THE SYSTEMIC EFFECTS OF BRONCHIAL CARCINOMA*

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During recent years it has become increasingly evident that malignant processes at various sites and involving various tissues, can produce a variety of systemic effects not directly due to either metastasis or to the mechanical effects of the tumour. Most of these manifestations have been recorded in association with bronchial carcinoma.[1]

These systemic effects make an interesting and profitable study because:—

(*i*) Several of them may precede the clinical detection of the carcinoma itself. Their recognition may thus aid in the early diagnosis of this often fatal disease.

(*ii*) Many of these conditions are distressing to the patient but show a tendency to regress if the tumour is treated. Recognition of the relationship of these manifestations to the bronchial carcinoma may indicate palliative treatment of the tumour with the aim of making the patient more comfortable where cure is impossible.

(*iii*) It is unlikely that the list of conditions is complete and there is room for original clinical observation in this field by all members of the profession.

(*iv*) Some of these features have ominous implications for the patient and can give information about the prognosis.

(*v*) These manifestations give us some interesting considerations about the very nature of malignant disease itself. To quote the authors of a comprehensive review of the systemic effects of cancers: 'Systemic manifestations in the absence of demonstrable metastasis strongly suggest that cancer is more than a simple derangement of local tissue growth'.[1] It seems likely that in some instances the tumour and its secondaries are secreting some humoral product or products, often quite unrelated to the normal functions of the tissue from which the tumour originates. In other instances the nature and occurrence of these manifestations give rise to speculation about a common aetiology of both tumour and 'systemic manifestation' and might be a pointer to further investigation of the cause or causes of malignancy—and nothing is going to assist prevention more than obtaining a definite understanding of the aetiology of the disease.

(*vi*) These manifestations give us an indication that the human body reacts to malignant disease in an ill-defined and ill-understood manner. An understanding of the body's reactions to infections and to various types of trauma has helped in the management and treatment of numerous conditions and a better understanding of the body's reactions to malignancy might well help us to strengthen the natural defences of the host against the invasive tissues and thus gain control of the disease process. Study of these systemic effects may well provide clues to the reactions that malignant disease excites.

In this paper only those effects of bronchial carcinoma that are not directly attributable to either the mechanical effects of the tumour or to metastases, will be considered. While most patients with bronchial carcinoma will present with respiratory symptoms (cough, blood-stained sputum, dyspnoea, chest pain) or with conditions directly attributable to metastases (e.g. back pain from spinal metastases, cerebral signs from brain metastases, jaundice from liver metastases, etc.), a minority of patients do present with or display these manifestations, and for the reasons outlined above, they are worthy of consideration. Because of their multiplicity and varied nature, the conditions will be classified and described according to the system in which they manifest themselves.

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DERMATOLOGICAL MANIFESTATIONS

Non-Specific Dermatoses

Intense pruritus,[2] acquired icthyosis and acquired hypertrichosis[3] have all been described as occurring in relation to bronchogenic carcinoma, the latter 2 conditions having actually preceded recognition of the occult lung neoplasm. Furthermore, Hill[3] noted that both dermatitis herpetiformis and herpes zoster occur more frequently in patients with cancer than in the general population, though not necessarily in association with bronchial carcinoma. Involvement of the spine at any level appears to increase the patient's susceptibility to herpes zoster in the spinal nerves at that level. These non-specific dermatoses occur only rarely in association with malignant tumours and possibly reflect the response of the skin to non-specific toxins or allergens, including carcinogens.[1]

Acanthosis Nigricans

Patients who are more than 40 years old and develop this condition invariably have a visceral malignant tumour. In 90% of cases this is an intra-abdominal adenocarcinoma, the breast and the lung being the most frequent sites of an extra-abdominal primary neoplasm. The skin lesion is evident at or before the time of diagnosis of the tumour in 78% of cases, appearing later in 22%, and the average survival time after discovery of the lesion is about 9 months.[4]

The skin lesion is characteristically pruritic, darkly pigmented, soft, confluent, verrucous and tends to occur in body folds and frequently to involve the mucous membrane. Removal of the tumour produces regression of the skin lesion, reappearance of which is associated with recurrence of metastases. Here then, is an interesting condition where a surface lesion appears to be an accurate index of the recurrence of a deep internal malignant process.

