How Does the Oncogene Theory Stand?

THE oncogene hypothesis propounded by Huebner and Todaro in 1969, and foreshadowed by the ideas of Bentvelzen (1968) and Payne and Chubb (1968), seeks to reconcile the apparently discrepant facts that, while most cancers do not have the characteristics of infectious diseases, at least some cancers of animals such as mice, cats and domestic chickens have a viral aetiology. At the same time the theory tries to explain how physical and chemical carcinogens act. In essence, Huebner and Todaro proposed, and have since maintained, that the cells of all animals which may suffer from malignant disease contain certain gene(s) which when expressed release those cells from the constraints which regulate their normal pattern of growth; and as a result the cells are rendered malignant. The genes of this set are the cell's oncogenes.

To bring RNA tumour viruses into this picture, Huebner and Todaro postulated that cells also contain a set of so-called virogenes, the genetic information required to specify an RNA virus of the same taxonomic type as the tumour viruses. If, they argued, both the set of oncogenes and the set of virogenes are activated in one and the same cell, that cell will not only be rendered malignant but also may be expected to release RNA viruses carrying the set of oncogenes; in other words the cell would release an RNA tumour virus. If, however, only the set of oncogenes is activated the cell would be rendered malignant but would not release an RNA virus.

Conversely, the virogenes alone might be activated, in which case the cell would not be malignant but would release an RNA virus closely related to the tumour viruses but lacking the ability to induce cancers in animals or to transform cells maintained in culture. The expression of oncogenes and virogenes is, the hypothesis states, determined chiefly by the genetic make-up of the individual cell but such environmental factors as exposure to physical and chemical carcinogens can influence whether or not these genes are expressed. According to this hypothesis, the RNA tumour viruses are oncogenic because on infection they introduce into a cell supernumerary sets of oncogenes that are in a state in which they can be expressed, even though the cell's endogenous oncogenes are inactive.

These then are the chief tenets of the oncogene hypothesis which, sweeping in its generalizations, has won as many opponents as supporters for, as is obvious, it is a hypothesis which it is impossible to disprove. Some indeed would argue that by seeming to provide an explanation which cannot be put to a rigorous test, the oncogene hypothesis has done more harm than good, stultifying rather than stimulating thought. But on the other side of the coin, the hypothesis has stimulated its proponents to do some remarkably interesting experiments which do suggest that mice and domestic chickens may have as part of their inheritance the genetic elements which can specify RNA C-type virus particles, some of which may be authentic tumour viruses.

Weiss and Vogt and their colleagues have, for example, exposed cultures of chick cells taken from apparently perfectly normal embryos to ionizing radiations or to chemical carcinogens and mutagens. Subsequently they detected the production of an RNA virus which by a variety of criteria they conclude belongs to the avian leukosis virus group. They find that this virus can be induced not only as expected from chick embryo cells which carry the group specific antigens of the avian tumour viruses but also from cells obtained from embryos which do not have detectable amounts of this antigen. In the face of this evidence it is hard to avoid the conclusion that all chick cells have the genetic potential for specifying a "leukosis" or C-type RNA virus. In terms of the oncogene hypothesis, all chick cells appear to contain virogenes and superficially at least there is a close analogy with a lysogenized bacterial cell. The crucial question now, of course, is simply whether the induced virus has the capacity to induce leukosis in chicks; in other words, does it also carry oncogenes?

Three sets of experiments recently published by groups working with the murine sarcoma and leukaemia viruses, Lowy *et al.* (*Science*, **174**, 155; 1971), Aaronson *et al.* (*ibid.*, 157) and Klement *et al.* (*Nature New Biology*, **234**, 12; 1971), all point to much the same conclusion. Lowy, Rowe, Teich and Hartley have succeeded in inducing with 5-iododeoxyuridine and 5-bromodeoxyuridine the production of murine leukaemia virus by cultivated but previously virus-free mouse embryo cells of the AKR high leukaemia strain. The complete genome of this virus must, therefore, be present but unexpressed in these embryonic cells. Aaronson, Todaro and Scolnick have used the same inducing agents to effect the activation and release of a C-type RNA virus, related to the murine sarcoma leukaemia viruses, from cultures of BALB/C 3T3 mouse embryo fibroblasts, which before induction were not producing such virus particles. Whether this virus has an oncogenic potential, or can acquire it on passage in malignant cells, remains a fascinating question. Finally, Klement, Nicolson and Huebner have caused rat cells transformed by mouse sarcoma virus, but not liberating progeny sarcoma virus, to yield such progeny by exposing the cells to bromodeoxyuridine. They believe, of course, that the drug activates genetic elements which specify a rat leukaemia virus and that this virus then provides the helper function required for the replication of the transforming sarcoma genome.

Taken together, the results of this set of three experiments indicate that rat and mice cells inherit virogenes and probably oncogenes. Similarly, Bentvelzen has over the past several years reached the conclusion that the mouse mammary tumour virus is probably vertically inherited by all strains of mice. It seems therefore that Huebner and Todaro's postulate that cells carry virogenes is true of rodents and chickens and these virogenes specify RNA tumour viruses. The characterization of the biology of these vertically inherited and inducible viruses, in particular, of course, tests for their oncogenicity and involvement in spontaneous carcinogenesis, is now a matter of some urgency. For if these viruses are, or are capable of becoming, carcinogenic the oncogene hypothesis will rest on firmer ground.