would be of definite value to nursing, dental and medical students, particularly in the area of imparting community health concepts.

2. Public Health Education

The value of formal exhibits dealing with similar concepts as those presented in Mediscope 1961 are well known, and have been exploited for educational purposes by health museums¹ all over the world. Especially, exhibits on normal development, prevention of disease, community health and advances of modern medicine could contribute extensively to health education of selected groups, provided they were made accessible on a year-round basis.

One of the major recommendations arising from the present assessment of Mediscope 1961 is the apparent need for a more comprehensive evaluation study which would shed some light on the educational effectiveness of exhibits and displays and their role in adult learning.

Such a study, in the author’s opinion, would have to take into consideration the probing of attitudes and measurement of behavioural changes resulting from viewing the exhibits.

The logical answers arising from such a study would most likely disclose the impact of the information presented, the degree of retention resulting from such an exposure to exhibits, and the resulting attitudinal and behavioural changes.

The author wishes to express his appreciation to J. C. Allison, M.D., Assistant Secretary, Ontario Medical Association, for his assistance in the present assessment of Mediscope 1961.

REFERENCES


GENERAL PRACTICE

Occult Manifestations of Cancer

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THE purpose of this communication is to summarize the numerous reports of various clinical syndromes which are either associated with malignancy or may herald its presence. Some of the diseases described are found in association with widely disseminated malignancy; in others, the primary lesion is small and may be unsuspected until the associated syndrome is recognized. Many of these conditions are non-specific and they simply suggest the presence of malignancy somewhere in the body. Generally speaking, the etiology and pathogenesis of such syndromes are unknown. In the following paragraphs these disorders will be classified and the various subdivisions of the classification will be discussed individually.

CACHEXIA

The etiology of malignant cachexia remains obscure and to date no satisfactory explanation for its occurrence has been proposed. Cachexia may be entirely due to tissue destruction by the tumour and the secondary diseases associated with it, or there may be other specific factors, as yet undetermined, which cause the disease process to advance more rapidly.

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ABSTRACT

Clinical syndromes occasionally associated with or heralding cancer are summarized and classified.

Some tumours present with manifestations of an endocrine or endocrine-like action; included in this group are thymomas, non-beta-cell tumours of the pancreas and carcinoids. Cushing’s syndrome, hypoglycemia, hypercalcemia, polycythemia and gynecomastia have been produced by a wide variety of tumours. Tumour emboli, non-bacterial thromboendocarditis and thrombophlebitis occasionally occur, but thrombophlebitis is not so frequent as was previously considered. Neurological syndromes are rare and show a great variety of presentations. Other occult manifestations of cancer include hypertrophic pulmonary osteoarthropathy, various skin diseases, obscure pyrexias and, in Hodgkin’s disease, pain secondary to alcohol consumption.
Endocrine System

Hypofunction of endocrine glands due to primary or secondary carcinoma gives rise to endocrine manifestations of the disease.

Tumours primary in a gland give rise to hyperfunction of the gland.

(a) Pituitary.—No functioning malignant tumours of the pituitary have been described.

(b) Thyroid.—In most thyroid malignant tumours endocrine function is either diminished or absent but the function of occasional tumours, and especially metastatic thyroid tumours, is at a normal level or these tumours are even hyperfunctioning.

(c) Parathyroids.—Occasionally primary parathyroid carcinomas are hyperfunctioning.

(d) Pancreas.—Malignant beta-cell carcinomas of the pancreas may function and produce insulin, giving rise to Whipple’s triad.

(e) Adrenals.—(i) Cortex: Malignant tumours of the adrenal cortex may produce Cushing’s syndrome, the adrenogenital syndrome, or hyperaldosteronism. (ii) Medulla and Paraganglia: Functioning pheochromocytomas may be found in either the adrenal medulla or the related paraganglia.

(f) Ovary.—Feminizing granulosa-cell tumours and thecomas are found in the ovaries. Arrhenoblastomas and hilar-cell tumours can produce masculinization.

