those thinking of buying blood pressure measuring equipment? Firstly, the mercury sphygmomanometer is the most accurate, reliable, durable, and economical of all devices for measuring blood pressure.[22] Secondly, semiautomated and automated devices should not be purchased unless the manufacturers provide independent validation of accuracy preferably published in a reputable journal.

Several major companies have behaved responsibly in assuring that their products are accurate, reliable, and value for money, but there are many products on the market (and the number is increasing) that are inadequately tested and sold at considerable profit. Some marketing strategies rely on an independent laboratory taking five years to produce verification and accuracy studies. Medical journals are often reluctant to publish such technical evaluations, and at least another five years may pass before enough published evidence accumulates to harm sales. The British Hypertension Society is determined to reverse this trend.

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Regular Review

Oncogenes and cancer

JONATHAN WEBER, MYRA McCLURE

During an era of increasing interest in holistic medicine research into carcinogenesis is paradoxically reaping benefit from a reductionist approach. Many disparate factors may cause cancer—for instance, smoking, viral infections, and ultraviolet light—but all cancers ultimately may be reduced to fundamental mechanisms based on cancer risk genes (oncogenes) within ourselves. An oncogene is a gene that encodes a protein that contributes to the malignant phenotype of the cell. They are derived from normal cellular genes expressed in an altered or abnormal form; oncogenes act synergistically, and one alone cannot cause cancer.

The concept that our own genes may cause cancer is disconcerting but not new. An association between the structure of the chromosome and subsequent carcinogenesis was first mooted nearly 80 years ago. In the 1940s carcinogens were shown to cause mutations and hence act through changes in the chromosomes. In 1960 the observation of the Philadelphia chromosome in chronic myeloid leukaemia firmly established the part that chromosomal abnormalities may play in specific human tumours. More recently, clonal analysis of many disparate human tumours has shown that they are monoclonal and may be derived from a single aberrant cell. Subsequent advances in the experimental manipulation of DNA, the genetic material of the chromosomes, have helped to pinpoint specific sequences for carcinogenesis. The part played by defined genes (oncogenes) in developing animal malignancies induced by retroviruses, along with the weight of evidence pointing to chromosomal abnormality in human tumours, led to the idea that oncogenes are important in human disease.

The discovery of oncogenes

The discovery of oncogenes arose from extensive investigation into the action of the cancer causing (oncogenic) animal retroviruses. These viruses have been known for more than 70 years and cause malignant disease in many species. Retroviruses are RNA viruses capable of producing a DNA copy of their genome (a process called reverse transcription). Their genome has only three genes—*gag*, *pol*, and *env*; these three genes code for all the proteins needed for viral replication. Using various genetic techniques, researchers found that the transforming—that is cancer causing—ability of retroviruses was independent of the essential replicative genes. Indeed, oncogenic strains of virus often could not replicate. This suggested that the transforming gene (the oncogene) replaces one of the three essential genes.

The Rous sarcoma virus of chickens was the first retroviral genome to be characterised and was found to contain an oncogene called *src*. An important advance came when a DNA probe complementary to the *src* oncogene of the Rous sarcoma virus was shown to recognise a homologous gene present in the DNA of normal non-malignant chicken cells. Indeed, it was also found in most vertebrates, including man. Similar results were obtained for other retroviral oncogenes, and all were found in the normal cell genome. This implied that viral oncogenes were derived from cellular genes that had been "hijacked" by the virus long before in evolution. These cellular genes have been called proto-oncogenes. Although RNA tumour viruses containing an oncogene have not been directly implicated in any human malignancy, these proto-oncogenes might be converted into oncogenes in situ by a non-viral mechanism.

Certain of these specific genes associated with neoplasia have been elucidated through "transfection" studies. The DNA from tumour cells can be extracted and inserted into normal (non-malignant) cells, a process known as DNA transfection. The normal cells chosen are generally a mouse fibroblast cell line known as NIH-3T3. These cells are normal in that they respond to contact inhibition; monolayers of these cells on a Petri dish will grow to confluence. Some oncogenes when transfected into the NIH-3T3 cells will cause a readily observable focal area of uncontrolled cell growth.

