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PARANEOPLASTIC SYNDROMES

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INTRODUCTION

The effects of cancer upon the host are varied and complex. In addition to direct tumor invasion, obstruction of vital organs and metastatic spread, tumors can elaborate soluble factors and humoral substances which influence the ability of the host to function normally. These remote effects constitute an assortment of 'paraneoplastic syndromes' which have perplexed scientists and clinicians for over a century. In this chapter we will review many of the commonly encountered syndromes, discuss their significance, and attempt to integrate them into the modern concept of oncogenesis with specific reference to the emerging understanding of the molecular genetics of cancer. We also refer the interested reader to the many excellent reviews on the topic which have been published in recent years (8, 70, 113, 116, 125, 153, 163, 171).

For the purposes of this discussion we define the paraneoplastic syndromes as symptom complexes which cannot be ascribed to local or direct effects of the cancer process and which appear to be mediated by factors elaborated by tumors during their growth and metabolism.

OVERVIEW

The exact incidence of the paraneoplastic syndromes is difficult to estimate. Failure to identify symptoms as paraneoplastic in origin, varied definitions, incomplete reporting of cases, and incomplete investigation of new symptoms as they arise in gravely ill patients make estimates of incidence highly problematic. Clinically significant paraneoplastic syndromes arise in only a minority of patients. However, their recognition is important, since (1) they may mimic metastases, thereby causing clinicians to abandon curative therapy, or conversely, (2) mimic signs of metastasis causing clinicians to embark on unnecessary therapeutic or investigative interventions, (3) significantly affect the patient's clinical condition in a way which may be entirely reversible, (4) serve as markers for regression or recurrence of tumor, (5) influence the ability of patients to tolerate potentially curative therapy.

ECTOPIC HORMONES AND ENDOCRINE PHENOMENA

The best known and most thoroughly studied syndromes are those caused by ectopic hormone production. As the name implies, the putative hormone is produced by a tissue not normally associated with the given product. For example, carcinoid tumors produce numerous vasoactive substances which give rise, in certain patients, to the carcinoid syndrome. These humoral factors are considered the normal product of this tissue type and are distinguished from the normal state in a quantitative sense only. Likewise, certain adrenal adenomas and carcinomas produce excessive quantities of adrenal corticosteroids. It would be erroneous to classify these products as 'ectopic.'

To establish whether a given clinical syndrome is truly the result of ectopic hormone production, several factors must be considered. Among these are whether the hormone is actually being produced by the tumor. This can be tested by measuring serum hormone levels following effective treatment of the tumor or conversely by measuring rises in hormone level in parallel with regrowth of the tumor. The measurement of a gradient across the tumor bed or actual *in vitro* production of hormone in primary tissue culture would definitively identify the source of the hormone. Unfortunately these latter techniques are technically challenging and rarely feasible in the clinical setting.

It is also essential to rule out coincidental processes which may mimic paraneoplastic phenomena. The presence of a benign parathyroid adenoma or renal cyst resulting in elevated erythropoietin levels might lead to the erroneous diagnosis of a humoral paraneoplastic syndrome. Similarly a tumor mass compressing renal tissue might cause elevated erythropoietin levels. The erythropoietin elevations would however, be the appropriate response of renal tissue to local hypoxia and not paraneoplastic in origin.

An example of such erroneous reasoning can be found in the condition known as progressive multifocal leucoencephalopathy or PML. This debilitating neurologic disease was once considered a neurologic paraneoplastic process, but has since been identified as an infectious disease caused by papovavirus (192). Its association with malignancy is that which relates depressed immune status to predisposition to infection and is no longer considered paraneoplastic.

It is important to avoid attributing therapeutic side effects to the malignant process. SIADH associated with vincristine or cerebellar dysfunction associated with 5-FU or cytosine arabinoside serve as potential sources of such errors.

Finally, it is essential to avoid artifactual identification of humoral factors. In this regard, the identification of beta melanocyte stimulating hormone in patients with cancer was believed to represent a distinct paraneoplastic process until

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B-MSH was recognized as an artifact resulting from the isolation of B-lipotropin and not the product of any known human tumor (5).

Bearing these potential pitfalls in mind, the study of humoral paraneoplastic phenomena is a fascinating area of oncologic research.

HYPERCALCEMIA

Hypercalcemia is a common biochemical abnormality in cancer patients. As many as 10% of all cancer patients will develop this complication at some time during the course of their disease (125). Although direct bony invasion is present in the majority of the patients, a significant number of patients with hypercalcemia have no evidence of bone involvement. These patients represent the humoral hypercalcemic syndromes and since Albright's original description in 1941 (1) have served as a paradigm of paraneoplastic phenomena. The mechanisms by which these patients develop hypercalcemia are the subject of considerable debate. Numerous investigators have identified elevated parathormone levels in hypercalcemia patients, most commonly in squamous cell tumors of the lung and aerodigestive tract (159, 174).

In addition, a parathormone gradient across a tumor bed has been reported (90), and actual synthesis of parathormone *in vitro* has been documented (72). Despite such cases, however, most investigators now feel that ectopic parathormone production is an uncommon cause of hypercalcemia of malignancy (134, 160, 163, 170).

Tashjian and coworkers convincingly established that prostaglandins of the E class could induce hypercalcemia in an experimental model (175, 176). Brereton *et al.* subsequently used indomethacin to control hypercalcemia in a patient with a renal adenocarcinoma (17). Numerous reports have since supported the role of prostaglandins in cancer related hypercalcemia (87, 143, 155, 173).

Human leukocytes stimulated by phytohemagglutinin release an osteoclast activating factor which stimulates bone reabsorption (105). This 20 K molecular weight peptide has been found responsible for hypercalcemia in a number of patients with hematologic malignancies (119). Alternative mechanisms include vitamin D-related sterols, which have been implicated in human lymphomas (18) and as of yet unidentified cyclic AMP activating factors (134).