(g) Testes.—Chorionepithelioma is a rare tumour which may produce feminization.

Tumours with Endocrine or Endocrine-like Function

(1) Manifestations due to Involvement of the Endocrine Glands

(a) Thymus.—Thymomas have been associated with myasthenia gravis, certain hematologic disturbances, agammaglobulinemia and Cushing’s syndrome. Of these syndromes, myasthenia gravis is the commonest, having been recognized in association with thymic tumours on several occasions since Weigert first described this syndrome in 1901.

Approximately 15% of myasthenic patients have associated thymomas, and more than 50% of the thymomas described are in patients with myasthenia gravis. In cases where myasthenia is associated with a thymoma, the disease often runs a more severe course, requiring higher dosages of neostigmine to control the symptoms, but these patients may gain considerable relief following thymectomy.

Instances of pancytopenia and aplastic anemia have been reported in connection with both malignant and benign thymic tumours. In some cases the thymic tumours have been known to antedate the blood changes, and in most cases some measure of improvement in the hematological conditions has been noted after resection of the tumour.

Another rare association of both benign and malignant thymomas is idiopathic acquired agammaglobulinemia. Resection or radiation of the tumour does not appear to have any effect on the globulin level, suggesting that some other factors, as yet unknown, are involved.

Cushing’s syndrome has also been reported with thymic tumours. None of these rare manifestations of thymic tumours have yet been adequately explained.

(b) Non-Beta-Cell Tumours of the Pancreas—With Zollinger-Ellison Syndrome.—The first three cases of this disease to be reported were described by Zollinger and Ellison in 1955. The syndrome described was of recurrent peptic ulceration; the ulcer was usually distal to the first part of the duodenum and often in the jejunum. There was an associated marked hyperacidity of the stomach together with a non-beta-cell tumour of the pancreas. Many of these patients required total gastrectomy to avoid complications or recurrent ulceration.

Since the initial description of this syndrome, many reports of intractable diarrhoea have been made, sometimes as an isolated finding and sometimes with the other manifestations of the syndrome.

In May of 1960 a report of such a case appeared in the Lancet. In this particular case a patient with recurrent ulceration, gastric hyperacidity and watery diarrhea was treated by excision of the tumour from the pancreas. This pancreatic tumour was assayed for histamine activity and was found to be within normal limits. The tumour was then assessed for gastrin activity, and when this was tested in dogs a very marked gastric secretion response was noted. The substance extracted from the tumour was chemically similar to gastrin, but the exact nature of the hormone has not been established with certainty.

(c) Carcinoids.—These tumours arise from the Kulchitsky cells of the bowel. A vasoconstrictor hormone was first described in 1884 and the tumour itself first described in 1888. The tumour was named in 1907, but the relationship between the hormone and the tumour was not recognized until Lembek described the association in 1953.

The carcinoid syndrome is found only when the carcinoid tumour has metastasized to the liver. The most prominent clinical findings are: cyanotic flushes together with hypertension, respiratory distress, right-sided cardiac failure, pulmonary murmurs, diarrhea and occasionally peptic ulceration.

The hormone released by the tumour is 5-hydroxytryptamine, and this is converted by deamination into 5-hydroxyindoleacetic acid, which is readily demonstrated in the urine.

Carcinoids are found in the terminal ileum, Meckel’s diverticulum, the duodenum and the rectum. The most common site of carcinoid tumour is the appendix, but tumours in this site are only very rarely malignant.

Tumours of the bronchus, often diagnosed histologically as benign bronchial adenomas, have been described, metastasizing to the liver and
giving rise to the carcinoid syndrome. This has also been reported in cases of anaplastic bronchogenic carcinoma. Of interest is the fact that the bronchial tumours giving rise to the carcinoid syndrome do not show the characteristic granules on silver impregnation.

