improvement in forced expiratory volume both before and after treatment with bronchodilators (p < 0.001) was seen in the group treated with methylprednisolone.

Several mechanisms might account for the improvement in lung function seen with the corticosteroid. Suppression of the inflammatory response could have reduced airflow obstruction. Beta-adrenergic-receptor responsiveness might have increased, or the steroid-induced erythema might have resulted in an increased respiratory effort. Corticosteroids given by mouth also have these properties, and so may be useful additional treatment for patients with chronic bronchitis and intractable symptoms of cough and dyspnoea which persist despite aggressive physiotherapy and bronchodilators.

The rational approach to treating chronic bronchitis is to attempt to achieve maximum reversibility of airways obstruction with bronchodilators and physiotherapy. If this fails to produce stabilisation or improvement a “trial of steroids” may be undertaken. Many physicians are reluctant to prescribe steroids for chronic bronchitis because of the complications associated with this treatment. Since, however, complications relate more to dosage than duration of treatment, a suitable regimen for a trial of steroids is oral prednisolone 25-30 mg daily for two to four weeks. This allows time for a response to develop and should not produce undesirable side effects. Regular objective measurements in the form of spirometry with and without bronchodilators and estimation of arterial gas tensions should be made throughout the trial. If improvement is shown to occur on objective tests, the dosage should be tapered to the lowest level that maintains that improvement. Lack of objective response is a clear indication that treatment should be stopped. Though the result of the work by Albert et al. is encouraging, the decision to undertake a trial of steroids should be made not indiscriminately but on an individual basis.


Radiosensitisers

The radiosensitivity of mammalian cells can be modified by changes in intracellular oxygen tension in vivo and in vitro. Cells that are severely hypoxic are up to three times less susceptible to radiation damage than those that are well oxygenated. Many human tumours have features such as areas of necrosis, large intercapillary distances, and arteriovenous abnormalities, all of which will contribute to a group of cells that are hypoxic yet have the potentiality of growth. Attempts have been made to estimate the effect of this com-

tponent, but its importance to the radioresponsiveness of any human tumour is still unknown. In clinical radiotherapy practice fractionation of dosage was used empirically long before studies of the effects of hypoxia in plant and mammalian cells; this fractionation probably permits some re-oxygenation of initially hypoxic cells, with cell death and loss initially occurring from the oxygenated compartment.

Given the poor response of many tumours to radiation, despite refinement of techniques using conventional sources of radiotherapy, several approaches have been used to try to enhance the radiosensitivity of tumours while not modifying the amount of damage caused to normal tissues. Three main tactics have been considered: hyperbaric oxygen to increase the oxygen tension in tumour cells during irradiation; use of particles of high linear transfer energy such as fast neutrons; and radiosensitisers.

The results of using hyperbaric oxygen have proved disappointing. Even with unusual fractionation schedules, irradiation of patients within a hyperbaric chamber at three atmospheres pressure has not been associated with a major increase in tumour control rates. The sources of neutrons are few and expensive: clinical trials of the effects of fast neutrons derived from a cyclotron continue in the MRC units at the Hammersmith Hospital and at the Western Infirmary at Edinburgh. In animals hypoxia has been shown to give less protection from the damage caused by neutrons than from conventional photon beams, but in man the benefits conferred by neutron irradiation have not yet been assessed adequately.

Attempts to find a potent and inexpensive chemical sensitisier have led to many different compounds undergoing limited clinical trial, including vitamin K, chemotherapeutic agents such as razoxane (ICRF 159), and, more recently, the nitrimidazoles. These last show high electron affinity, a feature of selective hypoxic cell sensitisers. They can substitute for oxygen: thus they diminish the radioresistance conferred by hypoxia, and do not enhance the radiosensitivity of cells with a normal oxygen tension.

Misonidazole was studied very briefly, but has given way to misondazole (Ro-07-0582), a compound with greater clinical potential. This drug is stable, not metabolised by cells, and can diffuse into areas of hypoxia. It needs to be present during irradiation to sensitize the cells, which seems to be dependent on the intracellular concentration achieved.1 The clinical limits are set by damage to the nervous system, which is dose-related. Like metronidazole, in large doses misonidazole induces nausea and vomiting;2 repeated high doses may cause convulsions, while lower doses may cause peripheral neuropathy. Though treatment with hepatic enzyme inducers such as phenytoin and phenobarbitone may reduce the half life of misonidazole, neurotoxicity limits the dose that can be used.

Misonidazole has been used in limited clinical trials in treating adult gliomas, some head and neck tumours, and a few cases of carcinoma of the uterine cervix. These preliminary studies suggest that this particular compound is unlikely to have great clinical efficacy, though much wider evaluation will be needed. Newer drugs in this group, with less neurotoxicity but comparable ability to sensitize hypoxic cells, are being studied in animals, and a more useful sensitiser seems likely to emerge.

