Interferon and cancer

The antitumour potential of interferon has generated tremendous interest over the past few years. Originally discovered in 1957 as a protein which interfered with viral infection, interferon has been the focus of much recent research in both the laboratory and clinic. Early work was hampered by the small quantities of naturally occurring interferon available for study, but the full power of modern molecular biology has now been applied to the problem of producing adequate amounts for clinical trial. The genes coding for human interferon have been cloned and recombined with bacterial plasmids. Such plasmids have been used to infect bacteria which can then be grown in culture to obtain highly purified interferon, and two pharmaceutical houses are now producing large amounts of “recombinant” interferon.

We have learnt much about the biology of the interferon system. After reaching its target cell interferon binds to a surface receptor and sets in motion a series of secondary messengers culminating in a change in the cell’s general metabolic state. These changes inhibit the ability of viruses to replicate using the genetic machinery of the host cell and also have a complex effect on cell growth and division. Interferon also has profound effects on the immune system, acting under some circumstances as a lymphocyte hormone.

A further problem in understanding interferons and in assessing their efficacy is their heterogeneity, for there are no fewer than three families of interferon: α—predominantly produced by leucocytes, β—by fibroblasts, and γ—by antigen or mitogen stimulated lymphocytes. Gene cloning has shown that in addition there are subtypes of the α interferon resulting in a total of at least 14 different molecular species making up the interferons. While one of their physiological functions is defence against viral infection, the other functions of these disparate molecules are not clear. We do not know, for example, whether inhibition of cellular replication is a feature of all or only a subgroup of these molecules.

But what of the clinical uses? The early preparations of relatively impure interferon were shown to have some effect in causing objective regression of tumours in patients with myeloma, breast cancer, and non-Hodgkin’s lymphoma. These responses tended, however, to be partial and transient. The pioneers in this work hoped that they might get better results if they gave patients greater quantities of interferon. Unfortunately, the early preparations had serious side effects, principally fever, malaise, and fatigue. Because of the impurity of the interferons used at that time it was uncertain whether these effects were intrinsic to interferon or were a result of contaminants. Answers to these questions are beginning to emerge now that very pure recombinant interferon is available for large scale clinical trials. Firstly, the recombinant interferons also cause objective regression in certain types of tumour and appear to be at least as biologically active as the naturally occurring preparation. Clearly, however, pure interferon has profound side effects which limit the dose that can be given. Careful pharmacokinetic studies have shown that patients cannot tolerate doses beyond 36 million units a day for longer than one month. Side effects at this dosage include anorexia, loss of weight, and central nervous system toxicity, which may present with features of a metabolic encephalopathy. Changes in the electroencephalogram observed in this syndrome include excess slow wave activity. All this makes the administration of interferon an arduous task for the clinical investigator.

Many trials are now in progress with recombinant interferon. So far regression of tumours has been observed consistently only in patients with myeloma, non-Hodgkin’s lymphoma, and breast cancer. A few patients have had well documented objective responses in diseases such as melanoma, renal cell carcinoma, lung cancer, and Kaposi’s sarcoma (S Krown, personal communication). The response rate in some of these tumours is low—less than 20%—but the patients studied in these early phase I trials have all had advanced disease, resistant to conventional treatment, so that any response is encouraging. Most of these responses have been partial, a reduction in tumour size rather than complete disappearance, and there are many problems in assessing tumour load in an individual patient. Nevertheless, most of these responses are probably real and interferon is having an inhibitory effect on the growth of at least some tumours, either directly or through the immune system.

The outlook for patients with the common solid tumours appears to have reached a plateau despite intense effort with conventional cytotoxic chemotherapy. Against that background further investigation of the antitumour potential of interferon seems reasonable. If indeed interferon works through an immunomodulatory mechanism then it might benefit patients with earlier disease in an adjuvant setting. Despite the low response rate when used as a single agent in advanced disease the combination of interferon with other drugs might be useful. Investigators will probably be prudent and work only with the highly purified preparations produced by genetic engineering techniques—so removing the possibility that impurities may be causing any antitumour effects as well as being able to reproduce precisely the production methods. Problems with varia-
Thyroid surgery for Graves’ disease

In most patients with Graves’ disease the hyperthyroidism is characterised by alternating episodes of relapse and remission over several years. A euthyroid state may readily be restored by treatment with drugs such as carbimazole; but antithyroid drugs have little or no influence on the natural history of the disorder despite their immunosuppressive action in reducing the serum concentration of antibodies against thyroid stimulating hormone (TSH) receptors. Indeed, at least two thirds of all patients treated with antithyroid drugs for six to 18 months will relapse, usually within one to two years of stopping treatment. The other third remain in prolonged remission and may even develop hypothyroidism in future years, a sequence of events first recognised last century. Clearly a single course of antithyroid drugs would be ideally suited to the “remission” group but would be inappropriate treatment for the “relapse” group. Unfortunately the course of hyperthyroidism cannot be predicted in individual patients when they present, though in some populations those who are HLA-DR3 positive and have serum antibodies against TSH receptors after a six month course of carbimazole are very likely to relapse in the short term. These observations require confirmation, but in the mean time neither HLA typing nor the measurement of antibodies against TSH receptors is widely available. With few exceptions, therefore—such as in pregnancy, childhood, and patients who depend on their vocal cords for a living—many British authorities prefer to advise subtotal thyroidectomy as the initial treatment for Graves’ disease in patients aged under 40. Whether surgery is the only alternative to treatment with antithyroid drugs is another matter; in the United States radioactive iodine is used much more liberally in patients of reproductive age.