In summary, hypercalcemia of malignancy is a multifactorial process. Appropriate clinical management is dependent upon the correct identification of causative mechanisms.

CUSHING'S SYNDROME

The identification of ACTH and related peptides in the serum of cancer patients with or without clinical signs of Cushing's syndrome has provided a wealth of information. Following Brown's original description of adrenal hyperplasia and Cushing's syndrome in a patient with oat cell carcinoma of the lung in 1928 (23) numerous such cases have been recorded. Liddle *et al.* (102) demonstrated high concentrations of ACTH in primary and metastatic malignant tumors in humans. Further characterization by Yalow, Berson and others (63, 198) has led to the current understanding of ACTH synthesis, processing, and release by normal tissues. ACTH is now known to be synthesized by tissues in the form of a prohormone or big ACTH. This molecule, a glycosylated peptide of 275 amino acids is cleaved into numerous biologically active fragments including gamma MSH, ACTH, CLIP, B lipotropin, enkephalin and endorphin. So varied are the activities of this molecule and its by-products, that its production can be responsible for paraneoplastic phenomena ranging from hirsutism to hypertension and hypercalcemia.

The major clinical situation in which ACTH elevations occur is lung cancer, which constitutes over 50% of such cases (12). Careful review of the literature has led Skrabanek and Powell (164) to conclude that this phenomenon only occurs in tumors of specific histologic types. They found that all tumors associated with ectopic ACTH production were of two subgroups:

(1) Enterochromaffin (Kulchitsky) cell, i.e., carcinoid, oat cell.
(2) Chromaffin cell, i.e., pheochromocytoma, ganglioneuroma, neuroblastoma.

Whenever a tumor of some other histologic subtype is considered responsible for ACTH production, careful review of the specimen is indicated to avoid misdiagnosis (116).

The important clinical features of this phenomenon are best enumerated as follows:

(1) Up to 2% of all patients with lung cancer develop clinical signs of Cushing's syndrome and 25% of all oat cell cancer patients have elevated cortisol levels.

(2) 15% of all patients with Cushing's syndrome have the ectopic ACTH syndrome.

(3) Hypocalcemia, alkalosis, hyperglycemia, hirsutism, or hyperpigmentation may be the presenting symptoms of patients with underlying malignancy.

The diagnosis of ectopic ACTH production can be made by measurement of A.M. and P.M. cortisol levels, measurement of ACTH, dexamethasone suppression, or in difficult cases measurement of an ACTH gradient across the tumor bed. Since oat cell carcinoma of the lung constitutes the single most common cause of this syndrome, many patients can be expected to achieve significant improvement with appropriate therapy. Furthermore thymomas, carcinoid tumors, and pheochromocytomas are surgically curable in a significant number of cases, so that aggressive management is clearly indicated in these cases. Though many authors have suggested ACTH as a marker for malignancy, the lack of specificity has limited the use of the substance (197). Nonetheless, more specific radioimmunoassays and attention of B lipotropin, CLIP, or other ACTH-related substances may offer new diagnostic tests in the future. The management of these disorders is best done by addressing the underlying malignancy. In refractory cases, the use of such agents as metyrapone, aminoglutethimide and O_1P^1-DDD can alleviate the signs and symptoms of hyperadrenalcortisolism in most cases without the need to resort to adrenalectomy.

Syndrome, inappropriate antidiuretic hormone

The association of hyponatremia and cancer has been recognized for half a century. The overwhelming majority of cases are from oat cell carcinoma of the lung. Fischman reported 86 cases of inappropriate secretion of antidiuretic hormone (SIADH) (59), 20 of which were in patients with cancer. Fourteen of these were lung cancer and oat cell was the predominant histology (59). Up to 10% of all patients with oat cell carcinoma of the lung have clinical evidence of SIADH with hyponatremia (97). However, numerous other tumor types have been associated with this phenomenon (97). Hansen *et al.* (76) reported that 32% of small cell cancer patients had elevated urinary ADH levels by RIA associated with plasma and urinary osmolalities suggestive of SIADH. No clear association with histologic subtype nor stage of disease could be discerned.

The clinical management depends upon the severity of symptoms which can range from mild obtundation to frank seizures. Fluid restriction, furosemide diuresis, 3% saline, demeclocycline and lithium carbonate all have been used. Clearly, however, the best management is treatment of the cancer itself (31). Several points must be remembered when managing patients with apparent SIADH. First, there are many causes of this syndrome including elevated intracranial pressure, central nervous system infection, head trauma, intrathoracic inflammatory conditions, stress, general anesthesia, opiate pain medication as well as cyclophosphamide and vincristine therapy. Secondly, patients may handle water loads poorly (a common constituent of chemotherapy treatment) despite apparently normal renal function, and caution in administering intravenous fluids is warranted.

Efforts to use ADH or neurophysins in diagnosis and/or follow-up have met with some successes and may ultimately serve as valuable parameters in the measurement of small cell lung cancer (109, 122).

GONADOTROPIN RELEASE

The gonadotropins LH and FSH as well as thyrotropic hormone and HCG are dimeric peptides. Each consists of an alpha subunit, which is identical in all classes and a beta subunit which confers functional and immunological identity to each (132, 184). These hormones are produced in large quantities by tumors of germ cell or syncitiotrophoblastic origin and BHCG is among the most useful clinical parameter in the management of such cases. Numerous investigators have identified HCG in the serum of cancer patients with a frequency of up to 13% (16). Rosen reported elevated HCG levels several months before clinical recognition of the tumor of origin (146). Recent experimental work has led to several important observations regarding synthesis and secretion of gonadotropins and related peptides:

(1) The synthesis of these substances is extremely common (120, 124).
(2) Subunits of HCG are frequently produced in an unbalanced way leading to excesses of one subunit over the other (147).
(3) Though large numbers of tumors synthesize intact or subunit fractions, these are often not released into the circulation (120).
(4) The HCG molecule is commonly produced by non-neoplastic tissues (15, 200).
(5) The HCG produced by malignant tissues differs from native HCG in terms of sialic acid residue content, thereby altering its serum half life (185, 199).
(6) Discordant synthesis rates may serve as specific markers for particular neoplasms in a manner analogous to light chains in multiple myeloma (147).

