spinal movement.

What laboratory tests are justified at the initial assessment of any patient with backache? The simpler screening tests include the erythrocyte sedimentation rate (which is abnormal in inflammatory and neoplastic disease); serum concentrations of calcium, phosphate, and alkaline phosphatase (which may indicate metabolic bone disease or neoplasia) and of acid phosphatase in men (for prostatic carcinoma); and measuring the plasma proteins, with electrophoresis (for myelomatosis).

Should the spine always be investigated radiologically to exclude the more serious causes of back pain in the absence of clinical pointers? In a survey[4] of patients with back pain referred to a rheumatology clinic at the London Hospital in no case did routine lumbar radiographs indicate such diagnoses when there was no clue from the clinical findings. The London authors doubted the value of routine *x*-ray films of the lumbar spine in the absence of more specific clinical indications. If their advice were widely followed the NHS would be saved many thousands of pounds every week.

When the initial assessment suggests that the pain is due to one of the structural causes, management of the patient is mainly based on the severity of his symptoms rather than on the defined cause. When the pain is severe treatment should consist of analgesia and rest lying flat on a properly supported bed. In most patients the symptoms will resolve within a few days or a week or two. For those who suffer continual or recurrent problems more complex treatments include traction, mobilising exercises, extension exercises, short-wave diathermy, mobilisation and manipulation, and various forms of spinal support. The value of most of these is unproved, but in one recent trial mobilisation and manipulation significantly hastened the resolution of symptoms in those likely to get better anyway, though making no difference to the long-term prognosis.[5] Postural and ergonomic advice is always important, and indeed when given in a formal way in a back pain school may be as useful as conventional physiotherapy.[6] Surgery is indicated only rarely and when a remediable lesion has been defined.

Most attacks of back pain will resolve sooner or later, but unfortunately the recurrence rate is high. Attempts to relate the prognosis to the presenting features have been disappointing: the only consistent correlate has been that on the whole patients with shorter lengths of history of pain do better than those with longer histories. In particular, analysis of radiographs gives no clue to the prognosis[4 5]—another reason for questioning their routine use. The way forward should come from greater accuracy in identifying the lesion causing pain in the individual patient. Only then will we be able to define the indications for the various forms of treatment.

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