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Medical Complications in Cancer Patients

Editors
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Volume 7

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Preface

Cancer therapy has greatly changed during the past years, owing to the increasing use and efficacy of chemotherapy. Previously, the medical aspects of cancer therapy were primarily restricted to the problems that the cancer patient shares with any other seriously sick patient and to the management of complications related to radiotherapy or surgical treatments that were often aggressive and/or extended.

Now the medical oncologist must use an increasing number of chemotherapeutic agents, often in combination, and must face the multiple side effects and the significant morbidity that result from their use. Since many patients can be cured or significantly improved by chemotherapy, it is essential to lower to an acceptable limit the inconveniences that might result from it.

There is a complex interrelationship in the cancer patient among the manifestations linked to the tumor itself or its abnormal secretions, the diseases afflicting the patient in addition to the tumor, especially those that become common with increasing age, and the iatrogenic morbidity primarily related to cancer chemotherapy. It has become increasingly necessary that the medical oncologist be aware of the need to consider these interrelated influences equally at all times.

Therefore, the medical complications in cancer patients have become of major concern to all physicians who are faced with the comprehensive management of the cancer patient. In this volume, we meet the problem following a system/organ-oriented approach. This is deemed appropriate because clinical signs and symptoms remain the basic guides to most clinical problems in medicine. This is why cardiac, pulmonary, renal, neurologic, gastrointestinal, and cutaneous manifestations related to cancer and/or its therapy are discussed in individual chapters. In addition, endocrine manifestations of tumors and important nutritional aspects in cancer patients are discussed. Special attention is paid to the prevention and therapy of chemotherapy-induced bone marrow failure. Bleeding and infections, common morbid manifestations in cancer patients, are extensively discussed in this respect, including considerations on hematopoietic reconstitution. Another area covered is the psychological aspect of cancer diagnosis, including cancer patient terminal care and the management of pain.

The roles of cancer and of its therapy in the different body systems are analyzed. The roles of the tumor or of its therapy may be more or less important, depending on the clinical syndromes presented by the cancer patient. These are summarized in this volume: Infection is most often the consequence of therapy, while endocrinologic manifestations usually reflect the activity of the tumor itself. Nonetheless, the purpose of this book is to present the cancer patient as the entity presenting himself or herself to the clinician and in whom

the natural history of the tumor is modified by the underlying clinical conditions and by cancer therapy. It is the role of the physician to sort out the various possible causes for the clinical signs and symptoms presented by the patient and to propose adequate treatments. Any approach not based on a comprehensive approach to the cancer patient would be biased toward a single and narrow aspect of cancer medicine.

Because our work is aimed at a global approach to the cancer patient, this volume will be useful to internists and oncologists alike; its purpose is to provide a system-oriented review of the morbid manifestations that can be observed in cancer patients whatever the causes may be. The editors believe that only such a comprehensive approach can be beneficial to both physicians and patients.

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Clinical and Biological Implications of Paraneoplasia

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The term paraneoplasia, or paramalignancy, is of recent date, but the phenomenon itself has been known and discussed for several centuries. The fact that patients with malignant tumors lose weight and appetite, develop fever, become anemic, and feel miserable is nothing new. Still we do not know anything crucially causal about the basis of these general symptoms. It is possible that an analysis of other, more special results of tumor metabolism will help us understand these more fundamental mechanisms. It seems as if the majority of symptoms with a known cause that are also reversible after radical treatment of a malignant tumor could be traced to one special group of substances, i.e., polypeptides (19).

ECTOPIC HORMONES

Several authors have been active in developing the concept of ectopic hormone production by malignant cells. Albright was probably the first to suggest that an increase in serum calcium, as we sometimes see in patients with malignant tumors, might be caused by some substance produced by the tumor. At that time it was taken for granted that metastases to bone liberated calcium through destruction, but Albright and Reifenstein (1) stressed the point that a high serum calcium level could also be found in patients who had no skeletal tumors.

The first authors who showed that removal of a carcinoma normalized the serum calcium values were Plimpton and Gellhorn (13). In their patient with an ovarian carcinoma, a relapse of hypercalcemia was seen together with the development of metastases. The term ectopic hormone production was coined by Liddle and his group when they described and studied the occurrence of Cushing's syndrome in patients with tumors arising from nonendocrine tissue. This is the key observation for understanding these processes. These authors (9) showed that the tumor cells produced adrenocorticotropin (ACTH) or ACTH-like substances that stimulated the adrenal complex. Work along these lines has produced very interesting results clinically, and the number of examples illustrating the connection between hormonal activity and cancer cells is large.