While clinical trials may have modified earlier, highly optimistic expectations for the radiosensitisers, interest remains, for they combine ready availability with low price and only partially explored potential. Their weak cytostatic
action has led to the suggestion that a place may exist for their use in combination with anticancer drugs.4 Certainly many tumours have hypoxic areas with cells poorly accessible to drugs and of low mitotic activity; in such cases environmental modification might well affect responses to treatment.


Yaws again

“There is now little clinical interest in yaws and opportunities for the study of its pathology are already probably extinct.” This statement1 by an acknowledged authority seemed true in 1967, but yaws is now returning in several countries from which it had disappeared after the successful campaigns by WHO and UNICEF.2 A timely reminder of the widespread suffering caused by yaws, and of the vociferous welcome accorded by its victims to the doctors whose injections of arsenic and bismuth made the multiple raspberry-like protuberances disappear as if by magic, is provided by a recent article in Tropical Doctor.3 Another recent publication is a book placing yaws in its historical context in pathology in Africa.4 Hackett’s account5 should send readers to their neglected textbooks of tropical medicine6 8 to read of the clinical presentations of a disease likely to increase in prevalence.

Skin departments in Western hospitals are unlikely to witness an influx of patients suffering from the florid lesions of early yaws, yet the late manifestations may pose problems of differential diagnosis7 8 in patients from countries where the disease has been, or will probably be, common.

The reappearance of yaws may reopen unresolved debates about the relations between yaws and non-venereal syphilis9 10 and also between such non-venereal infections as bejel, njorera, dichuchwa, and sibbens11 ("the Scottish yaws"), and South American pinta, caused by Spirochaeta carateum. Perhaps the newer medical schools in Nigeria, Malaysia, Fiji, and Brazil will rise to the challenge and investigate afresh such problems as subclinical infections, latency, the influence of environmental factors on clinical patterns, the significance of returning or persisting serological changes, and the nature and degree of cross-immunity.

Yaws was (and is again) a disease mainly affecting sparsely clothed children living in rural areas of high temperature and high humidity within the tropics. Infection is by direct inoculation of the causative organism, Sp. pertenue, through the abraded skin, perhaps deposited by a sucking fly. After an incubation period of a few weeks the initial lesion (“the mother yaw”) appears at the site of inoculation: this may be an exudative papilloma, or a group of dry papules, or a localised maculopapular rash.

Within a few weeks a more generalised rash consisting of scores of excrescences makes its appearance, each element being covered with a yellowish film replete with the organisms. The general health may be but little affected, but the picture of unrelied misery cannot be forgotten. During the next five years further polymorphic rashes appear from time to time—annular, circinate, serpiginous, or corymbiform—interspersed with periods of quiescence. In warm, moist sites they tend to be condlamotous. The palmar and plantar skin may become hyperkeratotic and fissured, and infective lesions may arise in the fissures. In the long bones there may be osteitis and periostitis.12

After these periods of clinical activity the lesions usually resolve spontaneously. Next comes a silent phase before the appearance of late lesions, such as hyperkeratotic plaques, rupia-like or gummatous skin ulcerations, osteitis (sometimes with the production of “sabre tibia”), destructive ulceration of the nose (gangosa), hypertrophic osteitis of the facial bones (goumdou), and scarring and cicatricial contractions. Juxta-articular nodules,13 deposition of typical treponemal distribution,14 considerable hyperkeratosis of palms12 and soles (“crab yaws”) are frequent sequels, with prepatellar bursitis and ganglion. When ainhum occurs in the young, framboesial plantar hyperkeratosis may be an aetiological factor.15 Many of these protean manifestations have their counterparts in other treponematoses, and their clinical differentiation is not usually helped by serological tests.17

The treatment of active yaws, early and late, was simplified18 when the old remedies (rubbing the ulcers with “bluestone” (copper sulphate) or intravenous arsenic and intramuscular bismuth subgallate or salicylate) gave place to a single intramuscular injection of 12 MU of penicillin G in oil gelled 2%, aluminium monostearate. This treatment cured the florid lesions of early yaws with dramatic rapidity and prevented relapse for at least two years. Where whole populations were considered to be contacts, half doses were given to all persons without lesions.

But all the early hopes of eradication founded because of inadequate facilities for effective follow-up, the potential infectivity of late lesions, and the lack of precision in the definition of radical cure.3 A single infectious relapse may become the index case of a localised epidemic of old-time florid yaws: such foci are now appearing in areas where eradication campaigns appeared to have been successful.