Molecular biology and cancer

A Nature conference next week is a modest celebration of the prospect that cancer will soon be understood. It does not imply that practical oncology will be transformed overnight.

THE question whether molecular biology has a contribution to make to the practice of medicine has now been answered. And positively. The half-dozen or so techniques for the diagnosis of genetic conditions and infection which are already in the hands of physicians are a sufficient proof of that. But when will molecular biology contribute something important to the practice of medicine, perhaps by helping to cure a disease and not by merely recognizing it?

For the past few years, there has been widespread excitement over the opportunities which seem to lie ahead for the treatment of genetic diseases and, more immediately, for the understanding if not the treatment of some of the many different forms of human cancer, which are in part at least genetic aberrations. That is one of the reasons why *Nature* is next week holding a conference on the subject in Boston, Massachusetts.

The opportunities in the field of cancer for molecular biologists are literally fascinating. They do cast a spell as can be told from the now wide currency of the word *oncogene*, which almost everybody knows of — and misuses. And there is a general opinion that oncogenes have something to do with viruses, whence the somewhat chilling suspicion that some forms of human cancer may yet turn out to be infectious (as, indeed, it seems that adult T-cell leukaemia is, at least in the coastal regions of southern Japan).

At times like these, it is therefore important to remember how long and tortuous is the history of the field that now seems so full of promise. It is well over half a century since the late Dr Peyton Rous, then a young man, first claimed that a sarcoma (in chickens) could be caused by a transmissible agent, an old-fashioned synonym for a virus. Rous persisted in the face of the sceptical politeness owed such a modest man and was rewarded, although not vindicated, by Richard Shope's discovery of the cell-transforming papilloma virus in the early 1930s. Only with development of techniques in the post-war decades was the reality of oncogenic viruses proved up to the hilt, first in rodents with polyoma (a DNA virus), then with the subset of the RNA viruses (collectively known as retroviruses) shown to cause cancer in animals.

More recently, the possibility of a connection between the retroviruses and the causation of human cancer has been answered with yes and no in an illuminating

way. The recognition within the past decade that there is often a close similarity between the nucleotide sequence of oncogenic retroviruses and certain unidentified genes in vertebrate cells was naturally a stimulus to investigation. Just over two years ago, three separate groups in the United States were able to show that a close similarity existed between the genetic structure of one strain of the ras retrovirus and a genetic structure in the DNA of cells taken from human bladder carcinomas.

By November of that year, two separate groups in the United States (at the Massachusetts Institute of Technology and at the National Institutes of Health) had been able to show that the aberrant structure, apparently that responsible for the causation of cancer, differed from that of a gene normally present in all human cells in apparently trivial ways. The normal version of the gene carries the code for a protein, called p21, whose existence had already been catalogued but whose function was unknown. The abnormal version of the protein, inferred from the structure of the abnormal gene, differs in only two amino acids in the sequence. From that point on, the attention of molecular biologists has been directed squarely at the human (and vertebrate) genome.

The picture that has emerged illustrates why the term oncogene is so commonly misused. At least in the case of the human bladder cancer (but probably many others), there is a normal gene which plays a crucial part in the biochemistry of all normal cells, and an aberrant version associated with the cancer. Strictly speaking, only the aberrant version deserves to be called an oncogene. In a careful world, the normal version would be called by a name indicative of its function.

So great has been the excitement since November 1982, that *Nature*, in a leading article on the outlook for 1983, offered the prospect that the causation of at least some forms of cancer would be understood within the year. In retrospect, that hope was over-optimistic; the function of p21 and its aberrant form have been glimpsed only in the past few weeks (see *Nature* 23 August, p.628, and references therein). But there have been other remarkable developments to make up for such disappointments as there may have been — the recognition that the oncogene called *myc* does appear to migrate from one chromosome to another in cases of human leukaemia and the startling recognition of a similarity of structure

of the gene responsible for the normal receptor for human epidermal growth factor and a true oncogene carried by the retrovirus known as erb-B. Whether the laboratory and clinical versions of the aberrant gene also interact with the biochemical system involving p21 remains to be determined, but it is hard to suppress the suspicion that the time is fast approaching when it will be worked out which properties of the cell surface have gone awry in cases of human malignancy.

These are only some of the reasons why the present is a time for modest celebration. But even now, it is far from self-evident that a better understanding of malignancy will help with the treatment of the human disease. That is a question that physicians rightly ask. They do so in the knowledge that even now, in other fields of human therapy, the development of successful drugs has ridden on the back of an understanding of how a disease is caused biochemically. It is only a hope that the field of cancer may be different, or that, say, the new techniques of molecular biology will provide a full understanding of the mechanism by which cells acquire genetic resistance to cytotoxic drugs.

The long history of people's attempts to deal with human cancer counsels caution. There have been too many crude disappointments for any other course to be safe. But even if the only certainty is that there will soon be a rounded understanding of the processes leading to overt disease, and ultimately perhaps of the interaction between genetic and environmental influences, it should at least be possible to put present strategies for the avoidance of cancer on a much sounder footing.

The role of *Nature* in such developments should not be misunderstood. Even a journal which enjoys the privilege of publishing many of the most important discoveries in such a field is not a scientific society in the strict sense but a vehicle for communication among active investigators and between them and the wider body of professional people. But the process of communication, in this field just as in any other, is more than the mere publication of information. The sense of excitement shared by those working in a promising field is also relevant. And there is much value in a forum in which those working at the bench can meet those whose work may be affected by what emerges. That is the spirit in which this conference has been designed.

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