(d) Cushing's syndrome.11-13—An association between Cushing's syndrome and malignancy other than primary tumours of the adrenals has been recognized for a considerable time, and malignancy in as high as 10% of patients with Cushing's syndrome has been reported.

This syndrome may present in one of three ways: (i) a typical florid Cushing's syndrome; (ii) the chemical findings of Cushing's syndrome with an increase in urinary 17-ketosteroids but no manifestations of the disease; and (iii) an abnormal adrenal response14 to the stimulus of ACTH.

Many neoplasms are associated with this syndrome, but bronchogenic carcinomas are the most common. Other tumours of importance are those of the thymus, thyroid, ovary, breast, and stomach.

The onset of the syndrome is usually acute, and death frequently occurs within a short time after the onset of the clinical manifestations, although adrenalectomy has been reported to be of some value.

(2) Other Manifestations of Endocrine-Like Dysfunction

(a) Hypoglycaemia.15, 16—This is occasionally produced by large malignant mesodermal tumours found in the pleural cavity or retroperitoneal space. These tumours present characteristically with Whipple's triad of cerebral disturbance on fasting, a low blood sugar, and relief of symptoms on taking glucose. The mechanism of hypoglycaemia production is not certain, but it may be due to any of the following mechanisms: (i) the metabolism of the tumour utilizing circulating glucose; (ii) stimulation of the adrenals by some hormonal release from the tumour; (iii) release of an insulinase competitor; (iv) production of insulin by the tumour; (v) diminished hepatic production of glucose.

Insulin17 may play an important role; it has been extracted from frozen tissue.

Hypoglycaemia has also been reported in the presence of hepatomas18 and rarely with other tumours. Hepatomas producing this syndrome are usually very large, and their action may be due to interference with normal liver function. Hypoglycaemia has been reported in as many as 30% of cases with massive hepatoma. Similar findings have not been reported with cholangioma.

(b) Hypercalcemia was first reported in association with multiple myelomatosis by Gutmann19 in 1936, and subsequently has been recognized in association with many other malignancies, but especially with carcinoma of the breast20 and bronchogenic and renal carcinomas. While most cases of hypercalcemia are secondary to bone metastases or hormonal therapy, there is a significant number of cases, approximately 20%, in which no such association can be demonstrated. In these cases removal21 of the primary growth may be associated with a return to normal of the serum calcium, phosphorus and alkaline phosphatase levels. The later development of secondaries may be associated with recurrence of hypercalcemia and its associated symptoms.

The possible mechanisms of hypercalcemia production are: (i) release by the tumour of some parathyroid stimulating hormone; (ii) sensitization to endogenous vitamin D; (iii) generalized bone demineralization secondary to some unknown substance released by the tumour.

Hypercalcemia22 usually presents with severe gastrointestinal upset, and renal and central nervous system symptoms, leading to rapid deterioration of the patient.

(c) Renal sodium loss.23-25—An increased renal sodium loss has been described in association with bronchogenic carcinomas, and this may produce hyponatremia. The association of other lung diseases and hyponatremia has been described more frequently. The most likely cause for the hyponatremia is an imbalance in the release of antidiuretic hormone.

(d) Polycythemia has been described in association with renal carcinomas,26 uterine leiomyomas, hepatomas and cerebellar hemangioblastomas.27 Polycythemia28 has also been described in association with non-malignant renal disease such as polycystic kidneys and glomerulonephritis.

The exact mechanism of production of polycythemia has not been determined, but the most likely mechanism is through production of an erythropoietin factor which stimulates the bone marrow to increased red-cell production. In cases where the tumour has been removed, the polycythemia has returned to normal, but a further exacerbation may take place if metastases appear.

(e) Gynecomastia29 has occasionally been reported in association with bronchogenic carcinoma. This is usually accompanied by some degree of testicular atrophy. Laboratory studies on these patients have at different times shown elevation of estrogen and depression of androgen secretion, but the exact etiology of this phenomenon has not yet been elucidated.