In spite of the fact that specific activity which manifests biologically or by immunological reactivity has been established, the discussion regarding the true nature of the molecules is still lively. Regarding the hypercalcemic factor, most authors seem to accept the fact that parathormone, possibly with various structural modifications and also occurring as "big" PTH, is the hypercalcemia-producing factor. On the other hand, such studies have initiated very interesting research regarding the importance of other substances for understanding calcium homeostasis. The prostaglandins seem to play an important part in some of these situations, but it is still impossible to prove their role in cancer hypercalcemia. This is partly due to the difficulties connected with quantitative determination of these molecules and their metabolites. The effects of substances such as aspirin and indomethacin, known inhibitors of prostaglandin synthesis, are also used as arguments in this discussion. Several authors believe that steroids may be involved, especially in hypercalcemia connected with mammary carcinoma. Extensive and critical analyses of sera from such hypercalcemic patients seem to have proved convincingly that PTH-like polypeptides are the most common cause. Analyses of such sera and also of sera containing ectopic ACTH have been valuable in the establishment of molecular heterogeneity among these hormones. This seems to have taught us that "big big," "big," and small molecules may occur, which is also important for understanding normal hormone production (2).

OTHER POLYPEPTIDE HORMONES

A number of other polypeptide hormones are produced by malignant cells, and most are not ectopic. They are formed by cancer cells arising from tissues that are normal producers of such hormones. Our knowledge regarding the products of the pancreatic islet cells would be meager if we had not had the opportunity to study patients with tumors from specific cell types. Beta-cell tumors producing insulin as a topical product are well known. During the last decade the number of products from alpha-cell tumors has increased remarkably. First among these tumors were the hypergastrinomas belonging to the Zollinger-Ellison syndrome with intractable gastric and duodenal ulcerations that healed after the removal of the tumor. Some of these tumors also produced severe diarrhea, and the diarrheogenic factor vasoactive intestinal polypeptide (VIP) has been isolated in these patients.

[The reader who has a feeling for the meaning of words must have a natural reaction against such terrible constructions as insulinoma, glucagonoma, or VIPoma! For the sake of biological clarity, however, these expressions are valuable. Hence these illogical constructions have come to stay.]

The alpha cells produce a factor that may be regarded as an antagonist to insulin, i.e., glucagon. The syndrome that results from the overproduction of this polypeptide was recently described (14). Its recognition at an early stage of the disease leads to complete postoperative cure of all the symptoms. The

effects of glucagon on carbohydrate metabolism are well known, but another symptom deserves special mention. It has been found that the amino acid levels in these patients are very low. Intravenous infusions of solutions containing amino acids have an almost miraculous effect on the condition of the skin in these patients, who suffer from widespread, chronic, debilitating, migratory, necrotizing dermatosis and also have a smooth, sore, bright red tongue (8). All these symptoms disappear after a few days if amino acid levels in the blood are increased. This means that the condition of the patients, as far as the skin is concerned, may become normalized preoperatively. Removal of a single tumor may give complete and lasting cure. Even if metastases are present, effects may be obtained by using a new antitumor agent that is specially effective in several types of alpha-cell tumors, i.e., streptozotocin. The reason this antibiotic should be more or less specific in this type of tumor is a problem that seems well worth investigating.

Another polypeptide hormone that may be produced by islet cell tumors is somatostatin. Recently a "somatostatinoma" was diagnosed and treated successfully. With the aid of fluorescent antibodies, it was possible to determine that the D-cells in the pancreatic islets contain somatostatin. The name means that this factor is in a way a negative, inhibiting, static hormone. It not only inhibits endocrine functions regarding somatotropin in the anterior pituitary, but also influences insulin, glucagon, pancreatic polypeptide, and the cholecystokinin–pancreozymin system, with effects on many metabolic functions. The fact that it does not have any "positive" effects makes the clinical diagnosis much more difficult. As a matter of fact, it is possible to obtain a reliable diagnosis only through quantitative determinations of the hormone in the serum. The basis for clinical suspicion is vague, consisting of dyspepsia, mild diabetes, and gallstones. As these symptoms are very common, it is clear that patients may have this triad without suffering from this very rare tumor. At the present moment it appears that no more than six cases have been diagnosed, and only one of the patients was successfully operated on and has remained asymptomatic during a follow-up of 2.5 years (3,6).

A recent publication reviews the syndrome, with a thorough study on a cooperative patient. To date, this review is the best basis for further information. The patient had multiple metastases and is now being treated with streptozotocin.