Curth *et al.*[4-6] have concentrated on a possible genetic mechanism in their thinking and discussion, but some of their postulates can be adapted to other possible aetiologies. Assuming a common cause, could not (for instance) a virus of some sort produce these 2 forms of epithelial hyperplasia in susceptible epidermal and glandular tissues respectively?

Dermatomyositis

Workers at the Mayo Clinic have noted that 15% of all adults with dermatomyositis have a carcinoma somewhere[7] and others have shown that this proportion rises to about 50%, if patients over 40 years of age only, are considered.[8]

There is therefore sufficient evidence to state as an axiom that: 'The onset of dermatomyositis after the age of 40 years should provoke search for an occult cancer somewhere'.[1]

The most common sites for the associated neoplasm are the stomach (in males) and the breast and ovary (in females), but the condition has been reported with bronchial carcinoma too. Of interest is the fact that a pure polymyositis has been described in association with some of the lesions but apparently not as yet with bronchial carcinoma.[9] The dermatomyositis may precede the discovery of the carcinoma or may occur later, but there is no correlation between the degree of spread of the tumour and the intensity of the skin reaction. Nevertheless, remission of the skin lesion frequently follows effective treatment of the primary neoplasm.

Clinically, patients with dermatomyositis show a combination of skin and muscle lesions (as the name implies). The skin lesion is characteristically an erythematous and oedematous rash involving especially the face and neck, sometimes violaceous and sometimes accompanied by subcutaneous telangiectasis under the eyelids and/or red atrophic knuckles. The muscles show proximal weakness and atrophy, sometimes confined to small groups of muscles, but at other times involving the muscles of the entire body.

It had been suggested in 1952, that this manifestation represents an allergic reaction to catabolic products of the neoplasm[10] and this has recently been confirmed.[11,12]

Erythema Gyratum Repens

This is a rare toxic response that has been described in association with oat-cell carcinoma of the lung and with poorly differentiated adenocarcinoma of the breast. It is an erythematous, gyrate, macular eruption tending to give the skin a knotty pinewood appearance and to change from day to day.

Treatment of the tumour either by irradiation or by surgery results in the disappearance of the reaction. A similar aetiology to that proposed for dermatomyositis has been put forward for this condition.[13]

NEUROLOGICAL MANIFESTATIONS

Dementia

Upsets of mental function showing features of a toxic confusional psychosis have been described in association with bronchial carcinoma in the absence of cerebral secondaries. In some cases, this breakdown of higher cerebral function has completely dominated the entire clinical picture, the associated neoplasm being discovered only on further physical or radiological investigation of the patient or at autopsy.[14]

Cerebellar Degeneration

This degeneration follows 2 forms. On the one hand, the patient may show what is primarily a condition of deficient cortical cerebellar function with varying degrees of vertigo, ataxia, dysarthria, diplopia, nystagmus and intention tremor. This type shows an acute onset and often a rapidly progressive course so that within a few weeks the patient is unable to walk or stand (though the condition may take a year to develop fully), the degeneration occurring alone or in association with the other neuropathies that can accompany bronchial carcinoma.[15,16]

On the other hand, the patient may show muscle wasting and weakness, paraesthesiae and loss of sensation combined with signs of cerebellar dysfunction. The two conditions can be differentiated histologically.[15]

Peripheral Neuropathy

Bronchial carcinoma is the most common cause of a carcinomatous neuropathy,[16] sensory neuropathies being particularly suggestive of an underlying neoplasm.[15] The patient complains of severe and persistent paraesthesiae and pain in the limbs, and this progresses to a loss of all sensation in the areas supplied by the affected nerves together with sensory ataxia, but little evidence of muscle wasting or weakness.