Embolization

Emboli can be produced from tumours by direct extension of the tumour into the veins. This has been most frequently described in renal carcinomas where massive tumour emboli can break off and produce severe pulmonary symptoms. The direct extension of the tumour into veins has been described in follicular adenocarcinoma of the thyroid and in bronchogenic carcinoma.

Venous thromboses associated with malignancy were first described by Trousseau in 1865. Venous
thromboses may present early or late and may be single or multiple. A high incidence of association between carcinoma of the tail of the pancreas and venous thrombosis has been reported. The association of carcinoma of the head of the pancreas, bronchogenic carcinoma and gastric carcinoma with this syndrome has also been reported, but not to the same extent.

Recent analysis of the problem has suggested that the early papers on carcinoma and venous thrombosis have drawn conclusions on the basis of inadequate evidence. Despite the statistics commonly quoted, it seems that too much emphasis has been laid on this phenomenon, and in fact venous thrombosis is very rarely an early manifestation of hidden carcinoma.

Non-bacterial thromboendocarditis has been recognized as a pathological finding for many years, and its association with carcinoma has been recognized in approximately 50% of autopsy cases. Usually it is an autopsy finding, but very occasionally emboli from this condition have produced symptoms prior to diagnosis of carcinoma. Thrombi are usually found on the mitral valve and occasionally on the aortic valve.

In a small percentage of these patients, multiple emboli have produced symptoms before death, and these symptoms are most often produced by emboli to the brain, spleen or the kidneys.

Hypertrophic Pulmonary Osteoarthropathy with Finger Clubbing

Hippocrates was the first to describe digital clubbing and his name has been associated with this sign. Hypertrophic pulmonary osteoarthropathy was first described in 1890 by Marie, who described "symmetrical osteitis of the four limbs chiefly localized to the leg".

Clubbing and osteoarthropathy are found in association with numerous diseases, clubbing being by far the most common finding. Clubbing may be associated with suppurative, cyanotic, liver or bowel disease. Hypertrophic osteoarthropathy has been said by some to occur only in bronchogenic carcinoma, but in one series of 1024 cases, hypertrophic osteoarthropathy was described in 51.7% of mesotheliomas, 9.5% of cases with bronchiectasis, 17.6% of cases with lung abscesses, and 5.2% of bronchogenic carcinomas. In groups of patients with bronchogenic carcinoma, it is usually the less malignant epidermoid carcinomas which give rise to this syndrome, and this may be related to the cavitation and infarction often found in this tumour. It is of interest to note that osteoarthropathy will show dramatic remission after surgery, relief of symptoms often being noted within a few hours of the time that the patient recovers from the anaesthesia.

Skin Diseases

Several dermatologic changes are associated with malignant disease. Most noted of these are acanthosis nigricans, scleroderma, dermatomyositis, acquired ichthyosis and acquired trichosis.

Both juvenile and adult acanthosis nigricans has been described, but only the adult variety is associated with visceral neoplasms. When the adult association is present, 65% of the tumours are gastric adenocarcinomas, and removal of the tumour results in improvement of the dermatological condition. An exacerbation of acanthosis nigricans often follows development of secondaries and at this time melanin pigmentation may occur in the operation scar.

Scleroderma and dermatomyositis show a very definite relationship to carcinoma and particularly to bronchogenic carcinoma. The dermatological manifestations may be present for several years before the clinical appearance of the carcinoma, and the skin disease may be improved by removal of the tumour.

Acquired ichthyosis and acquired hypertrichosis have similar implications to those of acanthosis nigricans. Herpes zoster developing in an adult suggests the presence of a visceral neoplasm, and adequate investigation is necessary to exclude this possibility.

Neurological Disorders

Several neurological disorders have been described in association with malignancy and in the absence of cerebral metastases. These have been referred to as carcinomatous neuromyopathies. A classification of neurological disturbances is as follows: (a) cortical-cerebellar degeneration, (b) mixed forms of degeneration, (c) sensory neuropathy, (d) peripheral neuropathy (sensory-motor) and (e) neuromuscular disorders.