It is interesting that so many of these hormone-producing tumors excrete several active polypeptides. Somatostatinomas have also been found to produce calcitonin (two cases) and ACTH (one case). Such findings may be explained in several ways. It is well established that there are many homologies between several of the gastrointestinal hormones, e.g., secretin, glucagon, and VIP or cholecystokinin and gastrin. Another important finding is connected with the pituitary ACTH system. Big ACTH with a molecular weight of 31,000 contains normal ACTH with 39 amino acids. Within this molecule, the first 18 amino acids correspond to melanocyte simulating hormone (alpha-MSH). No less than 91 amino acids in another part of big ACTH constitute a "beta-lipotropin"

(beta-LPH). This was first discovered by Li, who gave it the name beta-LPH. It contains beta-MSH and beta-endorphin consisting of 30 amino acids. A small but important part of this body peptide is the pentapeptide met-enkephalin. It is thus possible that large polypeptide molecules are formed first, and through the activity of intra- or extracellular proteases smaller fragments are set free. These may have different activities from the "mother" polypeptide.

A third possibility that must be taken seriously is that malignant cells have a tendency to derepress several independent polypeptide-forming systems in the same cell (17). Recent investigations have shown that many cancer patients have several unrelated active polypeptides in their blood. The number of ectopic nonactive, and therefore not determined, foreign polypeptides may be large.

B-LYMPHOCYTE IMMUNOGLOBULINS

I mentioned these instances of topic hormone production because they have taught us much about the biology and pathophysiology of certain cells, even though they are rare. Much more common and therefore more important from the practical point of view are such connections as immunoglobulin production by the descendants of B-lymphocytes. Practically all our knowledge regarding the structure of immunoglobulins has come from analysis of such products.

Unique in this field is the connection between one special type of myeloma and allergy. It was found that a patient with myeloma, observed at the Academic Hospital in Uppsala, Sweden, produced in pure form an immunoglobulin molecule that did not belong to the four types already established. At the same time, allergologists in the United States had found that the allergic reagin must be a special type of immunoglobulin that could be obtained only in minute quantities from very large amounts of serum from allergic patients. It was established that the myeloma globulin was of the same type, and antiserum against immunoglobulin E (IgE) was produced. With the aid of such antisera, the amount of allergic reagins that were IgE could be determined in the blood from patients with varying diseases. It may well be said that the availability of pure IgE, produced by a limited number of myeloma patients, gave a firm biochemical basis to allergology. Such experiments of nature—when a special clone of cells secretes a special product—have contributed much to the understanding of obscure biological mechanisms.

CARCINOID TUMORS

One of the most spectacular paraneoplastic syndromes is connected with metastasizing carcinoid tumors. Short intensive flushes with hyperperistalsis and diarrhea constitute the classical syndrome. Sometimes these patients also have signs of bronchoconstriction. The most surprising finding is the pulmonary and tricuspid valve lesions that develop after many years. It is quite clear that 5-hydroxytryptamine is responsible for a number of these symptoms. Carcinoid

heart disease must be regarded as a biochemically induced valvular heart disease (16). Rare instances have been described with carcinoid tumors arising in the stomach. These patients have a much more long-lasting bright red and blotchy flush (18). This symptom is connected with itching, and it is clear that the mediator is histamine released from the tumor. The signals on the skin as well as the general clinical picture are different in these two types of argentaffinoma (19).

Some of these patients develop signs that have been interpreted as indicating pellagra. Workers at the National Institutes of Health (U.S.A.) performed metabolic studies on these patients and showed that a very large part of the tryptophan pool is converted to 5-hydroxytryptamine (5-HT). It is therefore diverted from the normal pathway that leads to formation of pellagra-preventing factors (niacin). This is thus a unique example of tumor "parasitism," when the neoplastic cells consume an essential factor and thereby injure the patient. This has of course been hypothesized for years but proof is lacking to date. I am certain that the possibility of such mechanisms should be considered in other situations in oncology.

Two tumor sites are of special interest in this connection. It has been found that carcinoid tumors of the lung are not rare. Sometimes they produce the typical syndrome with flushing and valvular heart disease. The fact that these valvular changes are located in the left heart speaks strongly in favor of the assumption that blood coming directly from the tumor to the heart contains an active principle which influences the endocardium.