The exact mechanism of release, and possible functions of chorionic gonadotropins remains a mystery. Whether this substance serves as an 'autostimulant' means of communication between cells, or is simply an incidental finding will be the topic of research for years to come.

HYPOGLYCEMIA

Alterations in glucose metabolism are frequent in patients with malignancy. Most such examples reflect the altered nutritional status and poor general condition of this population. A minority of patients, however, will exhibit hypoglycemia which appears to be mediated by tumor-related humoral substances (108). Though uncommon, the relative frequency of various histologies in this syndrome are reported: mesenchymal 64%, hepatic 21%, adrenal 6% and miscellaneous 9% (125).

Most of these tumors are abdominal with a significant number being retroperitoneal in origin. Characteristically, these tumors are large, weighing up to 10 kg at the time of diagnosis. Though various mechanisms for the syndrome have been proposed, including ectopic insulin production, hepatic replacement by tumor, and excessive glucose utilization by tumors, the most tenable appears to be the elaboration of nonsuppressible insulin-like activity (NSILA) or somatomedin by malignant tumors (111). These low molecular weight peptides are the normal product of the liver, under control of growth hormone, and constitute a significant portion of the insulin-like activity in normal human serum (186).

Clinically, this syndrome presents with predominantly neurologic symptoms of somnolence, stupor, or even coma. It responds to glucose infusion temporarily, but definitive therapy relies upon surgical, radiation or chemotherapeutic management of the underlying tumor. If definite therapy is not possible due to the advanced state of disease or location of tumor glucagon, diazoxide or corticosteroids can be tried.

HEMATOLOGIC

Abnormalities of the formed elements of blood and of the clotting cascade are common constituents of the malignant process. Our discussion will center upon only those phenomena in which a humoral mechanism appears to be operative.

ERYTHROCYTOSIS

Erythrocytosis of malignancy is an elevation of the hematocrit, hemoglobin and red cell mass, occurring in association with an underlying tumor and in the absence of hypoxemia,

defective hemoglobin, or cardiopulmonary disease which secondarily could stimulate erythropoiesis. Hammond and Winnick (73) reported the frequency of various tumor histologies underlying this process in over 300 cases as:

Hypernephroma	35%
Hepatoma	19%
Cerebellar hemangioblastoma	15%
Uterine fibroid	7%
Adrenal tumor	3%
Benign renal cyst	14%

with the remaining cases distributed among several tumor types.

The predominance of renal tumors is not surprising considering the pivotal role of the kidney in normal hematopoietic regulation. While elevated erythropoietin levels have been identified in tumor tissue or serum of many patients tested (73), not all studies have confirmed this finding (188). Those patients who lack elevated erythropoietin may generate androgenic steroids or other erythropoietic factors as the basis for their elevated hematocrit. Alternate mechanisms include prostaglandin stimulation of erythropoiesis (52), and alteration in hepatic clearance or metabolism of erythropoietin (66).

The clinical implications of polycythemia are several. First, polycythemia is strongly correlated with certain tumor types, i.e., cerebellar hemangioblastoma and may be a tool both in primary diagnosis and in the identification of recurrence. Secondly, successful resection of the tumor has been associated with complete resolution of the syndrome in most cases (29). As such, careful evaluation of patients with polycythemia is warranted with particular attention to the possibility of renal tumor.

PURE RED CELL APLASIA

Severe anemia with total absence of erythroid precursors in the bone marrow has been identified in as many as 5% of patients with thymoma, usually of the spindle cell type (7, 49, 92). Conversely, up to 50% of patients with red cell aplasia have thymoma as the underlying cause (83). The underlying mechanism appears to be immunologic. The identification of IgG antibodies directed against red cell precursors led several investigators (93, 112) to treat their patients with cyclophosphamide and/or plasmapheresis with dramatic improvement reported (93, 112). In addition to thymomas, various carcinomas have been reported in association with red cell aplasia but these are limited largely to individual case reports (117).

HEMOLYSIS

Certain malignancies are frequently associated with a hemolytic diathesis. The lymphoproliferative disorders are well known to cause a Coombs positive autoimmune hemolytic anemia (AHA) (133). Less frequently, carcinomas have been identified as the cause of AHA (167). The process appears to be mediated by antibodies of the IgG or occasionally IgM class which sensitize red blood cells to phagocytosis by cells of the RE system. Steroids may help control the hemolysis, but appear less effective in this disorder than the idiopathic type of autoimmune hemolytic anemia.