Spontaneous remissions or arrest of the neuropathy are frequent and may occur without treatment of the tumour. On the other hand, removal of the tumour often has no effect whatsoever on the neurological manifestations.[15]

Myasthenia-like Syndrome

It is common knowledge in both professional and lay circles that carcinoma is often accompanied by general wasting of the body's muscle mass. There are a variety of easily understandable causes to account for this phenomenon, in particular such factors as nutrition (and there does appear to be evidence that the rapidly growing tumour takes more than its fair share of available nutrients), biochemical derangements, toxic products produced by tumour necrosis, causing anorexia and general malaise and the inevitable loss of muscle tissue from disuse and decubitus, as the patient's general condition continues to degenerate. Metastases by their pressure effects can aggravate any of these processes.

However, in 1959, Anderson *et al.*[17] reported a case of a patient who had prolonged apnoea following administration of succinylcholine during an operation for the removal of a bronchial carcinoma. Since then it has been recognized that patients with bronchial carcinoma may present with a syndrome in some respects resembling myasthenia gravis and therefore termed the 'myasthenia-like syndrome'.

Clinically, these patients are found to be easily fatigued and to have a weakness of the proximal muscles of the limbs, especially the pelvic girdles and thigh muscles, accompanied by aching pains in the limbs. On examination the patient's stretch reflexes are found to be absent or greatly diminished. Rook *et al.*[15] studied in detail, 19 patients with this condition who presented themselves at the Mayo Clinic and found that in every case this syndrome had been the precursor of a bronchial carcinoma of the small cell variety that did not become diagnosable until several months later. Brain has reported a tendency to spontaneous remission of this condition.[15]

As a result of their studies, Rook *et al.*[15] were able to point out the significant differences between this condition and true myasthenia gravis (Table I). So specific are the EMG findings, that 3 cases at the Mayo Clinic were suspected of having a bronchial carcinoma because of the electromyographic findings alone! Although these patients showed no signs of respiratory disease, they were investigated and each was found to have an occult, highly ana-

plastic, small-cell carcinoma of a bronchus—but unfortunately the tumours were so anaplastic that the prognosis was not improved although they had been detected before giving rise to pulmonary signs and symptoms.

TABLE I. A SUMMARY OF THE DIFFERENCES BETWEEN THE MYASTHENIA-LIKE SYNDROME ACCOMPANYING BRONCHIAL CARCINOMA AND TRUE MYASTHENIA GRAVIS*

Myasthenia-like syndrome	*True myasthenia gravis*
1. Weakness of proximal muscle groups, especially of pelvic girdle and thighs	1. This pattern of involvement rare
2. Bulbar and ocular muscles not involved except very mildly in a few cases	2. Bulbar and ocular muscles usually involved
3. Temporary increase in muscular strength after a few seconds of voluntary exercise as previously inactive fibres are thrown into contraction	3. Initial activity of muscle may be normal, but easily fatigued
4. Electromyographic findings specific and diagnostic—initial supramaximal stimulation produces an abnormally small potential because of a defect in neuromuscular transmission	4. Electromyograph shows characteristic postexcitation transmission delay
5. Muscle stretch reflexes in lower limbs decreased or absent	5. Muscle stretch reflexes not usually affected
6. Pharmacological reactions: (*a*) Unresponsive to neostigmine (*b*) Hypersensitive to d-tubo-curarine (*c*) Sensitive to depolarizing agents	6. Pharmacological reactions: (*a*) Characteristically responsive to neostigmine (*b*) Less sensitive to d-tubo-curarine (*c*) Insensitive to depolarizing agents

*Based on Rook *et al.*[18]

