Tumour therapy

The collective name *«cancer»* comprehends the formations of new tissue threatening with autonomous growth the functions and existence of the organism in which they develop. These new formations are found in all living species including the plants (fig. 319, 320) but seem to be most frequent of all in long-lived and highly differentiated multicellular creatures. This may be the reason why cancer is the most frequent disease in man and the second most frequent cause of death behind the cardiac and circulatory diseases.

Biologically intact associations of cells integrate into an association of tissue or an organ by self-guidance and self-control of their growth i. e. they arrest their growth where they meet with neighbouring structures. The cancerous tissue has lost this self-control, does not stop its growth at areas of contact, continues expanding and infiltrating and thus forms a complex of tissue i. e. a tumour outside the functional laws of the organism. The concept of *«tumour»* is largely used as a synonym for *«cancer»* even though is does not strictly correspond. The *«malignity»* results from the parasitical character (consumption and withdrawal of foodstuffs at the expense of the economic requirements of the host),

Tab. 54:
Frequency of cancer with separation of the organs expressed as percentages in men and women, according to the US American Cancer Society:

Affections

Men		Women
23%	skin	13%
3%	oral space	2%
	breast	23%
19%	lungs	5%
11%	colon	13%
9%	other digestive organs	7%
11%	prostate	
	uterus	14%
6%	urinary organs	3%
7%	leukaemia and lymphoma	6%
11%	all others	14%

Table 55:
Frequency of cancer with separation of the organs expressed as percentages in men and women, according to the US American Cancer Society:

Causes of death

Men		Women
2%	skin	1%
3%	oral space	1%
	breast	21%
30%	lungs	9%
12%	colon	15%
15%	other digestive organs	13%
9%	prostate	
	uterus	7%
6%	urinary organs	3%
10%	leukaemia and lymphoma	10%
13%	all others	20%

on the one hand, and from the stubbornness of the growth against sound neighbouring tissues, on the other hand.

Frequency

The increase of life-expectancy and the changes of the human biological environment have for consequence that in the highly mechanized, densely populated industrial countries every 6th–8th individual nowadays suffers from cancer. The frequency of the cases (tab. 52, 53) differs from the pattern of the causes of death by cancer, according to the percentages worked out in the USA (MAUGH, Th. N. and MARX, J. L., 1979).

Forms

From the more than 100 diagnostically differentiated kinds of cancer, actually 3 main groups can be abstracted namely the mesenchymal, epithelial and mixed tumours. With the mesenchymal tumours subdivided by the degree of maturity and by clinical viewpoints, the following grouping results:

1. Mesenchymal tumours
   a) sarcoma
   b) lymphoma
   c) leukemia
2. Epithelial tumours
3. Mixed tumours

Sarcomata originate from derivatives of the mesoderm (bones, cartilage, connective tissue, vessels, muscles), form solid, rapidly growing and, therefore, very malign tumours; they occur frequently in young persons. The rate of their frequency among cancerous diseases comes to somewhat below 2%.

Malign lymphomata originate from the thymo-lymphatic tissue. Undifferentiated lymphocytes of the thymus, spleen and peripheral lymph-nodes proliferate locally into complexes; an increased volume of the affected organs and an impaired function characterize the clinical symptoms. *Lymphogranulomatosis (Hodgkin's disease)* is the most important of the subgroups. Malign lymphomata make 5% to 6% in general cancer statistics.

In *leukemia*, unripe white bloodcells from the bone-marrow are washed out. The total quantity in the peripheral blood can, but need not, be increased. The ripening can be arrested in the phase of the mother cells or myeloblasts as in leukosis of childhood with an increase of the mononuclear prophases (leukemia of the mother cells, myeloblasts, micromyeloblasts) or in the prophases of the myeloic-granulocytary series with proliferation of the promyelocytes, my-

Fig. 319, 320:
Tumorous degenerations of trees (plane-trees); their biological development is prevented by continuous trimming.

elocytes and metamyelocytes. The unchecked proliferation of the unripe prophases of the one system suppresses the other systems.

Of the 655 000 cases of neoplasm diagnosed on an average every year in the USA (MAUGH and MARX, 1979), 3%–4% come under leukemia. Among the tumours of childhood, leukemia makes with 25% the largest group, followed by the tumours of the central nervous system.

