Australia.¹³ The relation appears to be one of cause and effect, since loss of weight lowers the serum urate concentration.^{14 15} Its exact nature is poorly understood but has recently been reviewed, together with the further difficult interrelation with hyperlipidaemia and impaired glucose tolerance.¹⁶

Finally, the part played by alcohol must be considered, in the light of A B Garrod's opinion over 100 years ago that "fermented liquors" are a powerful predisposing cause of gout. Is it due simply to the high energy content of alcohol, or to its role in "washing down huge platters of meat,"¹⁷ or, at least in former times, to heavy contamination with lead?¹⁸ Or is there a more specific association?

The last suggestion receives support from a number of studies. High concentrations of blood alcohol produce a rise in lactate, which competitively inhibits the renal tubular excretion of urate.¹⁹ Faller and Fox, of Ann Arbor,²⁰ have recently examined the effects of long term oral and short term intravenous administration of alcohol in patients with gout. During the long term study serum and urinary urate concentrations rose, as did urinary oxypurines and the daily turnover of uric acid. Short term intravenous administration of alcohol produced no substantial changes in urate clearance but urinary oxypurines were increased and after administration of radioactive adenine, urinary radioactivity was also increased. The conclusion drawn was that alcohol increases urate synthesis by enhancing the turnover of adenine nucleotides. This suggestion is not necessarily at variance with the lactate hypothesis. Plasma alcohol concentrations achieved in the Ann Arbor studies were considerably lower than those in the earlier work, and a picture emerges of chronic consumption of alcohol producing an increased synthesis of urate with acute intoxication adding an additional element of renal shutdown.

In a further interesting recent study Gibson *et al*²¹ gave a careful dietary questionnaire to patients with gout and controls. The average intake of most foodstuffs, including total purine nitrogen, was similar in the two groups, except that the patients with gout drank significantly more alcohol. Beer was the most popular alcoholic beverage, and it was suggested that the intake of purine nitrogen derived from beer was sufficient to have a clinical effect, augmenting the hyperuricaemic influence of alcohol itself.

These investigations have obvious implications for some patients in terms of correcting the causes of hyperuricaemia and the management of gout, well reviewed by Emmerson.²² Every patient with gout must be carefully assessed to determine, from history, examination, and investigation, the various factors which are contributing to his hyperuricaemia.²³ When these are explained he may be prepared to cooperate in correcting some possible contributory factors. A number of patients who do this will become normouricaemic and remain so, and of course improvement of life style in terms of overeating and overdrinking is desirable in itself quite apart from any link with hyperuricaemia. Drug treatment for hyperuricaemia and gout is effective but all too often is prescribed unnecessarily. It should be reserved for patients with gout who remain hyperuricaemic despite modification in their eating and drinking habits—or who, as is unfortunately often the case, disregard such wise counsel.

J T SCOTT

Consultant Physician,
Charing Cross Hospital,
London W6 8RF

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Cytotoxic drugs for non-neoplastic disease

Cytotoxic drugs are now being prescribed for conditions other than cancer more often than they were, but it is important to bear some reservations in mind. The expectations for new drugs often exceed their ultimate achievement and initial optimism has now been tempered by experience: not only is the choice of a drug important but so also is that of the patient to be treated.

Applying such principles may result in great benefit, relieving symptoms, improving the quality of life, and prolonging survival. Unfortunately, since we still have no way of identifying the patient who will or will not benefit, some patients will suffer the toxic effects of these drugs without the advantages which treatment will certainly bring to others. Experience is one guideline, and the creation of the specialty of medical oncology has meant that for cancer at least chemotherapy can be combined appropriately with other clinical modalities to meet the needs of the individual patient. The clinician planning to treat the occasional patient would therefore be well advised to seek advice from such a colleague.