In 1981 Weinberg reported that DNA extracted from human tumours could induce malignant transformation in NIH-3T3 cells, whereas human DNA from normal tissue could not. By repeated passage he was able to show that the transforming element in the human tumour DNA was homologous to an oncogene, *ras*, first described in the 1960s in a retrovirus inducing sarcomas in rats. Further studies in many laboratories showed that three human genes are related to this retroviral *ras* gene, and one of them is associated with the transformed phenotype in over 20% of human tumours.

The cancer causing genes in the animal retroviruses are therefore related to normal cellular genes that are presumably responsible for normal cell growth since they are found in phenotypically normal tissue. There are about 25 known different oncogenes, some of which are listed in the table. Out of some 50 000 different human genes, perhaps fewer than 100 are potential oncogenes. Several ways in which proto-oncogenes may be activated to functional oncogenes have been detected in human malignancies.

Site and biological action of some human proto-oncogenes

Oncogene	Property	Site
sis	Growth factor	Secreted
erb-B	Growth factor receptor	Surface
src	Tyrosine kinase	Cytoplasm
abl	Tyrosine kinase	Cytoplasm
mos	Tyrosine kinase	Cytoplasm
fms	Tyrosine kinase	Cytoplasm
H-*ras*	Guanosine triphosphatase	Cytoplasm
N-*ras*	Guanosine triphosphatase	Cytoplasm
myc	Affects DNA synthesis	Nucleus
myb	Affects DNA synthesis	Nucleus
fos	Affects DNA synthesis	Nucleus

Oncogenes and human malignancy

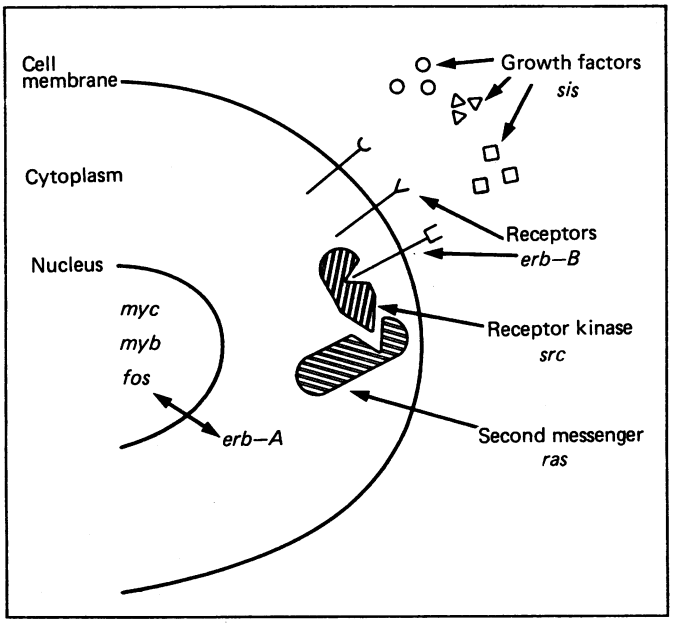
Mutation—The *ras* proto-oncogene may become oncogenic by a single point mutation, resulting in an amino acid substitution in the gene product. Even such a minor alteration at a critical point of the protein may alter the phenotype of the cell. Chemical and physical carcinogens may act by causing mutations at specific sites on cellular proto-oncogenes.

Amplification—The c-*myc* oncogene is associated with acute leukaemia and was the first oncogene to show amplification in malignant change compared with normal cells from the same patient. Amplification means the repeating of the DNA sequences, sometimes by as many as 50-100 times; this may lead to overexpression of the gene product. The N-*myc* oncogene has also been associated with gene amplification in the late stages of metastasising neuroblastoma. Whereas only a few leukaemias show c-*myc* amplification, the N-*myc* amplification associated with neuroblastoma is seen in over half of tumours.