Microangiopathic hemolytic anemia (MAHA)

Microangiopathic hemolytic anemia or MAHA is the term applied to a specific blood picture, often associated with mucin secreting adenocarcinomas, whose features include fragmented erythrocytes, teardrop cells, a uniformly negative Coombs test, and frequently, association with thrombosis and DIC. The process as described by Brain *et al.* (14) is believed to occur when red blood cells are damaged by passage through microvascular channels which have suffered endothelial injury secondary to tumor deposition or fibrinogen activation. The resulting hemolysis may be chronic and low grade, or severe and acute requiring multiple blood transfusions. A review of 55 cases, reported by Antman *et al.* (2) revealed that 55% of the cases were associated with gastric adenocarcinomas, 13% were of breast origin, 7% were lung, 10% were classified as unknown origin and the remainder were distributed between ovary, prostate, pancreas, colon, hepatic, biliary, and seminal vesicle (2). In their series, progression was rapid and mean survival from diagnosis to death was 21 days. When effective chemotherapy was available a significant proportion of patients improved (7/9), but heparin alone was largely ineffective (2). A newly recognized variant of the MAHA process has been described in patients receiving chemotherapy for adenocarcinoma (75, 77). These patients are frequently in complete clinical remission and present with a combination of MAHA, thrombocytopenia, and renal failure. Inconsistent but frequent association with mental symptoms, an ARDS-like pulmonary process, and poor tolerance of blood transfusions have all been described (20, 26).

An association between this process and high levels of circulating immune complexes has been noted but the exact etiology remains unknown (25). Treatment is largely supportive, although antiplatelet drugs, heparin, steroids, and plasmapheresis have been attempted with limited success. The process is characteristically fulminant and often fatal within several months of diagnosis.

Disseminated intravascular coagulation (DIC)

Both acute and chronic DIC can complicate the clinical course of cancer patients. The chronic form associated with a thrombotic tendency may underlie the so-called 'hypercoagulable state' of cancer and may have been responsible for the famous migratory thrombophlebitis reported by Armand Trousseau in 1865 (179). Release of procoagulants into the bloodstream is the postulated mechanism. Acute DIC is a fulminant and often fatal complication which can arise alone or in association with sepsis, acidosis, fungemia, hypovolemia, and transfusion reaction. The management is entirely dependent upon determination of the underlying cause. Heparin is frequently administered but randomized trials to establish its usefulness in malignancy have not been done.

An associated phenomenon is that of nonbacterial endocarditis, wherein the valves of the left side of the heart are encased with a fibrin-platelet matrix which, though sterile initially, can become secondarily infected or give rise to arterial emboli. This not infrequent complication, can give rise to a host of secondary embolic complications and may underlie the neurologic problems of a significant number of cancer patients.

LEUKOCYTES

A leukemoid reaction is defined as a marked elevation of circulating white blood cells, in excess of 20,000, usually mature in morphology, which arises in the absence of active infection, intercurrent inflammatory processes, direct marrow invasion, drug effects, or a frank malignant myeloproliferative disorder (195). This phenomenon has been recognized in human cancer patients for decades but recent *in vitro* investigations have shed new light on the process.

The isolation from transplantable mouse mammary carcinoma (46, 47) of a heat stable peptide of M.W. 55,000 which stimulates granulocytes colony growth *in vitro* led investigators to seek similar substances in human tumors (4). Robinson (144) reported 12 cases of human cancer associated with granulocytosis in which urinary and serum levels of CSA were 5–10 times the normal level. It should be noted, however, that attempts by those investigators to measure *in vitro* synthesis of CSA in two adrenal carcinomas were unsuccessful, leaving the question, in these patients, of actual synthesis by the malignant tumors unanswered. Conflicting evidence of tumor products of a granulopoietin suggests that several mechanisms may be operative in this phenomenon.

The clinical significance of the diagnosis stems from the need to rule out all other treatable etiologies including infection, marrow invasion, and unrecognized chronic myelogeneous leukemia. Once this has been done, observation and treatment of the underlying malignancy are the prudent approaches to management.

GASTROINTESTINAL SYMPTOMS

Gastrointestinal symptoms are common complications of cancer and its treatment. In most instances, direct tumor effects or nonspecific reactions to the disease process underlie the abnormalities and hence do not represent paraneoplastic phenomena. Similarly, Zollinger-Ellison syndrome, carcinoid syndrome, and pancreatic cholera are all associated with tumors of hormonally active tissues and do not fall under the rubric of ectopic hormone production or paraneoplastic syndrome. Several entities do warrant mention, including truly ectopic vasoactive intestinal polypeptide (VIP) and gastrin production, malabsorption and renal carcinoma associated hepatopathy. Zollinger-Ellison syndrome and pancreatic cholera are clinical entities associated with hypersecretion of peptide products by non-beta-islet cells in the pancreas. In rare instances both syndromes have been identified in nonpancreatic tumors (30, 114, 150, 151).

In a minority of patients, a syndrome of malabsorption associated with complete or partial villous atrophy has been identified (33, 45). The responsible tumors include colon, lung, prostate, pancreas and lymphoma. No humoral factor has been identified in this syndrome and the mechanism remains speculative, but histologic similarity between this and other immune enteropathies leaves open the possible association of an immune mechanism. Conversely, malnutrition could be responsible for some or all of the identified abnormalities.

The identification of abnormal liver function in a patient with cancer usually portends a grave prognosis due to hepatic metastases. However, a poorly understood hepatopathy has been recognized, primarily in patients with hypernephroma (29, 36, 183) but also in other tumors and at least one case of schwannoma (91, 92). The mediators of this process, which include increases in liver enzymes (74, 79) decreased albumin synthesis, and elevated alpha globulin, are unknown and attempts to isolate a humoral factor have been unsuccessful. The importance of recognizing this syndrome is obvious and should underscore the need for liver biopsy in questionable cases.

RENAL

Abnormalities of renal function occur frequently in cancer patients. Due to the dependence of many cytotoxic therapies upon renal excretory function and the nephrotoxicity from antineoplastic drugs, close attention must be paid to renal physiology and the influence of malignancy upon it. Most nephropathic processes in malignancy are not paraneoplastic in origin, but several important syndromes have been identified which clearly fulfill even the strictest definition of paraneoplastic syndromes.

