Management of Late Hodgkin's Disease

The best treatment for Hodgkin's disease limited to one side of the diaphragm is large field radiotherapy. There is less agreement about the management of the later stages. Most patients in stage III (disease on both sides of the diaphragm but limited to lymph nodes, spleen, and Waldeyer's ring) will at some time have treatment both by radiotherapy and by chemotherapy. Which is the better primary treatment?

Nowadays radiotherapy has become increasingly aggressive in the later stages of the disease, and a substantial dosage is commonly given to lymph nodes in all the standard regions. In order to allow for recovery of the marrow between courses the programme must often be extended over three months or more, though the patient may be under active treatment for only half this period. The time taken for this treatment is generally considered justified if it leads to a more prolonged and better quality remission than could be obtained with shorter courses of radiotherapy using lighter dosage.

In terms of aggressiveness, chemotherapy has not lagged behind radiotherapy. The results of treatment with the alkylating agents, though often dramatic, tend to be of brief duration; D. A. Karnofsky and his colleagues, for example, quote six to ten weeks as the average period of improvement after a single course of mustine. J. L. Scott has claimed that the duration of remission can be extended by maintenance therapy with chlorambucil, and this concept is certainly appealing enough to be put into wide clinical practice (commonly, however, using a maintenance regimen throughout, with drugs such as vinblastine by weekly injections or chlorambucil, cyclophosphamide, or procarbazine without initial intravenous loading). In the past 11 years the alkylating agents have been joined by vinblastine and procarbazine, drugs whose mode of action is sufficiently different from the alkylating agents and from each other for there to be no apparent cross resistance. They seem to be effective in about 60% of patients and to produce remissions of the same order of quality and duration as that produced by alkylating agents. A few years ago it seemed that the next step would be to determine the optimum order to give these agents, and a few attempts were made to do this.

The emphasis has now moved over to combination treatments. The impetus undoubtedly came from the successes achieved in the palliation of acute leukaemia by multi-drug regimens. P. P. Carbone initiated the present surge of interest, and the paper on page 7 by W. M. Nicholson and his colleagues is the first substantial British contribution on the subject. Carbone suggested a combination of prednisone, procarbazine, mustine, and vincristine to be given in 14-day courses interspersed with rest periods of at least 14 days. On this regimen he claimed 80% complete with an additional 10% of partial remissions in previously untreated patients. He and his colleagues also claimed the duration of unmaintained remission to be in excess of ten months. Nicholson and his colleagues have modified Carbone's regimen by substituting vinblastine for vincristine, thus gaining the greater specific effect of the former drug and avoiding the marked neurotoxicity of vincristine, though having to accept a greater risk of marrow depression. Their results in the previously untreated patients and in those who had had previous radiotherapy are very much in agreement with those of Carbone. They also show that the combination treatment is much less effective and more toxic in those who have already been given chemotherapy. The superiority of combination chemotherapy over the more conventional sequential chemotherapy should not, however, be accepted unreservedly. A trial of these two approaches would be valuable, perhaps drawing on those patients who have developed more general features after radiotherapy for early disease.

The prime concern in the palliation of malignant disease is relief of symptoms. Prolongation of survival must go hand-in-hand with improvement in the quality of living if it is to be registered as a gain. Thus ideally there should be a minimum of toxic effects from the treatment coupled with a maximum period of normal living (at home). Combination chemotherapy is designed to reduce toxicity to an acceptable level and at the same time to avoid unnecessary admission to hospital and so fulfills these criteria. The Kaplan type of approach to radiotherapy is now well established and undoubtedly effective, but it does have the disadvantage of requiring periods of hospital treatment extending over many weeks. As Nicholson and his colleagues suggest, a controlled trial is needed of these two approaches to the primary treatment of stage III disease. Since, however, Hodgkin's is such a complex disease—with many factors such as age, sex, and pathological classification, apart from the treatment, affecting the prognosis—such a trial must be arranged with careful stratification and many patients. At least one such multi-institutional trial is under way in Europe, including Britain.

Infantine Gastroenteritis

Infants should not be regarded as desperately ill simply because they have been admitted to hospital. The anxiety of a young mother because her infant is slightly off colour, the concern of a careful doctor who knows that an infant with a mild upset may rapidly become seriously ill, or poor home conditions may be more frequent causes for an infant's admission to hospital than its clinical condition. This is often the case with babies with gastroenteritis, especially in those under 3 months old, when maternal anxiety and medical concern are very understandable—as shown this week at page 20 by A. G. Ironside and his colleagues in a study of 339 cases of infantile gastroenteritis.

Infants do not die from gastroenteritis unless they become...
dehydrated. The cure of the illness lies, therefore, in the prevention or treatment of dehydration—usually a simple matter. In 329 of the 339 cases reported by Ironside and his colleagues fluids were given by mouth, and only 10 required intravenous fluids. The fluids must be chosen and administered with care, and it must be emphasized that the treatment of an infant with marked dehydration is a severe therapeutic challenge. Gastroenteritis varies in severity in time and place, and in some outbreaks there is a much higher incidence of severe dehydration than in the present series. Nevertheless, when an infant is rehydrated it is on the way to recovery, and, except for the occasional relapse, is soon on its full diet and fit for discharge. Is anything else required?