Chromosomal translocation—The transfer of a gene from its normal position to one on another chromosome is called translocation, and translocation occurs consistently with certain tumours. In chronic myeloid leukaemia there is precise translocation of genes, including another oncogene, *abl*, from chromosome 9 to chromosome 22; this is the molecular basis of the Philadelphia chromosome. In Burkitt's lymphoma there is a translocation between chromosome 8 and the immunoglobulin genes on chromosomes 2, 14, or 22. In both these examples the break occurs at the chromosomal site of the proto-oncogene; in Burkitt's lymphoma it is the c-*myc* gene that is brought close to the immunoglobulin genes. This rearrangement is probably associated with developing the specific B cell malignant phenotype.

Oncogene products

Genes are sequences of DNA on the chromosome that code for specific proteins. If a gene that is important for regulating cell growth were to become aberrant this might lead to uncontrolled cell division, the hallmark of malignancy. In the past four years several reports have shown the similarity between the oncogene products—that is, the proteins encoded by the oncogene—and certain growth factors, growth factor receptors, and enzymes associated with the receptors (kinases). For example, the *erb-B* oncogene product is a truncated form of the epidermal growth factor receptor; it does not bind epidermal growth factor but seems to fire signals into the cells as if it were permanently activated by the growth factor. The *sis* gene encodes one of the



Schematic representation of interaction of growth factors with cellular receptors.

polypeptide chains of platelet derived growth factor; several other oncogenes, such as *src*, encode protein kinases or nuclear proteins that can bind to DNA (figure).

Normal cells produce growth factors, proteins that regulate cell growth. These factors act on target cells by binding to specific receptors on the cell surface. The entry of these bound growth factors may be influenced by enzymes (kinases) that are part of the cytoplasmic domain of the receptor (figure). Whereas some oncogene products appear to be restricted solely to the cell cytoplasm, others such as *myc* and *myb* are restricted to the cell nucleus. The precise action of these proteins is unknown. Any of these steps may become activated, and the consequent uncoupling of the signals for growth may lead to neoplasia.

The different functions of oncogene products around expressing and utilising growth factors suggest a cascade of action: one oncogene may control the release of growth factors, another the availability of receptors, and a third an internal signal fired by the receptor. A cell that is switched to a growth factor and its receptor will become permanently stimulated to proliferate (a phenomenon known as autocrine stimulation).

Clinical applications

There are not yet any applications of oncogene research in routine clinical practice. The nature of the relation between the known oncogenes and human tumours is still being elucidated, and some reports are contradictory. There is still a poor correlation between oncogene expression and the clinical state of the patient or the grade of the tumour. Even oncogene amplification in late stage neuroblastoma is not sufficiently consistent to be used in prognosis. The *ras* oncogene has been found in a mutated form in many types of human tumour—but is not found in most tumours of each type. Nevertheless, as proto-oncogene alterations are better defined they might help in precise diagnosis. One example is the Philadelphia chromosome defining chronic myeloid leukaemia, which involves activating the *abl* oncogene at the chromosome translocation site.

The potential clinical benefit from this basic research in the long term is considerable. Oncogenes are not the cause of cancer, but proto-oncogenes encode proteins that are essential for normal cell growth and when altered contribute importantly to the malignant phenotype. Greater knowledge of the actions of these oncogenes opens the road to specific antioncogene treatment. A monoclonal antibody or a drug designed to compete for the *altered* oncogene product without affecting the *normal* protein would be an excellent form of chemotherapy: not blunderbuss as at present but specifically targeted at the malignant cells. For example, a guanosine nucleotide analogue that would compete for the enzyme activity of the mutated *ras* protein but not react with the normal *ras* product would be an important addition to the antitumour armament.

The more immediate clinical value from research into oncogenes will come from the new approach to tumour classification made possible by characterising the genes associated with particular stages of different tumours. In the future tumours may be typed and staged according to oncogene expression, opening up new approaches to prognosis, imaging for metastases, and even possibly screening of tissue sections for malignant cells.

We are still at the beginning of the human oncogene story, just starting to reap the benefits of 25 years of research into animal viruses. Even if clinical application proves to be 10 years away this research deserves close scrutiny by all doctors interested in cancer.

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