The medical oncologist's horizons have not, however, encompassed all the conditions in which cytotoxic drugs are used. It is indeed curious that, while the infrequent user is being discouraged from prescribing anticancer drugs for the

treatment of cancer, he is using these drugs more and more for other conditions. Perhaps the best documented is the use of methotrexate for resistant psoriasis,¹ but drugs with anticancer activity (often described as "immunosuppressive") have been tried in many other non-neoplastic conditions. These include rheumatoid arthritis,² idiopathic thrombocytopenic purpura,³ the nephrotic syndrome,⁴ systemic lupus erythematosus,⁵ verrucas of the foot,⁶ aplastic anaemia,⁷ primary systemic amyloidosis,⁸ renal transplantation,⁹ multiple sclerosis,¹⁰ ulcerative colitis,¹¹ myasthenia gravis,¹² and erythema multiforme.¹³ For some of these conditions anti-cancer drugs are used as a last resort; indeed, there may be no clear indication for their use beyond a desperate last attempt to control the disease. In others, such as psoriasis and rheumatoid arthritis, a growing list of reports imply that the disease may respond in some circumstances. Although some patients show clinical improvement after treatment with cytotoxic drugs, immunosuppression may not be responsible. Cytotoxic drugs inhibit cell division wherever this occurs, and, while this will impair immune function by inhibiting division of the lymphocytes, there may well be a direct action on the diseased tissues. Indeed, local radiotherapy may relieve the symptoms in rheumatoid arthritis rapidly, presumably in much the same way as the alkylating agents, but it is unlikely to cause much immunosuppression. In future we shall be able to evaluate the clinical importance of immunosuppression since the new generations of drugs can produce profound immunosuppression without inhibiting cell division.

The chronicity and heterogeneity of many of the diseases listed above make evaluation of treatment difficult. None the less, it is essential to do so if we are not to substitute chronic or even life threatening toxicity for chronic illness. Many experienced clinicians have used cytotoxic or immunosuppressive agents for the conditions described, but any real impact on the disease has remained largely undocumented. Nevertheless, the therapeutic limitations which apply to cancer also apply to these other conditions: the response cannot be predicted with certainty and consequently the choices of drug, dose, and duration of treatment are all arbitrary. There is thus no substitute for the clinical trial to identify a treatment suitable for general use. It is easy to be lulled into complacency by early responses to treatment, but toxicity must also be evaluated in parallel with the response. Ideally dose regimens should be standardised within clinical trials; nevertheless, in whatever circumstances they are used the serious complications of vesication, bone marrow toxicity, and haemorrhagic cystitis should be avoided and the risks minimised by frequent clinical review, modification of the dose, and limited duration of administration.

For cancer intensive chemotherapy may be taken to the limits of acceptable toxicity, but for non-neoplastic conditions treatment is likely to entail much lower doses over more prolonged periods. Inevitably, the side effects are more subtle but none the less established. Immediate toxicity is unusual and matches the idiosyncrasy found in all who take drugs. The major early complication is suppression of the bone marrow, and this is the greatest hazard of treatment. Over-dosage may result in an overwhelming opportunistic infection in a patient whose primary disease, in contrast, is chronic and disabling.

Prolonged low dose treatment may result in side effects so far unseen in the patient with cancer, as, for example, the hepatic fibrosis seen in patients with psoriasis after prolonged

administration of methotrexate. In long term survivors of certain malignancies who have been treated with chemotherapy and radiotherapy second malignancies seem to be occurring significantly more frequently than would have been expected. In ovarian carcinoma, for example, the incidence of second malignancy after prolonged low doses of chlorambucil is increased and the risk appears to be related to the total dose given. Malignancy has been reported in several studies in patients given cytotoxic drugs for conditions such as rheumatoid arthritis, multiple sclerosis,¹⁴ and psoriasis. This may be unrelated to treatment; indeed, the latent period in patients with cancer exceeds four years, so that cancer occurring in patients within a few months after beginning drug treatment for non-neoplastic conditions is almost certainly unrelated to this. A lesser but none the less important effect of cytotoxic drugs is diminished fertility, which is only partially reversed when the drug is discontinued.

Just as there are no ideal or even "standard" drug combinations for the patient with cancer so there are none for non-neoplastic disease. Unfortunately, a hit or miss use of drugs prevails—and while it does there can be no greater obstacle to progress. Patient benefit and safety must be the objects of drug treatment; the former is obvious, the latter cannot be assumed. The questions surrounding the use of immunosuppressive or cytotoxic drugs in treating non-malignant conditions remain largely unanswered; to answer them the strict criteria now established for good cancer trials require to be applied. Safety and optimum treatment should follow.

J M A WHITEHOUSE

Professor of Medical Oncology,
Southampton General Hospital,
Southampton SO4 9XY

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