immense. The element of fear raised by an equivocal or false result might cause severe anxiety in all but a few stoics and the exercise would make no sense either medically or economically. The way ahead must surely lie in improving the methods used in our tests, striving all the time towards greater sensitivity —a long and expensive business.

[1] Dawber, T R, *et al*, *American Journal of Public Health*, 1951, **41**, 279.
[2] Williams, R R, *et al*, *Journal of the National Cancer Institute*, 1977, **58**, 1547.
[3] Munro Neville, A, and Cooper, E H, *Annals of Clinical Biochemistry*, 1976, **13**, 283.
[4] Franchimont, P, and Zangerle, P F, *European Journal of Cancer*, 1977, **13**, 637.

Exercise-induced asthma

Heightened bronchial reactivity provides good laboratory evidence of asthma, and exercise is well known to trigger attacks. Nevertheless, in contrast to allergens, exercise is a non-specific trigger and may operate in most asthmatic patients. An odd aspect of exercise-induced asthma is that it is most readily produced by level running for about five minutes, whereas a brief burst of heavy exercise seldom produces such asthma. Patients can also run through their asthma, so that if they sustain exercise much beyond 10 minutes the stimulus wanes. This is probably why patients with asthma often do not identify exercise as an important cause of their symptoms, for few are likely to take steady state exercise of sufficient length and intensity to generate obvious asthmatic attacks.

The usual pattern is that the exercise itself produces some bronchodilatation, quickly succeeded by increasingly severe airway narrowing once exercise ceases.[1 2] Another odd thing is that the type of exercise is important. For similar levels of work (as judged by oxygen consumption) swimming is a very weak stimulus for asthma compared with sustained running on the flat. Between these extremes come cycling and downhill running.

When diligently sought the existence of exercise-induced asthma can be shown in most asthmatic patients, and this applies particularly to children. Godfrey found that in over 90% of asthmatic children airway narrowing could be shown after exercise if the few initial non-responders were tested again. The test itself is reasonably repeatable, and if a sufficient interval is left between tests asthma can be produced time and again. Its high frequency in asthmatic children may make it suitable as a marker for prevalence studies of asthma.

The important clinical use of exercise-induced asthma is in diagnosis. This is particularly true of patients, especially children, whose symptoms occur almost entirely at night and in whom lung function seems normal during the day. In these circumstances the patient can be asked to run for four to six minutes on the flat; the peak expiratory flow rate is then measured before and up to 15 minutes after exercise has ceased. A fall of over 10% is found in asthma.[3] As the asthmatic attack may occasionally be severe, the test should not be done in the presence of airways obstruction, when asthma may be diagnosed by observing improvement in the peak expiratory rate in response to treatment.

The cause of exercise-induced asthma is poorly understood, but the delayed appearance of airway narrowing after the end of the exercise, coupled with the refractory period of over two hours before susceptibility to this type of asthma is restored, has suggested that the mechanism may be release of mediators.[4] Probably during exercise sympathetic drive opposes and usually exceeds mediator release, and this accounts for the bronchodilatation observed. The underlying cause of the postulated release of chemical mediators is still unknown, however, and the evidence is largely negative: likely candidates such as Pco_2, hyperventilation, pH, and whole-body vibration have all been excluded. Nevertheless, the hypothesis is further supported by the effect on exercise-induced asthma of chemicals known to decrease or abolish mediator release. For example, sodium cromoglycate can often prevent it, and in some patients other bronchodilators such as atropine and beta-adrenergic agonists may have a similar action. Indeed, the highly effective role of beta-sympathomimetic bronchodilators such as salbutamol in preventing exercise-induced asthma hints that their action and value in asthma does not depend solely on their bronchodilator activity.[5] A recent study has also shown that, though both drugs are usually effective, in some patients atropine may prevent exercise-induced asthma when sodium cromoglycate is ineffective, whereas in other patients the effect is the opposite, with sodium cromoglycate active and not atropine.[6] Clearly there may be several mechanisms for both asthma and mediator release itself. To this confusion may be added the observation that corticosteroids usually do not prevent exercise-induced asthma—but that is only part of the larger puzzle of how they act at all in the treatment of asthma. Sadly, pharmacological measures useful in controlling exercise-induced asthma in an individual patient do not always work in controlling his asthmatic attacks, limiting the value of the test in identifying the best treatment and its dose.