GLOMERULOPATHY

Lee *et al.* (96) described 101 cases of nephrotic syndrome in which 11 or 10.9% had an underlying malignancy. Since that time, the association of nephrotic syndrome with cancer has been confirmed by numerous authors (53, 86). Lipoid nephrosis or minimal change disease is most clearly associated with Hodgkin's disease while membranous glomerulonephrosis occurs in association with non-Hodgkin's lymphomas and carcinomas (53).

The histologic patterns of renal impairment appears to reflect the pathogenic mechanism in each disease. T-cell abnormalities are implicit in the diagnosis of lipoid nephrosis (156). The T-cell dysfunction of Hodgkin's disease has been implacated etiologically in this process (100) and effective treatment of Hodgkin's disease has been shown to eradicate the nephrotic syndrome (118).

Membranous nephropathy is characterized by subepithelial electron dense deposits of immunoglobulin, complement, and tumor antigen. Its pathogenesis appears to reflect deposition of circulating antigens and immune complexes (128) and identification of tumor antigens and CEA in kidney biopsy specimens has been documented (101).

According to Row *et al* (148) 10% of 66 patients with biopsy proven membranous nephropathy had a malignancy underlying the process. It is therefore apparent that malig-

nancy must be ruled out in any patient presenting with signs and symptoms of nephrotic syndrome (148).

Renal tubular abnormalities have been associated with hematological malignancies (59). Multiple myeloma has been implicated in renal tubular dysfunction (152) and potassium wasting tubular defects are well known in myelomonocytic leukemia with lysozymuria (59, 126). Due to the multitude of cytotoxic drugs, antibiotics, and antifungal agents which many of the patients receive, it is often difficult to establish cause and effect relationship between the malignancy and the renal disease. Nonetheless, careful attention to renal function remains important of the cancer patient's management. With appropriate therapy the malignancy and its renal manifestations can be controlled in a significant percentage of cases (80).

NEUROMUSCULAR

The central nervous system can be affected by malignancy in a multitude of patterns. Direct involvement via metastatic disease or carcinomatous meningitis constitutes the majority of cases, but infectious, metabolic, endocrine, nutritional, vascular, embolic, thrombotic, hematologic, and paraneoplastic phenomena must all be considered in the differential diagnosis of any disturbance in neurological function. Several well studied paraneoplastic syndromes serve as illustrative examples of remote effects of malignancy and will be considered here.

SUBACUTE CEREBELLAR DEGENERATION

Brouwer (21) is credited with recognizing the association of cerebellar dysfunction and malignant disease. Brain (13) described 19 patients with this syndrome, which is characterized by acute or subacute cerebellar dysfunction with ataxia, dysarthria, hypotonia and diminished or absent reflexes, with or without dementia. The tumor most commonly associated is lung, with ovary, breast, gastrointestinal tumors, Hodgkin's disease, and non-Hodgkin's lymphomas, all associated to lesser degrees (51). The association with cancer is strong and the process has been known to precede the actual diagnosis by as much as 8 years (13). In rare instances, effective control of the disease has been paralleled by remission of the cerebellar symptoms (129), however, the course of the cerebellar disease is highly variable and is often disparate from the clinical course of the tumor.

LIMBIC ENCEPHALOPATHY

Subacute cerebral dysfunction, with ataxia, nystagmus, as well as sensory and motor neuropathy associated with inflammatory and degenerative changes in the amygdala and hippocampus is a rare concomitant of neoplasia (32). The process has been recognized most frequently with lung cancer. Its course is variable but almost always progressive. However, improvement in the neurologic picture with antineoplastic therapy has been reported (107). Additional syndromes of the central nervous system include optic neuritis and central pontine myelinosis.

The similarity of many of these conditions to viral disorders such as KURU and scrapie as well as the possible role of immune mechanisms like multiple sclerosis have led to many interesting theories regarding the etiology of each condition. To date, however, no clear mechanism has been established.

SPINAL CORD AND PERIPHERAL NERVOUS SYSTEM

Subacute and acute spinal cord dysfunction have been described in a limited number of patients (28, 190). The clinical presentation can be dramatic with rapid loss of sensory and motor function. In some patients a purely motor dysfunction, simulating amyotrophic lateral sclerosis has been described. The clinical picture of spasticity, hyperreflexia and fasciculations is indistinguishable from the idiopathic form and some authors have suggested that up to 10% of all ALS victims have an underlying malignancy (121).

PERIPHERAL NEUROPATHIES

Involvement of the peripheral nervous system has been observed as a paramalignant phenomenon in many neoplasms. Depending upon the stage of disease and criteria for inclusion, rates of occurrence have been reported as high as 16% (35) or as low as 1.4% (137). Malignancies of the lung appear most commonly associated (55). The neuropathies can be sensory, motor, or mixed. In addition, they may involve the axon, the neuromuscular junction or the ganglia (55). The peripheral neuropathies present in two general syndromes (35):

(1) Mild sensory dysfunction, usually symmetric, presenting late in the clinical course.
(2) Acute, severe, sensory-motor neuropathy which presents early in the course of the disease and can precede the clinical diagnosis of cancer.

Demyelination, axonal degeneration and elevated cerebrospinal fluid proteins are frequent findings. Dorsal root ganglionitis, manifesting as a subacute pure sensory deficits has been reported with intrathoracic neoplasms (35). Histologically, these tumors vary from primary lung carcinoma to lymphomas, but intrathoracic location appears common to all (181).

Immune mechanisms may underlie each of the processes described. Several investigators have detected antibodies directed against neurons in the sera and/or cerebrospinal fluid of patients (34, 193). Clinical evidence of response to corticosteroid in some patients also supports an immune mechanism.