The other situation in which a primary carcinoid tumor is found is with teratoma of the ovary. These patients have a complete syndrome, probably because the tumor products enter the inferior vena cava and are taken directly to the right heart. We have seen patients who no longer had clinical symptoms after extirpation of the tumor because they had no liver metastases. The biochemical findings also became normal, with a remarkable drop in hydroxyindole acetic acid. Initially the cardiac decompensation seemed to improve, but eventually both of our patients died from decompensated heart disease just like other patients who have carcinoid tissue in their liver metastases. We have seen one patient who had a very large hepatic tumor that was resected and had a long-lasting remission (19).

ANTIBODIES TO COAGULATION FACTORS

An interesting paraneoplastic situation is the development of specific antibodies against some coagulation factor. Such anticoagulants, active *in vivo* by causing bleeding, as well as *in vitro*, have long been known to be present in patients suffering from autoimmune disease, especially systemic lupus erythematosus (SLE). During the last few years some such inhibitors acting against factor VIII in hemophilia have also been described. Recently acquired von Willebrand's disease has been found in patients with lymphatic leukemia or lymphoma. The

specific antibody has been an IgG in two cases and an IgA in two. In all four observations the immunoglobulin was monotypical, but the mode of action was rather complicated. An interesting example of this situation was recently published by Zettervall and Nilsson (20).

DISCUSSION

Do we have reason to believe that many of the enigmatic connections between tumors and very special clinical signals will be clarified in the future? A few such examples may be cited. Acanthosis nigricans is one of the classical paraneoplastic phenomena. It has a strong association with tumors in the gastrointestinal tract but has also been seen in conjunction with other cancers. Some years ago we had a patient with an astounding degree of acanthosis (10). After removing a number of mediastinal and hilar metastases containing squamous cell carcinoma, the skin lesions completely disappeared and have not reappeared during an observation time of 4 years. It may be guessed that this tumor could produce an epithelial cell growth factor. Such substances are known to be polypeptides. Large amounts of this factor, which is otherwise difficult to produce, might be isolated from the excreta of such patients. The same could be true about other, similar factors.

Osteoarthropathy is known to occur with cancer of the lung. In rare instances extirpation of other cancers have also been successful in curing these changes. Ten years ago we reported some investigations of such patients with reversal after a successful operation of the lung tumor (15). We believed that increased levels of growth hormone might have been responsible for the changes in bone and soft tissue of the hands that in many ways resemble the changes seen in acromegaly. At present, it seems that increases in growth hormone are not obligatory in this syndrome. It is probable that other growth factors (e.g., somatomedin) may be responsible. This would be easy to investigate if a typical patient is found and the serum is analyzed by a competent biochemist.

The relationship of malignant tumors to the function of blood-forming organs has been of great interest for many decades. Normochromic anemia with a low serum iron and a normal or low transferrin level is a characteristic of tumor anemia; it is also found in other chronic diseases, however, and is therefore nonspecific. It seems probable that cancer anemia is caused by some substance(s) that inhibits the erythron. Stimulators of erythropoiesis are well-known products of tumors, especially those arising in the kidney. Erythropoietin has been the subject of extensive and well-organized attempts at isolation, but without much success; it is one of the most elusive active substances in medicine. It seems reasonable to assume that pooled urine specimens from patients with renal tumors producing erythropoietin might be the most promising source for the preparation of this substance. Furthermore, the fact that nonrenal tumors may produce excessive erythropoietin is probably important to the understanding of erythropoietin formation. The relation between renal cancer cells, the epithelial

lining of cerebellar cysts, and the smooth muscle in uterine myoma seems enigmatic. All three conditions are connected with polyglobulinemia, which may be reversed after operative treatment.

We may well discuss if erythropoietin should be regarded as a "hormone" active on the erythropoietic stem cell in a manner similar to the way pituitary tropins influence their target cell. Erythropoietin may also be compared to the fetal inducers, i.e., substances that induce the transformation of one type of cell to another. It is probable that one of the so-called thymic hormones that induce T-cell formation from a lymphatic stem cell is a similar substance.

There are tumors associated with marked thrombocytosis and others associated with extreme eosinophilia. In both of these instances specific poietins have been discussed. We know little about such substances in regard to platelets. We do know, however, that thrombocytosis is reversible after extirpation of the tumor. Recent work by Mahmoud and his group demonstrated the existence of eosinophilopoietin (7). This substance appears to be a polypeptide with a molecular weight in the range of 186 to 1,357. It is digested by pronase and practically inactivated by heat. Probably the excessive eosinophilia seen in some cancer patients is caused by this or similar substances. It has no eosinophilotactic activity, but work in Austen's laboratory demonstrated that comparatively simple peptides have a strong attractive influence on eosinophilic cells. It is therefore probable that eosinophilia in cancer patients may also be caused by the presence of such factors, especially when there is eosinophilia in the blood and in the tumor.