These neurological manifestations occur in the vast majority of cases in association with carcinoma of the lung, but (with the exception of the myasthenia-like syndrome) have also been reported in association with carcinoma of other organs. According to Brain and Henson,[15] they accompany about 5% of all lung cancers. The pathology of these manifestations has been recorded in most instances, but their pathogenesis has only been guessed at. Whatever the actual mechanism or mechanisms of the production of these conditions, one fact remains clear and that is that *the possibility of an occult carcinoma should be considered in any patient over* 50 *years of age in whom a neuropathy develops without apparent cause.*[1] An awareness of the interrelationships of the neural and pulmonary lesions may lead to a greater incidence of early recognition of the latter and may also be of help in the differential diagnosis of a doubtful lung shadow.[16]

CARDIOVASCULAR MANIFESTATIONS

Thrombophlebitis

Thrombophlebitis is a well-known complication of far-advanced cancer, but recently it has been shown that in about one-third of a series of 1,400 cases the thrombophlebitis preceded the appearance of the malignancy.[19] As a result of these investigations, it has been suggested that recurrent or migratory phlebitis that proves resistant to anticoagulant therapy and that has no apparent cause, is strongly suggestive of an occult neoplasm. In conversation with medical teachers, there appears to be a common belief that the gastro-intestinal tract is the likeliest site for the occult neoplasm, but the above-mentioned series showed that the neoplasm was most often bronchial carcinoma in males and cancer of the reproductive tract in females.

Amundsen *et al.*[20] have found that thromboplastin generation is accelerated in some patients with bronchial carcinoma, and that this acceleration is due to an increase in the plasma level of an anti-haemophilic globulin (AHG-like) factor, which is heat-labile and shows great ability in shortening the prolonged recalcification time of haemophilic plasma.

Even if the mechanism outlined above is the cause of the thrombotic phenomena associated with bronchial carcinoma, many questions remain to be answered. What is the source of this 'AHG-like' factor? Is it liberated by the tumour tissue? Or, is it perhaps a response on the part of the body to the threat of invasion; an attempt by the body to coat the tumour emboli with the products of blood coagulation and thus prevent the development of metastases by neutralizing the seeds?

Non-Bacterial Thrombotic (Verrucal/Marantic) Endocarditis

Although known as marantic carditis, this condition can occur in patients who are not markedly wasted and has been reported even in cases of occult carcinoma.[7] The essential lesions are friable, fibrinous, blood-cell containing accumulations on the heart valves that are capable of causing arterial embolism resulting in sudden death. In many cases, however, they are quite silent and only discovered at autopsy.

HAEMATOLOGICAL MANIFESTATIONS

Hypofibrinogenaemia

This condition has usually been described in association with metastatic carcinoma of the pancreas, but in 1960, Fountain and Holman[21] described a case where an anaplastic bronchial carcinoma that had metastasized to the adrenals, lumbar vertebrae and meninges presented with a plasma fibrinogen level of 40 mg./100 ml. and a clotting time of 10 minutes. No prostatic carcinoma or other prostatic abnormality could be detected.

Fibrinolysins have been extracted from some of these prostatic tumours[22] and have been used to explain the hypofibrinogenaemia,[1] but attempts to isolate fibrinolysins from bronchial carcinomas associated with hypofibrinogenaemia have failed. Stefanini *et al.*[23] noticed that in the peripheral blood of a case of bronchial carcinoma they could demonstrate clustering and precipitation of fibrin around nests of tumour cells acting as foci. It has thus been suggested that showers of emboli can lead to hypofibrinogenaemia on the simple basis of the demand for fibrin exceeding the supply.

This observation raises interesting teleological considerations. Does it, perhaps in conjunction with the rise of an 'AHG-like' factor, give us a clue as to one of the possible reasons why only a few of the myriads of embolic seeds that are sown into the blood-stream germinate and pro-

duce metastases? Or is it merely that the nests of tumour cells are recognized by the blood-coagulatory system as a foreign surface and thus excite this reaction? If the answer lies along this second line, we should expect to find hypofibrinogenaemia in close association with all tumours that are spread by way of the blood-stream. It has been reported with prostatic and bronchial carcinomas and further observation may bring to light other associations.