Even so, exercise-induced asthma is more than a matter of pharmacological and physiological curiosity. It helps in the diagnosis of asthma, it is occasionally a major source of symptoms, and its management may provide clues to the pathogenesis of asthma itself. The full story has yet to be told, but we already have sufficient information to help clinicians act rationally and to good effect.

[1] Godfrey, S, *Exercise testing in children: Applications in Health and Disease*. London, Saunders, 1974.
[2] Jones, R S, Buston, M H, and Wharton, M J, *British Journal of Diseases of the Chest*, 1962, **56**, 78.
[3] Godfrey, S, in *Asthma*, eds T J H Clark and S Godfrey. London, Chapman and Hall, 1977.
[4] McNeill, R S, *et al*, *Quarterly Journal of Medicine*, 1966, **35**, 55.
[5] Hetzel, M R, Batten, J C, and Clark, T J H, *British Journal of Diseases of the Chest*, 1977, **71**, 109.
[6] Chan-Yeung, M, *Chest*, 1977, **71**, 320.

Does radiation of the young brain affect growth hormone?

When children are given radiotherapy for brain tumours that cannot be removed completely it may be best to irradiate the spine as well as the brain. This deals with any seeding of tumour cells in the cerebrospinal fluid, such as may occur in medulloblastoma or poorly differentiated ependymoma. The same technique may be used in patients with leukaemia to treat or avert any spread to the central nervous system. Since, however, radiation directly affects the growing bone in the

young spine the height these patients reach in adult life may then be reduced. The reported incidence of growth impairment varies,[1 2] perhaps because of differences in dosage and technique. Children under the age of 2 (not an uncommon time for these tumours to occur) are especially at risk. Growth may also be significantly impaired if radiation coincides with the normal growth spurt at puberty.

Reduced height from the effects of spinal radiation can be distinguished from a generalised reduction in growth such as might be caused by lack of growth hormone if the sitting height as well as the standing height are measured (as should be done routinely). Indeed, does radiotherapy to the brain impair the output of pituitary growth hormone? Until recently we had no evidence of such an effect, even when the pituitary and hypothalamus were situated in the high-dose region,[3] and even now we cannot be sure that the radiotherapy is responsible for the changes. Other possible causes include raised intracranial pressure (or other tumour effects) before diagnosis; the use of large doses of corticosteroids to reduce such pressure; the possible effects of brain surgery; and now the increasing use of postoperative cytotoxic chemotherapy. Nevertheless, the findings in two recent reports are of interest.[4 5] Both groups carried out endocrine assessment on patients (some of them children, some adults) who had received radiotherapy for brain tumours, usually in childhood. In Manchester[4] 10 out of 27 patients had apparently abnormal growth-hormone response tests; in Guildford[5] 11 out of 15. In both groups there was little evidence of any other impairment of endocrine function.

Unfortunately, in neither paper was there any information about the dose of radiation to the pituitary and hypothalamic region. Any study of possible radiation effects should include estimates of the dose absorbed at different points. Lack of any dose-dependent relationship weakens the case against radiation. The Manchester workers[4] implied that all patients received radiation to the whole brain, presumably including the pituitary gland, but said nothing about dosage. The Guildford authors[5] divided their cases into two groups: those with a tumour in the pituitary-hypothalamic region, and those with "remote" tumours. Details of the dose given to the tumour and the beam sizes used were given, but the possibility or probability of radiation reaching the hypothalamus or pituitary and, if so, at precisely what dosage was not discussed.