There is no constant relationship between the course of the neuromyopathy and the course of the carcinoma. The central nervous system symptoms may antedate the other clinical manifestations of carcinoma by as long as three years, and the patient may show recovery while the tumour is still advancing. The removal of the associated tumour may have no effect on the progress of the central nervous system disease, and indeed the disease may not first appear until after successful removal of the cancer.

(a) Cortical-cerebellar degeneration.—Associated with loss of Purkinje cells and granular cells, this degeneration may present in either an acute or subacute form. Acute cerebellar disturbances may progress rapidly to produce death within a short time.

(b) Mixed forms.—The clinical manifestations of this group are widely distributed. Here the cerebellar disturbance is again present, but there may be degeneration of the anterior horn cells of the spinal cord and also of the pyramidal tracts. Microscopically, in this variety there is a perivascular lymphocytic cuffing of the blood vessels in the spinal cord.
(c) Sensory neuropathy.—A pure sensory neuropathy occurs occasionally, and this is usually associated with degeneration of the posterior root ganglia and posterior spinal columns. Again a perivascular lymphocytic cuffing is frequently found in association. The sensory ataxia which follows may be very marked and progressive.

(d) Peripheral neuropathy (sensory-motor).—In this group degeneration may be of both the sensory and motor areas of the spinal cord. In both the sensory neuropathy and the peripheral neuropathy, dementia may be a terminal feature.

(e) Neuromuscular disorders.—There is a heterogeneous aggregation of neuromuscular disorders associated with fasting, in various muscle groups. Included in this group are conditions closely resembling myasthenia gravis.

Etiology of the neurological disorders has not been determined. It may be some toxic factor in the tumour or it may be an inflammatory response to the tumour. A viral infection of the brain is possible and may account for the perivascular lymphocytic cuffing. Sensitization to the tumour is another possibility, and nutritional and endocrine disturbances may also be considered.

**Miscellaneous Syndromes**

There are other less well-defined manifestations of underlying neoplasia. Obsolete pyrexia is not an uncommon presentation of neoplastic disease and this is most often associated with lymphomas, especially Hodgkin’s disease, and also with Ewing’s sarcoma, renal carcinomas and hepatomas.

Generalized pruritus is occasionally associated with Hodgkin’s disease and may be a prominent feature. Pruritus associated with other tumours is usually secondary to jaundice.

Pain associated with consumption of alcoholic in Hodgkin’s disease was first described in 1950. The pain is present in a small percentage of Hodgkin’s patients, coming on 15 to 30 minutes after alcohol consumption and lasting a variable length of time. At first the condition was thought to be specific for Hodgkin’s disease, but it has now been described, as a rare occurrence, in several other conditions, including malignant thymoma, renal carcinoma and hepatoma.

The cause of pain in Hodgkin’s disease is not established, although it has been related to the histology of the tumour.

**Discussion**

On the basis of the foregoing descriptions it is possible to systematize the unusual manifestations of malignant disease. The following is given as a tentative grouping, since doubtless other syndromes will continue to be recognized.

1. Cachexia (wasting and anemia).
2. Endocrine and endocrine-like syndromes.
   (A) Ablation of glands by primary or secondary tumours.
   (B) Hyperfunctioning tumours of glands.

3. Emboli.
   (A) Tumour emboli.
   (B) Migrant thrombophlebitis and malignancy.
   (C) Non-bacterial thrombocytopenia.

4. Hypertrophic pulmonary osteoarthropathy and finger clubbing.
5. Skin diseases secondary to malignancy.
6. Neurological disorders secondary to malignancy.
7. Miscellaneous syndromes secondary to malignancy.