Simple Chronic Anaemias

Malignant disease, particularly of the gastro-intestinal tract, is often associated with a chronic loss of blood and thus gives rise to a hypochromic anaemia. However, apart from this, it has been noted that a normochromic, normocytic anaemia can be associated with bronchial carcinoma in the absence of any chronic loss of blood or extensive bone marrow secondaries. This anaemia commonly disappears after removal of the tumour, and an associated depressed serum iron concentration has also been reported to have returned to normal after removal of the primary bronchial carcinoma.[24]

Polycythaemia

Greatly increased erythrocyte counts have been reported in association with metastatic carcinoma of the lung,[1] apparently in the absence of a degree of deficient pulmonary ventilation which could account for the finding on the basis of a physiological response to hypoxaemia.

GASTRO-INTESTINAL MANIFESTATIONS

Peptic Ulcers

These have long been known to be associated with tumours of the pancreas (the Zollinger-Ellison syndrome), but it has recently been reported that there is an increased incidence of peptic ulceration associated with bronchial carcinoma.[25] This is not likely to be of much aid in the diagnosis of bronchial carcinoma, however, as the ulcers were found only at autopsy.

METABOLIC MANIFESTATIONS

The Carcinoid Syndrome

Carcinoids usually occur in the walls of the gastro-intestinal tract, but have also been reported in the lung. 10% of carcinoids occurring in the lung are said to be malignant.[26,27]

Gowenlock *et al.*[28] have recently reported a case of histologically proven oat-cell carcinoma of the bronchus that was apparently secreting 5-hydroxy indoles. Their patient showed ecchymoses around his knee and elbows, mottled palmar erythema and hepatomegaly, and had a raised urinary excretion of 5-hydroxy indole acetic acid (5-HIAA) *but no carcinoid could be demonstrated in any known site of the occurrence of these tumours.* Further investigation is clearly necessary before bronchial neoplasms can be definitely held to be capable of producing these abnormal amounts of 5-hydroxy indoles.

Serum Protein Abnormalities

Carpenter *et al.*[29] after the investigation of a large number of cases, have declared that pulmonary neoplasia is almost always associated with a marked derangement of the serum protein profile. In the early stages of the disease they noted abnormalities of the glycoproteins, followed later by elevations of alpha-1 and alpha-2 proteins which they related to the inflammatory responses developing around the tumour.

Bronchial carcinoma in particular, seemed to be frequently associated with an elevation of beta-2 and gamma-1 glycoprotein and this latter was shown by ultracentrifugation and electrophoresis, to be macroglobulins with flotation rates of 19 to 22 S and not demonstrable in normal serum. This protein is not, however, specific to bronchial carcinoma but is also found in rheumatoid disease and hepatic cirrhosis.

These observations raise the intriguing possibility of a biochemical screening test for the detection of occult bronchial carcinoma. Should such a test become easily available, it would exert an inestimably profound effect on the prognosis of the disease.

Hypercalcaemia

It has long been known that hypercalcaemia is one of the sequelae of advanced malignant disease, presenting with the following symptoms:

(*a*) Neurological: drowsiness, lethargy, mental confusion and episodes of coma;

(*b*) Gastro-intestinal: anorexia, nausea, vomiting, constipation;

(*c*) Renal: polyuria, polydipsia, albuminuria, renal failure;

(*d*) Cardiovascular: tachycardias, arrythmias, ECG abnormalities and hypersensitivity to digitalis.

What has only recently been appreciated, however, is that hypercalcaemia may occur without any bony metastases (although these are usually associated with the development of this complication of malignant disease). Hypercalcaemia can, of course, only be considered as a systemic effect, in the sense of this paper, if a full autopsy with full bone histology has shown no metastasis.