In a small percentage of patients with Hodgkin's disease, classic symptoms of acute idiopathic polyneuritis or Guillain Barré syndrome develop (24, 37, 104). Clinically, patients present with ascending paralysis often requiring respiratory support. Cerebrospinal fluid proteins are elevated. In patients who succumb to the process, pathologic findings have been consistent with Guillain Barré syndrome (24). Careful clinical pathological evaluation of 3 cases led Lisak *et al.* to ascribe the development of this process to T-lym-

phocyte dysfunction which has been characterized in Hodgkin's disease (104).

MYASTHENIA GRAVIS

The association between myasthenia gravis and thymoma has been clearly established. Up to 10% of patients with myasthenia gravis have an underlying thymoma, and as many as 30% of patients with thymoma will develop myasthenia gravis during the course of their disease (7, 67). The association of other solid tumors with myasthenia gravis, however, is more speculative. Though a variety of neoplasms have been associated with myasthenia gravis, clear causal relationship has not been established, nor has underlying thymic pathology been clearly ruled out in each case. To further cloud the issue, it has been stated by some investigators, that thymic abnormalities predispose patients to malignant diseases (130). But this too has been challenged by other authors (187). The exact association of myasthenia and malignancy remains a mystery and further study to clarify the relationship is warranted.

EATON–LAMBERT SYNDROME

Since the original description in 1956, by Lambert and Eaton (94) of a mysterious syndrome characterized by incremental motor strength with repeated stimulation, a characteristic electrophysiologic picture, and a strong association with malignancy, a significant number of patients with this condition have been recognized. Clinically, pelvic girdle and proximal weakness are associated with muscle pain, fatigue and parathesias. Ptosis may or may not be associated. Response to edrophonium is characteristically poor, but patients often show improvement with guanidine hydrochloride.

The mechanism is disputed, but similarity to Mg^{2+} toxicity and to botulinus toxin effects, led Elmquist and Lambert to post diminished acetylcholine release as the basic pathology (54, 95). An alternative explanation maintains that enzyme induction leads to increased acetylcholine esterase activity in the synaptic cleft, resulting in diminished amplitude of the end plate potentials (162).

Effective therapy for the malignancy has been reported to control the neuromuscular symptoms (89) but the process is often progressive and extremely debilitating.

DERMATO/POLYMYOSITIS

Certain paraneoplastic syndromes are so strongly associated with malignancy that their identification in a patient warrants prompt and thorough evaluation. Dermatomyositis is characterized by muscle weakness, pain and tenderness, elevated muscle enzymes, spontaneous activity with myopathic changes on EMG, perivascular inflammation with mononuclear cell infiltration and characteristic skin changes (50). Dermatomyositis has been associated with a 5 to 7 times increased incidence of malignancy over the population at large (6). However, in certain subsets of the population, specifically males over the age of 40, a 66% malignancy rate has been found in dermatomyositis sufferers (3). The malignancies most closely associated with dermatomyositis are those of the ovary and stomach, while colorectal tumors overall, appear underrepresented (6).

Numerous case reports support the recommendations that aggressive treatment of the underlying neoplasm may result in clinical remission of the dermatomyositis. Corticosteroids are also effective but may be less useful than in the idiopathic form (145).

SKIN

Cutaneous signs of internal malignancy are frequent and diverse processes which may be specific or nonspecific in nature. It is important to distinguish remote effects from direct invasion and to separate malignant epiphenomena from true paraneoplastic events. Cutaneous involvement in mycosis fungoides is a nearly universal component of this disease. In addition, up to 0.5% of patients with Hodgkin's disease display skin involvement (166). Patients with carcinoid tumors may develop cutaneous symptoms while virilizing tumors of the ovary or adrenal may cause hirsutism. These processes are readily explicable by mechanisms directly related to the tumors and as such as not considered here under the heading of paraneoplastic syndromes.

ACANTHOSIS NIGRICANS

Acanthosis nigricans has been recognized as a paraneoplastic syndrome for over a century. The finding of velvety hyperkeratotic areas of hyperpigmentation in the auxillary, anogenital or intertriginous areas of the body occasionally associated with palmar and plantar keratosis and areolar keratosis is a clear warning to the clinician that malignancy may be present (22, 39).

Curth has divided acanthosis nigricans into separate classifications (40) and introduced the concept of pseudoacanthosis nigricans for the endocrine associated phenomena (42). Numerous benign conditions are associated with acanthosis nigricans including insulin-resistant diabetes mellitus (180), and congenital lipodystrophy (140). Drugs such as nicotinic acid and DES have also been associated with acanthotic skin changes.

The overwhelming majority of cases with malignancy have an adenocarcinoma of the gastrointestinal tract but squamous cell histologies as well as extraintestinal sites of origin have been well documented (43, 60, 115). In some cases the malignancy and the cutaneous findings seem to run a parallel course. Resolution of the skin changes with effective therapy is known to occur (115) but in many patients the two processes progress independently.

Endocrine mechanisms appear involved in the pathogenesis of acanthosis nigricans and in this light, the presence of APUD cells identified in gastric cancer tissue from a patient with acanthosis nigricans seemed intriguing (69). However, subsequent attempts to identify similar cells in gastric cancer tissue from affected patients have not supported this finding (41) and the exact mechanism remains unclear.

THE SIGN OF LESER–TRELAT

First described by Edmund Leser and Ullysee Trelat in the 19th century, the sign of Leser Trelat is an unusual finding which is, however, extremely strongly correlated with internal malignancy. It is defined as a rapid increase in the size and number of seborrheic keratoses on previously unblemished skin which is accompanied by pruritus and strongly correlated with malignancies usually adenocarcinoma of the GI tract (44, 103). No clear mechanism has been identified. The possible role of epidermal growth factor or other growth factors has been postulated but thus far not substantiated (38). Its appearance in any patient warrants careful evaluation for a gastrointestinal neoplasm.

