Towards improved ways of localising tumours

THERE are many current investigations aimed at improving methods for localising both primary and metastatic tumours. Non-specific radio-labelled proteins, for example, have been used by some investigators (Spar *et al., Cancer,* **20,** 865, 1967; Bonte and Curry in *Radioactive Isotopes in the Localisation of Tumours,* 80, Heinemann, 1967). Recent findings in experimental and human tumour immunology have, however, generated renewed interest in the possible use of specific reagents, namely radiolabelled antibiodies, as a novel type of localising agent.

The success of this approach will depend, among other considerations, on the specific activity of the labelled antibody, its specificity for the tumour cells and on tumour site, cell composition and size. Although little success has been claimed for such studies using some experimental tumour systems, specific and significant *in vivo* localisation of labelled antibodies against a tumour-associated transplantation antigen of a methylcholanthrene-induced rat tumour was attained by Izzo *et al.* (*Proc. Soc. exp. Biol. Med.,* **139,** 1185; 1972).

The carcinoembryonic antigen (CEA) is a human oncofoetal antigen associated with the glycocalyx of tumour cells, and is released into the plasma and other body fluids. It was originally considered to be associated solely with endodermally-derived carcinomas (Gold and Freedman, *J. exp. Med.,* **122,** 467; 1965); further studies have shown that CEA, or 'CEA-like' materials, are released into the body fluids from a wide variety of neoplastic and some non-neoplastic conditions (see, for example, *Br. J. Cancer,* **26,** 335; 1972). Last year, Primus *et al.* (*Cancer Res.,* **33,** 2977; 1973) reported that a mucus-secreting carcinoma growing in immunologically-depressed hamsters and derived by serial propagation in hamsters from a human colonic carcinoma, exhibited preferential uptake of radiolabelled heterospecific anti-CEA antibodies. In this week's issue of *Nature,* Mach and his colleagues now report similar findings for a human colonic carcinoma growing in nude mice and that this antibody accretion may be detected by suitable external scintillation scanning equipment. Unfortunately, in both studies, the labelled antibody was not located specifically in tumour tissues and there was a long delay after its administration before optimal tumour content of the label was attained.

Iodine is not the ideal scanning isotope; so far, it has only yielded labelled antibody with a relatively low specific activity. Isotopes with superior scanning properties such as technetium-99m may give better results, although the initial rate of isotope accumulation will be important in determining the usefulness of the method.

Other practical limitations include the presence of significant amounts of circulating antigens which may bind the heterospecific antibody and the presence of appropriate autoantibodies on the tumour cell surface. Both phenomena will serve to decrease the amount of labelled antibody eventually located in the tumours. The studies of Primus and Mach and their colleagues have been carried out in optimal conditions of tumour site and type, yet the smallest detectable lesion weighed 200 mg and was located superficially. Moreover, the presence of extensive tumour necrosis was also a limiting factor which, when considered with the problem of circulating antigen excess, reveals that there are many difficulties to be overcome before hepatic metastatic lesions of colorectal carcinomas with their characteristic central necrosis will be visualised in this manner in patients.

Consequently, this approach to tumour localisation does not have immediate clinical applicability. It does, however, reveal another possible area of fruitful investigation which may eventually yield not only improved diagnostic aids but also therapeutic regimes through the use of antibodies, coupled to anticancer agents.

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Beyond systems ecology

WITH the increasing disturbance of natural systems by modification of the environment, the need for a way to predict the behaviour of complex ecosystems is rapidly becoming paramount. Because of the scale of the problem, the study of ecology is moving away from simplified systems and the analysis of elemental interactions towards systems in which the numbers and kinds of interactions are not under control and cannot be isolated. Extrapolation from two- or three-population models to large scale systems is often inappropriate and can give drastically misleading results.

The first attempts to derive a predictive theory of complex ecosystems were based on techniques well known to engineers under the general heading of systems analysis. A systems model is defined in terms of elements, each of which has one or more inputs and outputs and is specified in terms of the relationships between the various inputs and outputs of each element. With this very broad definition virtually all models are systems models of some kind but the term is usually used in cases where the number of elements in the system is large enough for detailed analysis of each one to be impossible.

Systems models have been applied on a small scale to ecological problems for the past one hundred years or so, usually in agricultural pest control or wildlife or resource management. The emphasis in most of the earlier applications was on the factors which affect a single population, usually one of commercial importance. These systems models were successful and widely used but limited in extent by the amount of calculation necessary to analyse them. With the development of high-speed computers, Watt of the University of California, Davis and Holling of the University of British Colombia, and others, recognised that systems models in ecology could be used on a larger scale. The logical basis for their approach to the problem is the same as in the simplest models, but the availability of computers made it possible to use the models to determine and use the input–output relationships for all the populations within a community rather than only one of them.

The systems approach to ecology seemed so promising and the need for useful predictive models so great that between 1964 and 1972 funding of participation in the International Biological Program (IBP) has been at the level —unheard of in ecological research—of more than $40,000,000 per year. Ecologists, engineers, meteorologists and mathematicians were gathered for the study of several systems ("biomes"), such as deciduous forest, intertidal zone, short and long grass savannah and desert. Extensive measurements were proposed as the basis for equally extensive computer models whose value could be determined only by a full scale program.

One of the reasons for the appeal of the systems approach, particularly to those not directly involved in ecological research, is its apparent objectivity. Ideally a systems model could be constructed by somebody with no prior knowledge or intuition of the system he is studying. The relationship between the elements would become clear