It has been noted that the administration of cortisone lowers the serum calcium in these cases[30] and also that careful calcium studies may give an index of the progression or regression of the tumour.[31] This last point may be of value in gauging the effectiveness of radiotherapy.

Cushing's Syndrome

The bronchial carcinomas associated with Cushing's syndrome have all been of the oat-cell type. Some of these have metastasized to the adrenal glands and some have not[7] and so metastasis to this area is not thought to be connected with the development of the syndrome. However, Onuigbo[32] has pointed out that adrenal metastases of lung cancers tend to develop inside pre-existent adrenal adenomas and has suggested that the adenomas may provide a good soil for the deposition of oat-cell carcinoma secondaries. How often Cushing's syndrome due to these adenomas occurs concurrently with bronchial carcinomas has not been established.

The signs and symptoms of the pulmonary lesion usually develop simultaneously with the Cushing's syndrome, but occasionally the tumour has been found only at autopsy.[33] Hepatic metastases have been noted as common accompaniments of a Cushing's syndrome associated with bronchial carcinoma. A constant feature of this endocrinological upset is that there are exceptionally high glucocorticoid levels in blood and urine, figures of up to ten times those

normally found with Cushing's syndrome having been recorded.[34]

After much discussion had raged about the pathogenesis of this manifestation, Liddle *et al.* in 1963,[35] managed to demonstrate that the tumour itself was the source of a corticotrophin (ACTH-like) substance. This secretion of an ACTH-like substance by an oat-cell carcinoma has been independently confirmed.[36,37]

Observations have also been made about the prognostic significance of this manifestation. Werk *et al.*[38] have summarized their findings as follows:

If the 17-hydroxycorticosteroid (17-HCS) levels are normal, the prognosis is 30 weeks or more;

If the 17-HCS levels are raised, the prognosis is between 5 and 30 weeks;

If the 17-HCS levels are markedly raised, the prognosis is usually less than 5 weeks.

The subject is arousing great interest at the moment and further clarification of the probably complex interrelationships of bronchial carcinoma and Cushing's syndrome may be expected.

Gynaecomastia

True gynaecomastia occurs occasionally in males with normal liver-function tests and underlying bronchial carcinoma. It has even on occasion been the patient's presenting symptom.[39] In this case, surgery of the neoplasm caused regression of the gynaecomastia, but before the operation, it was found that although the patient's liver-function tests were normal and although his testes appeared to be normal, the quantity of oestrogens being excreted in his urine was 3 times the normal level. At autopsy the primary tumour was found to have produced metastases in the liver, kidneys, spleen and cerebral hemispheres.

At least 2 other cases have been reported with gynaecomastia and raised circulating oestrogen-levels.[40,41] Two sources have been suggested for this excess of oestrogens; (1) the tumour itself; and (2) the adrenal cortex, possibly under stimulation from the tumour.

Renal Sodium Loss

Hyponatraemia associated with an excessive renal sodium loss has been described in association with several cases of bronchial carcinoma; these are always tumours of the oat-cell type[42] and successful treatment of the tumour has corrected the electrolyte imbalance. The essential lesion in this condition appears to be an inappropriate secretion of antidiuretic hormone of some sort and Niels and Transbol[43] proved the existence of such a hormone in 1963. They were not, however, able to establish the source of this vasopressin which was demonstrated by bio-assay.

SKELETAL MANIFESTATIONS

Digital Clubbing

Clubbing of the fingers and to a lesser extent of the toes is a well-known accompaniment of bronchial carcinoma. That form of clubbing associated with neoplasms is often painful, may develop rapidly and appear acute, because of a red rim in the skin around the base of the nail, and tends to regress after treatment of the tumour.[1,7]

Pulmonary Hypertrophic Osteoarthropathy

In this condition, the patient complains of painful joints and swellings over the distal ends of the long bones, the arthralgia often resembling that of rheumatoid arthritis. Up to 12% of bronchial carcinomas are said to be accompanied by this manifestation.[1] Together with the clubbing mentioned above, these lesions are said to be more severe when pulmonary suppurative disease exists together with the carcinoma, and also to be more frequent when the tumour is located in the periphery of the lung and shows central necrosis. The associated tumour is usually, but not always, a squamous cell carcinoma or adenocarcinoma.