MIGRATORY NECROLYTIC ERYTHEMA

Neoplasms of the alpha cells of the pancreatic islets with hypersecretion of glucagon resulting in a syndrome of diabetes, weight loss, diarrhea, and migratory skin rash, have been recognized in recent years (81, 106). The cutaneous eruption, characterized by areas of annular or circinate erythema, with shedding and superficial necrosis which resolved with time, was originally believed pathognomonic of glucagonoma. However, in recent years, this phenomenon has been described in a variety of other conditions including benign pancreatitis (65, 178, 189).

Mechanisms conidered responsible have included zinc deficiency (177), essential fatty acid deficiency (11) and hypoaminoacidemia (106, 123). Response to amino acid supplementation (123) supports the latter mechanism, but amino acid deficiencies have not been present in all patients with this condition, raising questions of alternate mechanisms in these cases.

BAZEX SYNDROME

In 1965, Bazex and colleagues described a new cutaneous neoplastic syndrome now known as acrokeratosis paraneoplastica or Bazex's syndrome (9). This process, which has been described primarily in caucasian males, is specifically related to cancers of the aerodigestive tract, and presents as erythematous, psoriaform eruptions of the fingers and toes. With time it can involve the bridge of the nose and ears and may further progress to violaceous eruptions of the legs and chest. Histopathologic changes include lymphatic infiltration, parakeratosis, hyperkeratosis, and occasionally fibrinoid degeneration. Treatment relies entirely upon removal of the tumor, which in the majority of cases, results in complete resolution of the cutaneous findings (10).

ACQUIRED ICHTHYOSIS

The characteristic lesions of ichthyosis with scaling, xerosis, and shedding of skin, have been described in malignancy, specifically lymphomas and Hodgkin's disease, but also in solid tumors (78). Its appearance in an otherwise well patient warrants evaluation and may serve as the first sign of malignancy. Numerous additional skin changes have been described in malignancy including alopecia mucinosa, Sweet's syndrome, hirsutism, exfoliative dermatitis, lanugo hair growth, and others. It behooves the clinician to remember the diversity of these cutaneous syndromes when confronted with bizarre or inexplicable skin changes, for they may underlie malignant disease in an otherwise well patient.

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

Hypertrophic pulmonary osteoarthropathy and the closely related phenomenon of digital clubbing have been recognized as clinical entities since the time of Hippocrates (460–375 BC) (82). Clubbing is defined as the painless swelling of the soft tissues of the terminal phalanx of the digit (161). Hypertrophic pulmonary osteoarthropathy is less easily defined but may be regarded as a condition affecting both bones and joints which is characterized by radiological evidence of periosteal new bone formation. Bone pain, oedema and synovial effusions are frequently associated findings (161). While hypertrophic pulmonary osteoarthropathy is often associated with malignancies, specifically of the lung, clubbing is found in a variety of benign conditions including congenital cyanotic heart disease, regional enteritis, biliary cirrhosis, and bacterial endocarditis. All of the latter are virtually never associated with hypertrophic pulmonary osteoarthropathy (56). The exact etiology of hypertrophic pulmonary osteoarthropathy is unknown. Neurogenic (27, 138, 196) hormonal (64, 169), and humoral factors have all been suggested. In addition, prostaglandins of the E and F2 alpha varieties have been implicated as the cause of clubbing in patients with cystic fibrosis (99). Malignancies arising in or metastasizing to the thoracic cavity constitute an important cause of hypertrophic pulmonary osteoarthropathy with which digital clubbing is often associated.

Transection of the vagus has been used as a means of controlling symptoms from hypertrophic pulmonary osteoarthropathy. In a large number of cases, resolution of the symptoms and signs of hypertrophic pulmonary osteoarthropathy has been effected by treatment of the tumor. Surgical resection is the most frequent mode of treatment but radiation therapy and chemotherapy have both been used (57, 136) to good effect in controlling this phenomenon. The major differential diagnosis in cases of hypertrophic pulmonary osteoarthropathy is actual bone or joint involvement with metastases. Though uncommon, malignant arthritis must be considered and can be diagnosed by synovial fluid cytology (58).

Paraneoplastic syndromes in animals

The human species is not the only victim of malignant disease. Likewise, paramalignant phenomena when sought can be found in virtually all animal species. Domestic animals and beasts of burden are, for the most part, the only species where such processes have been studied. It is not surprising that paraneoplastic syndromes arise in non-human species for the same factors which predispose humans to these conditions should be operative in animals. A review of the literature reveals examples of animal para-

Table 1.

Specie	*Syndrome*	*Disease*	*Reference*
1. Dog	Hypercalcemia	Leukemia	(48)
		Breast cancer	(127)
		Circumanal gland adenocarcinoma	(127)
	Hypoglycemia	Leukemia	(48, 127)
	DIC	Hemangio sarcoma	(98)
		Adenocarcinoma	(176)
		Thyroid	(165)
	HPO	Lung, mammary, bone and melanoma	(19)
	HPO	Rhabdomyosarcoma of urinary bladder	(71)
2. Rhesus monkey	Gynecomastia and Galactorrhea	Undifferentiated carcinoma	(142)
3. Bull	HPO	-	(84)
4. Horse	HPO	-	(85)
5. Lion	HPO	-	
6. Cat	Hypercalcemia	-	

neoplastic syndromes which have been described and they are listed in Table 1 with references.

Though less well studied, these phenomenona represent syndromes similar to those in humans. The cross species similarities underscore the conclusion that the mechanisms underlying paraneoplastic syndromes are similar, and may lead to greater understanding of the malignancies in all species.