**Summary**

A number of interesting syndromes, apparently secondary to neoplastic disease, have been reported in the literature. These syndromes may be associated with massive neoplasia, but many are associated with small tumours, and as such the recognition of these syndromes becomes of great importance in the diagnosis of neoplastic disease. In many cases the mechanisms of production of the syndromes have not been established, and only an empirical relationship can be demonstrated. The course of the neoplastic disease can in some cases be followed by the exacerbations and remissions of these secondary manifestations of the neoplasms.

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**References**

CASE REPORT

Acute Interstitial Pulmonary Fibrosis Caused by a Smoke Bomb

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CIVILIAN as well as military physicians may be required to diagnose and treat casualties of smoke-bomb fumes. In military operations smoke generators are used to provide concealment, and they are occasionally used in civil life in firefighting exercises. Inhalation of fumes is rarely hazardous except in situations where smoke is generated indoors or in a confined space outdoors. The greatest number of such cases was that reported in 1945 by Evans,¹ who described 10 deaths within a week of exposure and 35 instances of smoke pneumonitis among 116 persons exposed in a tunnel in Malta during World War II. Exposure occurred when enemy bombs ignited a store of 79 smoke generators situated at the mouth of the tunnel.

The present report deals with smoke pneumonitis occurring in a fireman who took part in a firefighting demonstration in which a smoke generator was used to provide realism. The case is of interest not only because it serves to draw attention to this unusual hazard but also because of the exceptionally long survival which allowed the development of advanced pulmonary fibrosis and early right ventricular hypertrophy.

A 35-year-old fireman was admitted to Hotel Dieu Hospital, Kingston, Ontario, a few minutes after exposure to chemical smoke during a fire prevention exercise. The generator had been ignited at the bottom of a depression a few feet below ground level and surrounded by buildings on three sides. The patient had attempted for several minutes to extinguish the bomb with a fire extinguisher, although a less hardy colleague was forced to withdraw almost immediately.

Both patients presented at the hospital outpatient department with nausea, sore throat and chest tightness made worse by deep inspiration. The man whose exposure had been brief recovered rapidly and was discharged in less than 48 hours. The second man was treated with aminophylline and codeine, with some relief, but his temperature had risen to 101.2°F a short time after admission. By the next day he felt well enough to request discharge, although he still had chest pain on deep inspiration and his temperature remained elevated. A radiograph of the chest at this time showed prominent pulmonary markings, particularly in the left cardiophrenic area. This was attributed to obesity and shallow inspiration (Fig. 1 shows the radiographic appearance at one day and at 18 days). Eighteen instances of smoke pneumonitis among 116 persons exposed in a tunnel in Malta during World War II. Exposure occurred when enemy bombs ignited a storage of 79 smoke generators situated at the mouth of the tunnel.

The present report deals with smoke pneumonitis occurring in a fireman who took part in a firefighting demonstration in which a smoke generator was used to provide realism. The case is of interest not only because it serves to draw attention to this unusual hazard but also because of the exceptionally long survival which allowed the development of advanced pulmonary fibrosis and early right ventricular hypertrophy.

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Thirty hours after exposure his respiratory rate rose to 50 per minute and he rapidly developed slate-blue cyanosis, confusion and coma. At this time his lung fields remained clear to percussion and auscultation, but the pulse rate was rapid and regular at 150 per minute. He was treated with oxygen, prednisone, penicillin, chloramphenicol and heparin, and regained consciousness within a few hours. His condition remained critical for the rest of his time in hospital. He was unable to tolerate even brief periods outside an oxygen tent without marked tachypnea, cyanosis and a rise in blood pressure. On the 11th day he developed thrombophlebitis of the long saphenous vein in the right thigh. Heparin therapy, discontinued on day three, was restarted at this time and continued for the remainder of his hospitalization.

From the Departments of Medicine and Pathology, Hotel Dieu Hospital and Queen's University, Kingston, Ont. Presented at the Annual Meeting of the Canadian Heart Association, Montreal, June 1969.