Although the lesions may develop along with the carcinoma after the patient has come under observation for the latter, cases where the osteoarthropathy is the presenting complaint are not uncommon. The patient usually experiences a striking relief from pain following excision of the tumour, many being completely free from pain on waking.

The essential lesion in this condition seems to be a subperiosteal overgrowth of vascular connective tissue around the tendons and distal ends of the long bones[44] resulting in a periosteal proliferation in these areas and producing the painful non-pitting swelling that is detected clinically. The mechanism that produces this overgrowth is not clear, but the important fact for the clinician, is that bronchial carcinomas may occasionally present as joint and limb lesions with or without clubbing of the digits.

SUMMARY AND DISCUSSION

The many and varied systemic effects of bronchial carcinoma have been discussed under the various systems in which they occur. An attempt has been made to indicate how the manifestations might be related to the tumour and indications have been given of the ways in which these manifestations can assist in the diagnosis, prognosis and treatment of patients suffering from bronchial neoplasms.

If it does nothing else, a review such as this brings to light many gaps in medical knowledge, and most of all, our lack of understanding of what is the essential cause of neoplastic disease. What is this unknown agent or agents that can, not only alter the nuclear structure of cells in such a way that they proliferate uncontrollably, but can also so alter their biochemical structure that they secrete humoral products that are in no way related to their original function?

Besides this aetiological puzzle we are left with teleological considerations. Just what do these systemic effects represent? Are they an indication of the body's reaction to invasive neoplasms, or are they just another weapon with which these malignant tissues attack their hosts? And why is it that bronchial carcinoma (above all others) is the neoplasm most frequently associated with most of these conditions?

It is interesting to note the figures released by the Registrar-General of England[45] and Wales concerning cancer mortality in those countries during 1964:

Deaths from cancer (all forms): Males 56,247 (2,441/million population); Females 48,451 (1,989/million population)

Deaths from lung cancer alone: Males 21,476 (932/million population); Females 3,895 (160/million population).

These figures show us that the clarification of the questions posed above will help to meet what has become one of the greatest challenges to medicine in the twentieth century and to control what has become one of the major killing diseases of Western civilization.

REFERENCES

1. Greenberg, E., Divertie, M. B. and Woolner, L. B. (1964): Amer. J Med., **36**, 106.
2. Winkelmann, R. K. (1961): Proc. Mayo Clin., **36**, 187.
3. Hill, E. M. (1960): Minn. Med., **43**, 838.
4. Curth, H. O. (1955): Arch. Derm., **71**, 95.