SUMMARY AND CONCLUSIONS

No single theory or mechanism can explain all the paraneoplastic syndromes encountered in patients. Clear distinctions can be made between those phenomena of immunological origin such as autoimmune hemolytic anemia and nephrotic syndromes and those associated with ectopic elaboration of humoral factors, such as ectopic ACTH, ADH secretion and hypercalcemia. Conceptually, the immune related syndromes can be viewed as one of a variety of mechanisms: (1) cross reactivity of neoplastic and normal tissues (2) the exposure of 'forbidden' antigens, (3) the consequences of circulating immune complex deposition or (4) combinations of these processes. Greater understanding of immune regulation, technical improvements in monoclonal antibodies, and methodologic advances in antigen antibody dissociation and characterization will lead to improved diagnostic and therapeutic modulation in these processes in the coming years.

The more vexing and yet ultimately more revealing syndromes are those associated with ectopic peptide synthesis and humoral factors. The past 15 years have witnessed an unprecedented expansion in our basic understanding of oncogenesis. The concept of oncogenes and the identification of active oncogenes in human tumors has reduced the once mysterious cancer process to a molecular disease, not unlike the similar advances in the understanding of sickle cell anemia. We now appreciate that malignant transformation is associated with alterations in the structure and/or function of the genomic library. This may take the form of distinct and reproducible karyotypic abnormalities i.e. chromosome 22:9 translocation in CML (149) or the p13 region short arm deletion of chromosome 11 in Wilms' tumor-aniridia (141). Alternatively the process may reflect a point mutation such as that causing the substitution of valine for glycine in a peptide product in bladder carcinoma, and presumed to contribute to malignant transformation (139, 172).

What emerges from these discoveries is the realization that carcinogenesis in humans and animals, can be viewed as a perturbation in the balance of cellular functions and that biochemical processes such as methylation of cytosine, or phosphorylation of tyrosine underlie these perturbations. Normal and neoplastic cell functions do not necessarily differ in absolute but in relative terms. The production of HCG, ACTH, or ADH do not occur as random events nor do they only occur in malignant cells. Rather, specific histological subtypes of tissue elaborate humoral substances and the relative amounts reflect the efficacy and appropriateness of the control mechanisms involved.

All somatic cells contain all of the genetic information necessary to perform all bodily functions. This has been conclusively proven from experiments in animals where the transplantation of a somatic cell nuclei into an enucleated egg of a frog resulted in the growth of a normal tadpole (68). Even more convincing is the fact that normal tadpoles resulted when triploid nuclei from renal cell adenocarcinoma tissues were similarly transplanted (10). Indicating that even in the transformed state, cells retained intact compliments of DNA information which under the appropriate circumstances could be normally transcribed.

Clearly, biochemical processes must be at work which allow malignant cells to escape their normal controls of contact inhibition, mortality, and differentiation, and allow these cells to exemplify otherwise uncharacteristic features. If these mechanisms allow expression of fetal antigens, fetal

enzymes, or ectopic hormones, then the clinical syndromes reflecting these processes arise. How then might the wealth of genetic information come to be expressed by malignantly transformed cell populations?

Gene de-repression, either as a consequence of proliferation or a selective increase in transcriptional activity has been suggested (61, 62). This concept could be used to explain many aspects of ectopic hormone production. However, it would require that transformed cells be transcriptionally more active than their normal counterparts, a feature which has not consistently been found true (157). This could be explained on the premise that only the most readily transcribable or 'de-repressable' regions would be activated, consistent with Williams description of DNA 3 (194), and that such activation takes place at the expense of other transcriptional activity.

Dedifferentiation is a concept which has been proposed to explain malignant transformation for decades. In its most basic form the principle process is a retracing or retrograde differentiation of cell lines to forms which express fetal antigens and enzymatic activities (182). Though attractive in its ability to explain numerous paraneoplastic phenomena, there is no convincing evidence that any human cell line is capable of dedifferentiation.

Cell Hybridization – the observation that Human X Mouse somatic cell hybridization resulted in the production of intact human immunoglobulin molecules (154) led to the widespread application of hybridoma technology in medicine. The same process of somatic cell hybridization has been proposed as a mechanism for the ectopic production of hormones in malignancy (191).

According to this theory, transformed cells would spontaneously hybridize with somatic cells to form malignant subclones which would manifest the features of one or both of the parent cell lineages. The cell lines produced by each union would reflect the characteristics of the parental genomes and could result in the production of immunoglobulins, protein hormones, enzymes, cell surface markers, or other humoral factors. Animal studies have shown that hybridization of tumor clones results in the expression of specific tumor markers derived from the parent cell lines (88, 168).

Furthermore, hybrids of human somatic cells have been shown to produce CEA (158), and a mouse X human hybrid has been found to produce human chorionic gonadotropin (91).

The role of hybridization remains unclear. Nonetheless, several features make it an intriguing possible explanation for many paraneoplastic syndromes.

A somewhat different mechanism has been forwarded by Baylin and coworkers (8). The theory maintains that all epithelial surfaces are comprised of subpopulations of cells, some of which manifest endocrine cell features. These cells are derived from primordial epithelial elements *in situ*, and do not migrate from neuroectodermal tissues as Pearse has proven for certain endocrine tissues in animals (131). In this context, the neoplastic process would cause an imbalance in the relative ratios of mature/differentiated cells to immature/less differentiated cells. This disproportion might result in the overgrowth of cells which express fetal antigens such as CEA, AFP, etc. If the processes were to specifically transform a clone of cells which are committed to endocrine activity, then proliferation of this clone could result in increased endocrine products. Alternatively, some external factor might influence the heterogenous population of transformed cells to differentiate towards the endocrine active forms.

As we stated in the introductory comments no single theory will explain all paraneoplastic phenomena. Nonetheless, the mechanisms postulated by these investigators have significantly improved our understanding of this once obscure topic. In the near future many of the remaining enigmas will be explained and the paraneoplastic syndromes will come to be regarded in the same light as many of the medicines heretofore mysteries.

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