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 car-

cinogens 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.

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

Site and biological action of some human proto-oncogenes

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