The fact that some of the tumor products are not so much ectopic as asynchronous (i.e., they represent a return to fetal production) is also an important factor in paraneoplasia. Fetuin is one such substance of great practical importance as a tumor signal (19).

It is well known that fetal liver cells produce a special protein that migrates on electrophoresis between albumin and α_1-globulin. This protein has been called α-fetoprotein, and with the aid of specific antibodies its presence can be demonstrated in the serum of adult patients with malignant hepatoma. The connection between this substance and the type of liver tumor is obscure, and about one-third of patients with malignant hepatoma lack an increase in the protein. It is also remarkable that aflatoxin hepatoma does not induce formation of α-fetoprotein, whereas other carcinogens may cause hepatomas that do. No differences in histology have been found.

There are similar examples that are still more enigmatic. Several years ago we saw a patient with a carcinoma of the lung who had severe intractable anemia and no less than 35% fetal hemoglobin in his red cells (11). Hypothetically, the tumor may produce a substance that "turns on" the synthesis of the fetal chain in globin. If this substance exists and could be recognized, this could mean much for the treatment of two of the most widespread global diseases: thalassemia and sickle cell anemia. Increased production of fetal hemoglobin could become a valuable aid in improving the anemia in these patients.

There are other interesting reversals to fetal conditions seen in carcinoma patients. One of the most astounding is the development of the "monkey face" in patients with tumors. This is explained by the fact that fetal hair (typical lanugo) grows all over the body including ears and forehead (5). As yet nobody has observed reversal after successful operation, but it does not seem far-fetched to assume a specific lanugo-promoting factor or inducer.

The examples quoted have mostly been polypeptides; a great many others may be found. In a few instances complete protein molecules have also been observed, but it is striking that single gene products are so common. This may offer a clue to tumorigenesis. We know that the greatest part of the complete genome is repressed, i.e., nonactive. The question is if all these polypeptide-synthesizing systems are dead or dormant. In the latter case they may be awakened, derepressed (17).

We have already discussed parallels with fetal physiology and the activity of inducers. Developmental biology *(Entwicklungsmechanik)* may perhaps offer some arguments for this discussion. Gurdon, an eminent experimental zoologist working in Oxford and Cambridge, performed interesting experiments in this connection (4). He showed that a nucleus from a somatic cell, if transferred to the enucleated cytoplasm of an egg from the same frog species, could induce the development of a whole fertile animal. This experiment must prove that the complete genome in every body cell is in a dormant state that can be derepressed under favorable conditions. It therefore seems probable that individual genes could be derepressed in cancer cells and start synthesizing fortuitously diverse polypeptides. As a matter of fact, recent work has shown that a great many cancer patients have numerous foreign polypeptides in the blood that can be discovered with the aid of sensitive radioimmunoassay methods.

REFERENCES

1. Albright, F., and Reifenstein, E. C. (1948): *Parathyroid Glands and Metabolic Bone Disease,* p. 93. Williams & Wilkins, Baltimore.
2. Benson, R. C., Jr., Riggs, R. C., Pickard, B. L., et al. (1974): Radioimmunoassay of parathyroid hormone in hypercalcemic patients with malignant disease. *Am. J. Med.,* 56:821–826.
3. Ganda, O. P., and Soeldner, J. S. (1977): "Somatostatinoma": follow-up studies. *N. Engl. J. Med.,* 297:1352–1353.
4. Gurdon, J. B. (1974): *The Control of Gene Expression in Animal Development.* Harvard University Press, Cambridge, Mass.
5. Hegedus, S. I., and Schorr, W. F. (1972): Acquired hypertrichosis lanuginosa and malignancy. *Arch. Dermatol.,* 106:84–88.
6. Krejs, G. J., et al. (1979): Somatostatinoma syndrome: biochemical, morphologic and clinical features. *N. Engl. J. Med.,* 301:285–292.
7. Mahmoud, A. A. F., Stone, M. K., and Kellermeyer, R. W. (1977): Eosinophilopoietin: a low molecular weight peptide stimulating eosinophil production in mice. *Trans. Assoc. Am. Physicians,* 90:127–134.
8. Mallinson, C. N., Bloom, S. R., Warin, A. P., et al. (1974): A glucagonoma syndrome. *Lancet,* 2:1–5.
9. Meador, C. K., Liddle, G. W., Island, D. P., et al. (1962): Cause of Cushing's syndrome in patients with tumors arising from "nonendocrine" tissue. *J. Clin. Endocrinol.,* 22:693–703.