5. Curth, H O., Hillberg, A. W. and Machacek, G. F. (1962): Cancer (Philad.), **15**, 364.
6. Curth, H. O. and Aschner, B. M. (1959): Arch. Derm., **79**, 55.
7. Andersen, H. A. and Bernatz, P. E. (1964): Med. Clin. N. Amer., **48**, 921.
8. Arundell, F. D., Wilkinson, R. D. and Haserick, J. R. (1960): Arch. Derm., **81**, 772.
9. Howard, F. M. jnr. and Thomas, J. E. (1960): Med. Clin. N. Amer., **44**, 1001.
10. Curtis, A. C., Blaylock, H. C. and Harrell, E. R. (1952): J. Amer. Med. Assoc., **150**, 844.
11. Grace, J. T. jnr. and Dao, T. L. (1959): Cancer (Philad.), **12**, 648.
12. Curtis, A. C., Hackaman, J. H. and Wheeler, A. H. (1961): J. Amer. Med. Assoc., **178**, 571.
13. Shammy, H. K. (1963): Proc. Roy. Soc. Med., **56**, 904.
14. Charatan, F. B. and Brierley, J. B. (1956): Brit. Med. J., **1**, 765.
15. Brain, R. and Henson, R. A. (1958): Lancet, **2**, 971.
16. Diamond, M. T. (1961): Ann. Intern. Med., **54**, 1259.
17. Anderson, H. J., Churchill-Davidson, H. C. and Richardson, A. T. (1953): Lancet, **2**, 291.
18. Rook, E. D., Eaton, L. M., Lambert, E. H. and Hodgson, C. H. (1960): Med. Clin. N. Amer., **44**, 977.
19. Liebermann, J. S., Borrero, J., Urdaneta, E. and Wright, I. S. (1961): J. Amer. Med. Assoc., **177**, 542.
20. Amundsen, M. A., Spittell, J. A. jnr., Thompson, J. H. jnr. and Owen, C. A. jnr. (1962): Ann. Intern. Med., **56**, 683.
21. Fountain, J. R. and Holman, R. L. (1960): *Ibid.*, **52**, 459.
22. Swan, H. T., Wood, K. F. and Daniel, O. (1957): Brit. Med. J., **1**, 495.
23. Stefanini, M., Giammzalvo, J. T. and Karaca, M. (1963): Amer. J. Med. Sci., **246**, 58.
24. Hagedorn, A. B. (1962): Ill. Med. J., **121**, 365.
25. Rama, S. J. and Chomet, B. (1962): Cancer (Philad.), **15**, 1117.
26. Luparello, F. J. and McAllister, J. D. (1961): Ann. Intern. Med., **54**, 1266.
27. Stanford, W. R., Davis, J. E., Gunter, J. U. and Hobart, S. G. jnr. (1958): Sth. Med. J. (Bgham, Ala), **51**, 449.
28. Gowenlock, A. H., Platt, D. S., Campbell, A. C. P. and Wormsley, K. G. (1964): Lancet, **1**, 304.
29. Carpenter, C. M., Henkell, C. L., Weimer, H. E., Fukuda, M., Yachi, A. and Wada, T. (1961): Dis. Chest, **40**, 245.
30. Locks, M. O. (1962): J. Lancet, **82**, 165.
31. Myers, W. P. L. (1960): Arch. Surg., **80**, 308.
32. Onuigbo, W. I. B. (1963): J. Path. Bact., **86**, 541.
33. Allott, E. N. and Skelton, M. O. (1960): Lancet, **2**, 278.
34. Brickner, P. W., Lyons, M. and Landau, S. J. (1961): Amer. J. Med., **31**, 632.
35. Liddle, G. W., Island, D. P., Ney, R. I., Nicholson, W. E., and Shimizu, N. (1963): Arch. Intern. Med., **111**, 471.
36. Pfohl, R. A. and Doe, R. P. (1963): Ann. Intern. Med., **58**, 993.
37. Nichols, J. and Gourley, W. (1963): J. Amer. Med. Assoc., **185**, 696.
38. Werk, E. E. jnr., Sholiton, L. J. and Marnell, R. T. (1963): Amer. J. Med., **34**, 192.
39. Goldman, K. P. (1961): Brit. J. Dis. Chest., **55**, 162.
40. Huckstep, R. L. and Bodkin, P. E. (1958): Lancet, **2**, 342.
41. Hardy, J. D. (1960): J. Amer. Med. Assoc., **173**, 1462.
42. Schwartz, W. B., Tassel, D. and Bartter, F. C. (1960): New Engl. J. Med., **262**, 743.
43. Niels, A. T. and Transbol, I. (1963): Amer. J. Med., **35**, 257.
44. Holling, H. E., Brodey, R. S. and Boland, H. C. (1961): Lancet, **2**, 1269.
45. *The Cape Argus,* 21 April 1965.