Carcinoma (cancer in strictly sense) develops from epithelial tissue of the outer and inner limiting surfaces of the body. Starting points are the skin, mucosae of the respiratory, intestinal and urogenital tracts incl. their glands. Tumours of the central nervous system belong to this group as far as of ektodermal origin. About 85% of the human tumours are carcinoma, and the higher age-groups are more affected than the young.

Mixed tumours make a group of about 4% of the total. *Embryonic mixed tumours*, tumours of ovaries and testicles belong to them.

Principle of pathogenicity

Malign tumours have 4 common properties:

1. *Disproportion between the nucleus and cytoplasm;*
2. *Unchecked and uncontrolled growth;*
3. *Disdifferentiation in the sense of a formal arrest in prophases of cell maturation*
4. *Formation of metastasis.*

The disproportion between the nucleus and cellular body probably constitues the decisive fundamental principle of the cancer cells. The flow of energy and biochemical regulations depend on a harmonic coordination between the nucleus and cytoplasma organelles. With the *«genetic space» (nucleus)* growing in proportion to the *«economic space»* of the cell (space between the cytoplasma membrane and nuclear membrane including the organelles) the ecologic harmony of the cell is lost. This misguidance is probably double-countertracked: the nucleus conveys its information wrongly coded (fig. 321) or not at all via the nucleolus to the centrioles and ribosomes. The centrioles lose the mechanism controlling the cell-division, the ribosomes can no longer form specific proteins integrable into the body. As all cell organelles depend on the information of the nucleus, the economic space of the cell can no longer exert its function of providing the cell with the substances and products of synthesis necessary for the correction of the false development. The accumulation of genetic material (DNA), which cannot be converted reasonably into structures (RNA-proteins), compels the centrioles to follow a dividing strategy as the comparatively small space of cytoplasm threatens the existence of the nucleus because the latter is inadequately supplied. The unchecked growth of formations that cannot be integrated into the systemic ecology is the fundamental principle of the malignity of the cell. The malignity of the boundless growth, which, unintegrable, does not stop before the physiological structures, is due to this mechanism.

The unchecked, uncontrolled in the sense of the systemic function, growth is accounted for by the loss of the ability to arrest the growth when getting into touch with neighbouring cells. On principle, primitive embryonic properties are redeveloped. The mesenchyme (from Greek «enchein» – to fill in) fills by rapid growth during the embryonic period the spaces between the endoderm and ektoderm, thus achieving virtually the form of a mammal organism. But where-

as here the interplay between the mesenchymal dynamics and the ektodermal control works, this control mechanism no longer exists beyond the embryonic period.

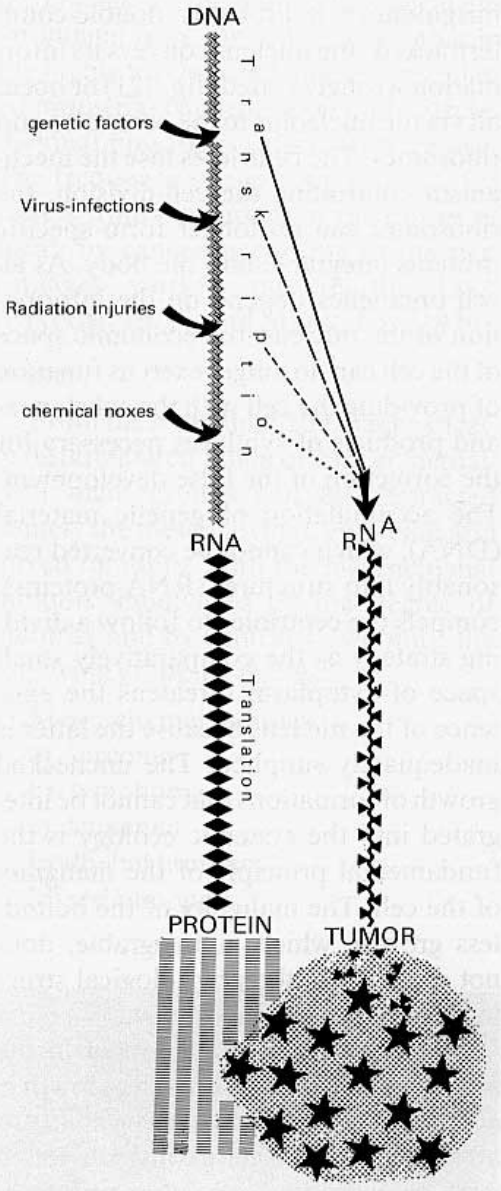

Fig. 321:
Theory of tumour genesis. Various noxae can change the transcription of the DNA so that with an abnormally coded RNA necessarily a protein differing from the autogenous structural law i. e. not integrable protein will develop. The ripening of the affected tissular formations may come to rest at any phase of development (= unripe tissues).