A moderate dose of radiotherapy, insufficient to cause any damage to normal tissues, will frequently reduce overactivity in the pituitary gland (as when acromegaly is treated without surgery). But the normal gland is unlikely to be affected by quite high doses of radiation (5-6000 rads), as used, for example, for treating carcinoma of the nasopharynx.[6] Occasional exceptions have been reported, however,[7] and clearly further studies are needed to answer the important question whether children receiving radiation to another part of the brain, with little or no radiation to the hypothalamic-pituitary region, show impairment of growth hormone response (or any other endocrine abnormality).

In the absence of any clinical effects (other than an occasional slight reduction in height) evidence of impaired growth hormone response might be of little more than academic interest. On the other hand, if children's growth was substantially impaired after irradiation of brain tumours, and if this were shown to be due partly or wholly to an endocrine effect, then—whatever the precise cause might be—the matter would be by no means academic. Giving growth hormone replacement therapy (preferably only under Medical Research Council supervision) might prevent impairment of growth.

[1] Probert, J C, Parker, B R, and Kaplan, H S, *Cancer*, 1973, **32**, 634.
[2] Bloom, H J G, Wallace, E N, and Henk, J M, *American Journal of Roentgenology*, 1969, **105**, 43.
[3] Bouchard, J, *Radiation Therapy of Tumours and Diseases of the Nervous System*. London, Kimpton, 1966.
[4] Shalet, S M, *et al*, *Lancet*, 1975, **2**, 104.
[5] Harrop, J S, *et al*, *Clinical Endocrinology*, 1976, **5**, 313.
[6] Schryver, A, de Ljunggren, J G, and Baryd, I, *Acta Radiologica; Therapy, Physics, Biology*, 1973, **12**, 497.
[7] Larkins, R G, and Martin, F I, *British Medical Journal*, 1973, **1**, 152.

Death from ischaemic heart disease

Mortality data published by the Registrar General for England and Wales show that among people aged 30-75 the total death rate has declined during the past 25 years in both sexes and at all age groups. This decline has been accompanied by changes in the pattern of causes of death, and in particular the proportion of deaths attributed to heart disease has risen sharply. For example, among men aged 45-49 heart disease accounted for 20% of deaths in 1951 and 40% of deaths in 1971.

The description of ischaemic heart disease as a modern epidemic is mainly based on mortality trends. Yet interpreting these trends is beset by difficulties. One of these is that reported mortality rates may rise merely because of an increased awareness of a disease, so that the diagnosis is transferred from one disease category to another. Another is that mortality rates may be influenced by the periodic changes made to the International Classification of Diseases used to code death certificate data. To counter these objections to using mortality data as an indicator of the incidence of ischaemic heart disease, we must therefore look closely at the several diagnostic categories into which these deaths may be coded.

Clayton, Taylor, and Shaper[1] have recently examined in detail death rates from 35 to 64—a time of life when death from ischaemic heart disease might reasonably be regarded as premature—between 1950 and 1973. In that time the International Classification of Diseases was revised twice: the seventh revision in 1958 contained no important changes in coding heart disease, but the next revision in 1968 did. All deaths occurring in 1967 were coded according to both the seventh and eighth revisions so that the equivalence of new and old diagnostic categories could be established.

From 1950 to 1967 deaths attributed to arteriosclerotic heart disease increased sharply, more than doubling in the younger age groups in both sexes. In contrast, during the same period deaths coded as "other myocardial degeneration," an entity which lacks a specific clinical or pathological description, fell by 75%. Deaths attributed to hypertensive heart disease fell by a similar amount. Clayton *et al* concluded that changing diagnostic fashions had resulted in a transfer of deaths from "other myocardial degeneration" to arteriosclerotic heart disease. They also attributed at least part of the decline in hypertensive heart disease to a change in diagnostic fashion, for it seems unlikely[2] that treatment of hypertension has been a major influence in the decline. They therefore combined the three disease categories to give the most conservative estimate of the increase in mortality from ischaemic heart disease, and continued the trends into the period of the eighth revision by using the equivalent diagnostic categories "ischaemic heart disease," "other myocardial insufficiency," and "hypertensive disease."