Somatic genes

Ways with drug resistance

ONCOGENES are merely the frosting on the cake of the application of molecular biology to the problem of cancer. By common consent, last week, the need to trace the effects of the gene products through the biochemical apparatus of the cell is plainly urgent. Why does the activated (mutated) *ras* gene have such profound effects? The first steps in what may be a long cascade have been described (see *Nature passim*). Other areas cry out for attention.

Alexander Varshavsky's account of the phenomenon of the acquired resistance of cancer cells to not just one but several cytotoxic drugs suggested a fruitful field for investigation. The problem all too often presents itself in the chemotherapy of cancer patients. Although Varshavsky was at pains last week to emphasize that multi-drug resistance can be acquired in several different ways (mutation of the target gene which may make its product less susceptible to attack by cytotoxic drugs, other mutations which may affect the regulation of the gene or the import and export of the cytotoxic drug through the cell membrane), the mechanism of gene amplification is the most commonly discussed.

Whatever genes are amplified may be up to 600 times more common in drug-resistant cells, for which reason Varshavsky argued strongly for direct interaction between drug and DNA rather than for the evolution of a labile genome under selective pressure. Many of his audience were eager to know why hydroxyurea should apparently be a powerful stimulus to resistant cells (in culture) to shed copies of the resistant genes (but could not be satisfied). The practitioners' concern is to characterize those genes which are amplified in resistant cells and whose functions are not already known. (Resistance to methotrexate usually entails the amplification of the gene for dehydrofolate reductase, but multi-drug resistance seems often to involve a decrease of membrane permeability to the drug associated with amplification.) Varshavsky and his associates are struggling with genetic fragments more than 1,000 base-pairs in length, but Dr John R. Riordan (Hospital for Sick Children, Toronto) offered the information that a relatively small glycoprotein (molecular weight about 20,000) has been consistently isolated from multi-resistant cells.

Genetic amplification causing drug resistance is one thing—genetic changes in somatic cells associated with cancer, or in germ cells which carry a predisposition to certain forms of cancer, are another. R. White left his audience last week with two clear impressions. First, the map of the human genome is now reasonably well sprinkled with potential genetic markers so that the identification of the usually rare genes carrying a predisposition to hereditary cancers may often be successful. Second, the interlocking familial studies of cancer incidence and genetic constitution based in Utah (whose large Mormon population makes the construction of kindred trees more feasible) has already provided an invaluable resource for the investigation of the genetics of cancer incidence. Dr F. Gilbert confirmed the practical potential of such developments.

The genetics of carcinogenesis, and of tumour promoters, is in a different ballpark. I. B. Weinstein was anxious that people should understand that the effects of tumour promoters on the cells in which they engender malignancy are usually direct, not via the genome. So much is clear from studies with protein kinase C (PKC), whose targets include a growing list of the molecular components of cells such as growth factor and insulin receptors and even myelin basic protein.

These lines of development are quite distinct from the pursuit of oncogenes. They offer the prospect that even when the list of oncogenes is complete, there will remain as vast a canvas as that which now appears to stretch ahead for the exploration of how malignant cells are the products of their genes. □

Avoidance is the best cure

CANCER as a preventable disease, the ideological basis of the National Cancer Institute's National Cancer Control Program, was urged on the conference last week by Dr Richard Peto. He urged a clear distinction between the identification of causes and of mechanisms, and that "it is possible to show that the disease is avoidable without knowing how to avoid it".

The argument is epidemiological: if cancer rates vary over a wide range from one part of the world to another, and if people migrating to new dwelling places acquire the cancer rates of their new surroundings, it follows that cancer is not an externally determined fate.

Within developed countries, Peto says, tobacco consumption is responsible for 35 per cent of cancer mortality, and for one million deaths a year worldwide. Peto's rearrangement of priorities on the international demographic canvas puts liver cancer following hepatitis-B infection high on the list—100,000 liver cancer deaths a year in China alone. □

Strategy

How to reduce mortality?

REDUCING the rate of cancer mortality in the United States by half by the end of the century, the National Cancer Institute (NCI)'s promise to the US Congress last November, requires only the application of knowledge now available according to Dr Peter Greenwald of NCI. With present cancer rates, and allowing for the age-structure of the increased population of the United States by the year 2000, annual cancer deaths would increase from 414,000 to 575,000. So NCI's goal is to reduce the annual mortality to 288,000.

Reduction of cigarette smoking should yield a 15 per cent reduction in mortality, as should the extension of improved methods of treatment to the whole country and the use of techniques (such as body scanning) for the detection of micrometastases. Perhaps the most controversial element of NCI's prospectus is the calculation that cancer mortality will be reduced by 5 per cent by changes in US diet (more fibre, less fat), chiefly by effecting a reduction of mortality from colon cancer. Persuading people to change their diet is uncharted territory. Continuing professional disputes about the efficacy of fibre in reducing colon cancer should, however, in Greenwald's opinion, be outweighed by the number of reports tending in this direction.

Greenwald says that NCI's new objective is deliberately to apply present knowledge in the avoidance and treatment of cancer. Hitherto, he says, reports identifying the causes of cancer have been published, but little has been done to show that agencies such as NCI can successfully intervene. The objective for the coming decades will be to mount demonstration projects which can thereafter be applied elsewhere in the United States. In this programme, Greenwald says, molecular biology may have important functions to perform as, for example, in the identification of the mutagens presumed responsible for cancer of the colon, now the second cause of cancer mortality in the United States.

The cost of the Cancer Control Program is necessarily speculative at this stage. Greenwald hopes that funds will begin to appear in NCI's budget with the beginning of the next administration next January. By the end of the century, the cost will be $10,000 million. The spur is that for each of the known causes of cancer in the United States, there is some society elsewhere which seems successfully to have avoided it. And even within the United States, the mortality from cancer among Seventh Day Adventists in the western states is only two-thirds of the national average. □