The term *«disdifferentiation»* is derived from the fundamental idea of a regression into embryonic prophases. For the pathobiological and therapeutic problems of malign tumours it would probably be more expedient to suppose a disturbance of ripening rather than a regression.

A further consequence of the uncontrolled growth is the formation of metastasis i. e. the property of malign tissues to form colonies in other regions of the body not immediately connected with the tumour.

Etiology

Without entering into particulars of etiological problems, it should be stated that 4 groups of causes are discussed for the origin of cancer because narrow connections between these noxae and cancer can be taken for granted.

1. *Genetic causes*, due to the accumulation of tumours and special kinds of tumour over generations of a family.
2. *Radiation genesis*, proved by the radiation cancer in the X-ray pioneers, the accumulation of leukemia after explosions of atomic bombs, the increased disposition to cutaneous cancer as a result of excessive exposure to natural radiation (cutaneous cancer of farmers) or radioactivity in the mining industry (« Schneeberger's lung-cancer»).
3. *Chemical carcinogenesis.* Of the nearly 1000 compounds capable of producing cancer both in vitro or in man, some are of special importance as part of the natural environments. They provoke chiefly carcinoma of the outer (skin), still more of the inner contact (lung, nasal cavity) or excretory (bladder) surfaces. The most important substances belonging here are (MILLER, E. C., 1972):

soot, smoke of cigarettes, tars, mineral oils; 2-naphtylamin, 4-aminodiphenyl, benzidine, N-N-Bis (2-chlorethyl)-2-naphtylamin, Bis (2-chlorethyl) sulphide compounds of nickel and chrome, asbestoses.

The carcinogenetic substance used most frequently in experiments on animals is benzpyren.

4. *Viral carcinogenesis.* Two arguments have prevented any serious discussion of virus genesis for decades. Viruses normally lead to a specific immunity, not to a tumour; on the other hand, tumours are not infectious, as one should expect from a viral genesis.

Of the DNA viruses, adeno-, papova, SV40-, polyama viruses can provoke tumours in experimental animals and transform cells in the culture. But a connection with human cancer has been proved so far neither here nor for the herpes viruses (RAPP, F., 1974; TODARO, G. J., and HUEBNER, R. J., HUEBNER, R. J., 1972). The strongest indications are those for the *Epstein-Barr-virus*, which is said to account for the existence of the *Burkitt lymphoma.* Of the oncogenous RNA viruses (oncorna viruses, RNA tumour viruses), especially the C-RNA viruses classified in group C provoke mesenchymal tumours (sarcoma, lymphoma, leukemia). B-RNA viruses are associated with malignomata of the mammary glands, A-RNA viruses are not oncogenous.

The theoretical possibility with virus infections is there, as shown in a model by SHANNON, W. H. Everything depends on whether or not the DNA modified by viruses can be integrated into cellular DNA. Non-integration means proliferation of viruses and, possibly, subsequent immunity whereas integration effects a chimerism between the systemic DNA and viral DNA, with failure of the transcription and translation, which leads to a transformation of the cells (fig. 321).

From the safe proofs of all 4 etiological groups appears the absence of a common cause though the initial point of the malign transformation of the cell seems to be largely uniform. The structural change of the DNA may be traced out genetically in the one group; in the chemical and radiation groups, chemical changes especially formations of epoxyde, and in the viral genesis, foreign nucleic acids will cause aberration of the DNA architecture and incorrect codes.

Tumour immunology

The disappointing results of the conventional therapies have much contributed to a renascence of the tumour immunology during the last years. H. HOEPKE (together with HEMPFING) mentioned already late in the twentieths and early in the thirtieths years of this century the importance of the «body-own defense», of the thymus and of the lymphocytes. In the fiftieths, HOEPKE resumed the tumour research with thymus and spleen implantations in animals, with different but not satisfying, after all, results. At the beginning of this century already, tests were conducted to take a

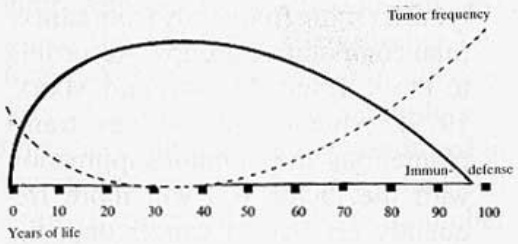

Fig. 322:
Reciprocity between the power of immunoresistance and frequency of tumour in the life profile.

therapeutic initiative with tumour transplantations.

