carcinogen, the nitrofurantoin FANFT (Cohen *et al.*, 1978). It is not known how saccharin acts as a promoter, but undoubtedly tumours promoted by saccharin show a wide variety of differentiation patterns both within the tumour and in adjacent, non-neoplastic areas of the urothelium. This suggests that saccharin in some way disturbs the normal control of differentiation and, like vitamin A deficiency, encourages random gene transcription, thus increasing the chance of expression of any neoplastic modification of the growth-controlling genes introduced by pre-treatment with an initiator. Saccharin also causes urothelial hyperplasia in some but not all animals, and increased numbers of cells enter mitosis. Thus saccharin has two properties characteristic of skin promoters: it appears to increase the chance of random transcription of the genome and at the same time it encourages cell division, thus promoting and propagating tumour growth.

The final result of neoplastic transformation in any tissue is an altered phenotype, such that the cancer cell expresses certain properties which differ from those of normal cells from which they were derived. It appears to be a disease in which some concomitant phenotypic change in differentiation is obligatory. However, the changes which occur in a tissue during carcinogenesis may also illustrate many changes in differentiation which are not necessarily a part of the neo-

plastic growth syndrome. Promoters encourage random gene expression and the production of multiple phenotypes, among which may be the phenotype associated with cancer growth if the tissue has previously been exposed to an initiating carcinogen.

This work has been supported over a number of years by generous grants from the Cancer Research Campaign.

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PROPERTIES OF SARCOMA GROWTH FACTOR AND OTHER PEPTIDE HORMONES PRODUCED BY MOUSE AND HUMAN TUMOUR CELLS

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MOUSE 3T3 cells have been transformed in culture by a variety of agents, including DNA-containing viruses (SV40, polyoma), RNA-containing viruses (*e.g.* MSV, avian sarcoma viruses) as well as by various chemical carcinogens and radiation. Of these, the clones transformed by MSV specifically demonstrate a loss of cell-surface epidermal growth factor (EGF) receptors. The basis for this apparent loss of receptors is shown to be the production by the MSV-transformed cells of a low-mol.-wt peptide (9-11K) related to EGF. This sarcoma growth factor (SGF) stimulates

normal fibroblasts to assume a "transformed" morphology in monolayer cultures and to form progressively growing colonies in soft agar. EGF, under similar conditions, stimulates cell division in monolayer cultures but not anchorage-independent growth in semi-solid medium.

SGF has been purified from serum-free medium of MSV-transformed 3T3 cells. A critical step in the purification involves the use of formalin-fixed human carcinoma cells, designated A431, that have exceptionally high levels of EGF receptors (2.2×10^6 receptors/

cell). The SGF will bind to the receptors at neutral pH and elute from them in weak acid with the biological activity (induction of anchorage-independent growth, stimulation of cell division, specific binding to EGF receptors) retained. Cells lacking EGF receptors are unable to respond to either EGF or SGF. The two growth factors differ from one another in several ways. Antiserum to EGF does not immunoprecipitate SGF, and antiserum to SGF does not immunoprecipitate mouse EGF. By isoelectric focusing EGF has a pI of 4.4, while SGF has a pI of 6.8. They also migrate differently from one another on polyacrylamide gradient gels. Most importantly, SGF acts in many ways as a "transforming" protein while EGF does not.

Certain human tumour cells have been found to produce a peptide growth stimulat-

ing factor that is similar in many respects to SGF. A factor produced by a human rhabdomyosarcoma cell line, A673, has been partially purified. It has an apparent mol. wt. of 21,000 and competes with EGF for EGF-specific membrane receptors. Like mouse SGF, it induces normal cells, of either rodent or primate origin, to proliferate in soft agar, and it also brings about a rapid morphological transformation of cells in monolayers. Binding to and eluting from the EGF receptor-rich human carcinoma cells, A431, results in substantial purification of this growth factor. The exact relationships between human SGF and mouse SGF remain to be determined. The possibility is considered that SGF is a more "virulent" form of a normal growth-regulatory protein.

ECTOPIC HORMONES—AN EPIGENETIC CHANGE EXPRESSED IN NEOPLASIA?

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THE PRODUCTION of a peptide hormone by a tumour arising in a tissue or organ not normally associated with that hormone is now a well established phenomenon in the biology of human tumours, particularly those of bronchial origin (Rees & Ratcliffe, 1974). This apparent phenotypic change accompanying the emergence of a neoplasm presents an attractive model in which to examine the relationship between the expression of cell differentiation and the new acquisition of specifically neoplastic characteristics.

First it is necessary to establish that a true heritable change in differentiation has taken place, not that there is simply a neoplastic emergence of a small hitherto cryptic population of hormone-producing cells. The normal lung contains populations of cells sharing ultrastructural (McDowell *et al.*, 1978) and histochemical (Taylor, 1977) characteristics with known peptide endocrine cells of the APUD series, but current evidence has failed to demonstrate the normal existence of any of the more commonly tumour-associated peptide hormones (*e.g.*, ACTH, calcitonin or vasopressin) in these cells. On the contrary, tissue-extraction studies have shown a rise in

one of these peptides, ACTH, in extracts from the lungs of a dog subjected to a potentially carcinogenic stimulus and from a range of human pathological lung tissues (Yalow, 1979). This suggests that a phenotypic change can occur in pathological conditions, though it is not clear which cells of the several types within the lung are involved.

Evidence on the nature of the hormones produced by the lung tumours suggests that they have essentially the same chemical identity as normal hormones or their precursors or fragments (*e.g.*, ACTH and related peptides in a small-cell Ca lung (Bertagna *et al.*, 1978), although the enzymes responsible for processing the hormones for release in their "normal" form may be absent or inappropriate (Lowry *et al.*, 1976). This suggests that the change which has brought about the hormone production is an epigenetic one in which the "normal" gene for the hormone is being expressed in an abnormal or inappropriate way.

The direct relationship between the phenotypic change and the neoplastic initiation is not yet clear. Evidence from other systems suggests that carcinogens can effect pheno-