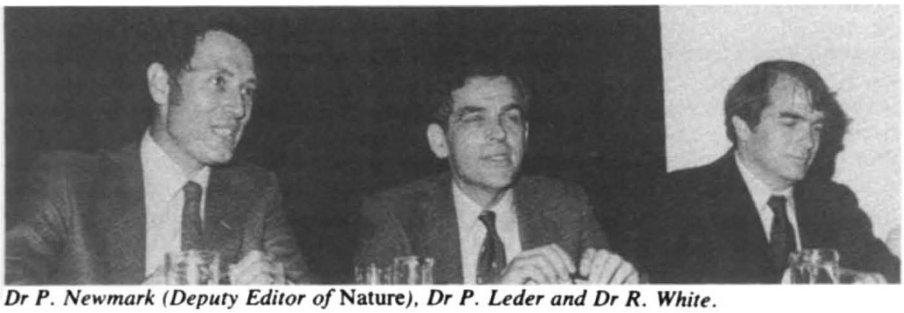
Growth factors

Ambivalence in plenty

GROWTH factors may inhibit growth, and inhibitors may sometimes have the opposite effect. This ambivalence of the compounds on the steadily lengthening list of the gene products of the known oncogenes emerged most clearly from Dr Michael Sporn's survey of the field last week.

Much of the interest at last week's conference has been stimulated by the recognition that the interaction between growth factors and oncogenes may be crucial to the development of malignancy. Notable among these are the links between the *sis* oncogene and platelet-derived growth factor (PDGF) and between the *erb*-B and the receptor for epidermal growth factor.



Dr P. Newmark (Deputy Editor of Nature*), Dr P. Leder and Dr R. White.*

Sporn emphasized last week the common features of the architecture of many of the growth factors whose role in carcinogenesis is coming to light. Although similarities of amino-acid sequences ("homologies" in slang) are many fewer than might have been expected, Sporn and Dr George Todaro agreed that the character of the molecules is determined by three disulphide bonds between as many pairs of cysteine molecules. (Insulin, two peptides held together by two disulphide bonds, is—significantly—not very different.)

So the hunt for growth factors which are somehow linked with oncogenes is now fast and furious. Sporn reported last week a significant difference between the two versions of the growth factor TGF (for tumour growth factor) called alpha and beta, which have been isolated from rat tissues (among others). Heroically, Sporn and his colleagues have been able to determine the sequence of beta-TGF by wringing 40 micrograms of pure substance from 14 kg of bovine kidney.

Although similar in their architecture, the two molecules differ profoundly in their effects on cells: alpha-TGF is always stimulatory of cell metabolism, beta-TGF may be inhibitory. This argues for distinct receptors but also for the more philosophical view that growth factors are regulatory elements in the same category as some hormones (insulin), the lymphokines (interleukin I and II for example) and the interferons which are recognized as "growth factors" only in relation to malignant cells.

Sporn and Todaro agree on the importance of deciding how the growth factors produced by transformed cells play a part in malignancy as such. On the autocrine model, cells produce growth factors which stimulate themselves. Todaro thinks the circumstances may be rare, perhaps occurring in Weinberg's transformed neuroblastoma cell-line. Whatever the detailed mechanism, Todaro thinks it likely that the effects of the secreted products of oncogenes on cells (including themselves) may be to activate proteases (perhaps by phosphorylating tyrosine residues) which then cleave precursor molecules to yield activated growth factors, much as proinsulin is converted into insulin.

The interest of Todaro, now more than a year with the company Oncogen, is guided by the suspicion that the common recognition of growth factors produced by transformed cells may conceal the way in which, in normal tissues, their stimulatory effects are balanced by those of inhibitory factors. Against some of the odds called in recent years, shadowy materials such as tumour necrosis factor (TNF) are now well on the way to being characterized. Todaro's people are embarking on assays of these and other materials in the urine of cancer patients, processing up to a litre of urine at a time in what seems to have been a successful if preliminary demonstration that TGF is secreted in cancers of the lung, breast and colon, and in melanoma, but not by leukaemic patients or normal controls. Who said that molecular biology is pico-biochemistry? □

Front end virus

CLINICIANS, these days, are as often as not closet molecular biologists. Dr Samuel Broder said last week that working with T-cell leukaemia virus is the "front end of cancer". There is, he said, a "basic duality" in knowing whether the conditions that arise are direct consequences of the neoplasm or secondary consequences of the immune suppression accompanying T-cell leukaemia. □

Biology

No genuflection

CANCER may not be what it seems even now, oncogenes notwithstanding. That was the theme of the iconoclastic message delivered by Dr John Cairns (now at the Harvard School of Public Health) in a clear English accent.

After "genuflecting" towards the oncogene, Cairns faced the conference with interlocking pieces of evidence that the development of malignancy in a cell is a long-term process, as follows.

- Irradiate cells in culture, allow them to grow to fill up the culture dish and, after 10–12 generations, the number of malignant foci will be that determined by the Poisson statistics describing the distribution of rare events. In a parallel experiment, remove part of the cell mass; the average number of malignant foci will be the same. But trypsinize the cells to break up the cell mass at an intermediate stage, and the number of foci will increase, suggesting that the progeny of a large proportion of the original cells have inherited the propensity to malignancy.
- Paint rabbits' ears with coal-tar (following 1920s' experiments by Peyton Rous), sampling tissue by some traumatic procedure (such as using a punch); the outcome suggests that many more cells are rendered by the trauma susceptible to transformation than become malignant under the influence of the promoter.
- The incidence of lung cancer and smoking in human beings argues that the development of malignancy must require both early events (because lung cancer develops only after long exposure) and late events (because giving up the practice sharply reduces the relative risk within two or three years).

In the interpretation of these and other data, Cairns said that "we have been brainwashed by current ideas of evolution and mutagenesis". In his view, both the arguments of Gould and others in favour of "punctuated equilibrium" in evolution and Barbara McClintock's work on the occurrence of mobile genetic elements in maize suggest that "mutation rates are not constant" but are, instead, increased by "genomic stress".

To molecular biologists, Cairns commended the study of long terminal repeats and of parvoviruses. In his opinion, the study of the role of hepatitis-B virus infection as the stimulant of liver cancer is, numerically, the most valuable contribution that could be made. But for those who would reduce the mortality from cancer, the objective should be prevention of cancers with known causes. The role of diet is obscure and needs urgent investigation.

Oncogenes, Cairns says, will "give us a fascinating insight into how cells manage their affairs" but will not contribute to public health in the near future. □