No doctor should give a patient a drug unless he has a clear and precise reason for doing so. In the treatment of infantile gastroenteritis antibiotics should certainly not be prescribed unless a pathogen sensitive to the antibiotic is isolated. Such a pathogen was isolated in only 56 of the 339 cases (16%) in Ironside’s series, an incidence which is probably typical of sporadic cases in Britain today. In most hospitals the results of faecal culture are not available in less than 24 hours, but in that time most infants, even those requiring intravenous rehydration, are recovering. Can an antibiotic given at this stage do the individual infant any good? Any doctor who thinks it can ought to be able to say exactly what improvement he expects, and he should also be able to show that the antibiotic cannot possibly do the infant any harm. Perhaps some doctors can do both, but many would hesitate to make either claim. When an infant fails to improve in spite of successful rehydration septicaemia may be present, and an absorbable antibiotic is then indicated, but most infants respond to rehydration, and antibiotics have no obvious place as far as clinical cure in concerned.

There remains the problem of cross-infection. An infant with gastroenteritis is certainly infectious. Its stools are teeming with the infectious agent, and within a few hours of its admission every square inch of its environment can be heavily contaminated. But even the most motile micro-organism moves at a microscopical pace and would probably require a century to get from one cubicle to another on its own. It must be transported there, wafted on air currents, swept along in dust, or carried on hands, and only by the most painstaking attention to the details of barrier or cubicle nursing can one hope to stop its passage. The administration of an antibiotic to the infectious infant 24 hours after admission will not stop the spread of pathogens already shed. It may not even stop the excretion of pathogens in the infant’s stool, although even without antibiotics the numbers shed drop rapidly as stools become more formed. In the infants treated with antibiotics by Ironside and his colleagues 25%, were still excreting the pathogen when discharged from hospital. This is not an unusual bacteriological failure rate, and it is surely high enough, with organisms as infectious for infants as Escherichia coli, to disturb anyone’s faith in antibiotics as epidemiological weapons.

In an explosive outbreak of severe gastroenteritis in an infants’ ward or nursery there is no need to wait for faecal cultures in every case once the epidemic strain is known. To that extent the situation is different, and if one decides to use an antibiotic it can be given from the onset of symptoms. All kinds of pressure other than clinical or bacteriological may be brought to bear on the doctor to use an antibiotic, and no one would criticise a doctor who decides to do so under such circumstances, but the treatment of these ill infants is rehydration, and the doctor trying to control the outbreak will be wise to regard the use of antibiotics as of very secondary importance to the ruthless application of administrative and physical means of tackling the spread of infection. If the strain of Escherichia coli is resistant to antibiotics it is nonsensical to use them, and there have already been outbreaks in Britain where the strain was resistant to all available antibiotics. Such resistance can be transferable, and every time an antibiotic is used the possibility of creating more transferable drug resistance must be borne in mind.

The indiscriminate use of antibiotics is a form of environmental pollution, and in an environment already polluted with micro-organisms it is doubly dangerous. Most infants with gastroenteritis get better without antibiotics, and in hospitals where the detailed technique of barrier nursing is understood and applied the spread of the disease can be controlled. When control breaks down and disaster threatens there may be a place for antibiotics as a possible aid in eradicating infection at its source, but it is a doubtful role. In the routine treatment of the disease antibiotics have no place and should not be prescribed.

Androgenic Function and Impotence

Impotence may be defined as the persistent inability to develop or maintain a penile erection sufficient to conclude coitus to orgasm and ejaculation. The condition may result from organic pituitary-hypothalamic or testicular disease, though it is uncommon for patients with such disorders to present with a complaint of impotence. It may also complicate severe depressive illnesses and schizophrenias or be due to treatment with certain antihypertensive agents or phenothiazines. In the vast majority of impotent patients, however, none of these factors can be implicated, and their disability has usually been assumed to be of psychogenic origin.

This week at page 17, Dr. Alan Cooper and his colleagues report the results of a study of urinary testosterone excretion in a group of patients with impotence. Excretion of testosterone is probably the best available measure of Leydig cell function and hence of androgenic status, since it is little affected by peripheral conversion of other corticosteroids. The mean excretion of testosterone was significantly lower (45.7 μg per 24 hours) in the impotent men than in healthy controls (73.1 μg per 24 hours). Of the sixteen patients who were grouped as predominantly “constitutional” only three had testosterone excretion above the mean whereas only one of the nine in the predominantly “psychogenic” group had a level below the mean.

Cooper 2 had defined these two major groups of patients presenting with impotence in previous studies. “Psychogenic” impotence usually occurred in young men who themselves sought help for their disorder, which was of short duration and had some specific physical or psychological precipitant. The anxiety they experienced appeared to be the major cause of their subsequent impotence. All of these men still experienced sexual desire, were aroused by appropriate stimuli, continued to masturbate, and had regular morning erections. By contrast “constitutional” impotence