There is probably a connection between the formation of a tumour and immunizing processes because the life profile of the immunocapacity practically constitutes a reciprocal to the frequency of tumours (fig. 322). During the last few years, the interest has been concentrating chiefly on the so-called *«onco-fetal antigens»*. According to this theory, supported by many especially by RENNER(H. RENNER, 1977), the tumour cells have on their membranes antigens differing immunologically from surface antigens of body cells. These membrane-associated tumour antigens provoke an immunoresponse of the body after the injection of fetal tissues (fig. 341). The *«theory of immunesupervision»* says that tumour cells are produced during the entire life but are destroyed by the immune-defense till this mechanism fails to work. This most probable of all theories is based on several facts:

a) the accumulation of tumours in the marginal periods of life of the not yet ripened (1st-5th years of life: leukemia, CNS tumours) and exhausted immune-defence (increasing frequency of carcinoma in old age, see fig. 322).
b) 10% of the patients with genetic syndromes of deficient immunocapacity suffers of tumours (GOOD, R., 1974; WALDMANN, T. A., et al., 1972).
c) Patients treated immunosuppressively suffer more frequently from cancer than comparative groups. According to PENN, I. (cit. MAUGH and MARX, 1979), patients with kidney transplantations and immunosuppression with the factor 100 will more frequently get sick of cancer than the equal agegroups.

There is no answer to the question whether the failure of the tumour-defense is caused finally by *«blocking antibodies«* (HELLSTRÖM, K. E. and HELLSTRÖM, I., 1974) or by *«eliminating the immune-defense»* with an excessive supply of antigens or by reducing the potential of immunocompetent cells. A correct estimation is difficult as immuno-stimulations accelerate rather than inhibit the growth of tumours under certain condition *(«enhancement phenomenon»)*.

Therapy

Though the fundamental research is chiefly preoccupied with the elementary processes of cellular transformation, the therapy has so far been following virtually other ways. *«Steel and radiation»* i. e. operation and X-ray therapy have limited possibilities on primary tumours. Chemotherapy has been successful in several systematized tumours such as leukemia and lymphoma, but seems to provide disadvantages rather than advantages in the most frequent kinds of cancer.

P. NIEHANS maintained early already (between 1950 and 1960) that cell therapy had a cancer-preventing effect; unfortunately his catamnestic reports in this respect on more than 1000 cell-treated patients have never been evaluated.

Starting from the basic process of cell transformation i. e. the prevention of the transfer of genetic information into corresponding structures, the RNA is no doubt very important. If the development of structures in plants is prevented by artificial interventions e. g. continuous trimming (fig. 319, 320), tumorous formations will originate. This circumstance was the primary starting point for the use of fetal connective tissue in cancer research, a trend from which later the product *«fetal mesenchyme* of the umbilical cord» (denoted as *«Resistocell®»*) developed.

Comprehensive experimental and clinical experience on the effect of this fetal mesenchyme is available, namely systems of cell cultures (LANGENDORFF, v. L., 1977, 1979), morphological studies (HOEPKE, H.; LANDSBERGER, A., 1977–1980), immunological studies (RENNER, H., 1977, 1979, RENNER, H. et al. 1980); (FUENTE DE PERUCCHIO et al., FUENTE CHAOS, della A., GIANOLI, A. C. and PEREZ-QUADRADO, S., 1979) and clinical studies (LANDSBERGER, HOEPKE, HAGMAIER, RENNER, 1979; ENDERLE, E., 1979; SCHNITZLER, A., 1978; HAGER, D. 1981; RENNER, K. H. et al. 1982).

The differentiation of the cell-culture systems has allowed to test fetal mesenchyme in 2 kinds of tumour in the tissue culture (LANGENDORFF, v. L. W., 1977, 1979). Arrangements of tests and results with a *Hodgkin-like lymphoma* will be given hereafter in the original, the results with a Wilms' tumour tissue as a summary.