though sometimes occurring for only short periods during a day. Such patients may show localized tenderness in the region of the appendix but no other abnormal physical signs. Can they be said to be suffering from "chronic appendicitis"? These cases are certainly the most difficult to assess, but increasing experience soon tends to dispel any scepticism about the existence of this type of appendicular disease. We have all had our share of surprises in this field. Patients about whom we were extremely doubtful before operation have shown unexpected pathological changes in the appendix; others who have had an apparently normal appendix removed have been magically cured of their symptoms. In all such patients the history is usually vague and inconclusive. Diagnosis depends upon the single physical sign of persistent localized tenderness and upon our assessment of the type of patient with whom we are dealing; here again the general practitioner can be of enormous help to the consultant with his knowledge of the domestic and personal background of his patient. Clinical impressions of this type assume great importance when we consider that accessory aids to diagnosis are often of little value. Radiographic examination of the appendix is uncertain and its results are often equivocal.

From this discussion the position with regard to the various types of "chronic appendix" may be summarized as follows: (a) With a history suggesting *recurrent subacute appendicitis* or *recurrent appendicular colic* we are on safe ground in advising removal of the appendix. (b) A similar history followed by the development of persistent pain and tenderness in the right iliac fossa may reasonably be called *chronic appendicitis*, and here again appendectomy can be safely advised. (c) *Chronic appendicitis* without a previous history of recurrent "attacks" of pain is a more difficult problem. Children should always be given the benefit of any doubt, but in adults the decision to advise removal of the appendix will rest largely upon the general practitioner's knowledge of his patient's character and his interpretation of the nature of the symptoms.

3. Functional Pain

Last of all we come to those patients with no evidence of organic disease apart from the appendix and in whom we are not satisfied that the appendix itself is genuinely responsible for their symptoms. Few patients with pain in the right iliac fossa are true malingerers, and if we are correct in assuming that there is no organic cause for their pain we are dealing with examples of the *anxiety state*.

These patients have genuine symptoms and need help, but great patience and tact are required if that help is to be given. It is surprising how often a sympathetic attitude will reveal a psychological basis for the symptoms, and sometimes the mere unburdening of his troubles will help the patient enormously. Some people are quickly assured if they are satisfied that we have made a thorough and complete examination and can convince them that there is no evidence of serious disease. Others are more difficult to manage and do not readily accept the idea that their pain is nervous in origin in spite of a completely negative examination and a series of negative investigations. The psychiatrist cannot help if the patient is uncooperative, and if our common-sense approach to the mental problem does not produce conviction we are likely to have a dissatisfied patient. But at all costs we must avoid advising appendectomy in someone we know to be a true neurotic.

All too often such patients will continue to seek further opinions until they find someone who will remove the appendix, but we must not be responsible for such action if we consider it ill advised. It is better to lose a disgruntled patient than to have him return with the same pain after an operation to which we have agreed against our own judgment. It is also better to lose such a patient than to be responsible for that dreadful sequence of events which culminates in subsequent operations for adhesions or other mythical maladies and leads to the creation of a confirmed hypochondriac.

GENERALIZED HYPERTROPHIC OSTEOARTHROPATHY IN ASSOCIATION WITH BRONCHIAL CARCINOMA

A REVIEW, BASED ON 24 CASES

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During the past seven years we have encountered in the West of Scotland no fewer than 24 examples of generalized hypertrophic osteoarthropathy in association with bronchial carcinoma. As it would appear to be the largest reported collection of patients suffering from this fascinating syndrome, and because modern surgery may handsomely reward early clinical recognition, it seems to be an opportune time to review the known facts and some theories of pathogenesis.

While the literature on the subject of generalized osteoarthropathy continues to grow, there has been little increase in our knowledge of the cause and real nature of the pathological changes of this condition since the first known description by von Bamberger in 1889. Marie (1890) named the syndrome "hypertrophic pulmonary osteoarthropathy" and defined it as a "symmetrical osteitis of the four limbs chiefly localized to the phalanges and terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the roots of the limb and flat bones and accompanied by a dorsal kyphosis and some affection of the joints." This description requires little alteration to-day.

Although Hippocrates (1923), as early as the fifth century B.C., had described clubbing of the finger-nails, it was not until late in the nineteenth century that von Bamberger and Marie drew attention to the changes in the extremities associated with certain diseases. The confusion existing prior to Marie's description is illustrated by a case described by Saundby (1889) as one of acromegaly: a man aged 37 with thickening of the hands and joints died after five months, and necropsy showed "a sarcoma of the left lung with caseating pneumonia, a discovery which could only be coincidental." His illustrations put beyond doubt that he had unwittingly dealt with a case of osteoarthropathy.

Numerous reports have appeared dealing with the association of arthropathy with a variety of internal diseases. These diseases have most frequently affected the respiratory tract. Chronic lung abscess, putrid bronchiectasis, and empyema, all now fortunately rare, predominated. Brooks (1913) and Locke (1915) pointed out that at least a proportion of cases of osteoarthropathy had a malignant chest lesion. We have found it in a patient with metastatic lung tumours, and it has been reported in association with such intrathoracic lesions as arteriovenous aneurysm of the lung (Adams *et al.*, 1944), fibroma of the visceral pleura (Price-Thomas and Drew, 1953), and benign tumours of the lung and chest wall (Van Hazel, 1940).

It is interesting to note that osteoarthropathy has been described in a dog with a bronchial carcinoma (Wissing and Weisz, 1943) and in rats (Sutro and Pomerantz, 1939), a horse (Liénaux, 1909), and even a lion (Ball and Lombard, 1926).

It has been witnessed in many apparently unrelated diseases such as carcinoma of the nasopharynx, myeloid leukaemia, colitis, and steatorrhoea. Although a few cases of idiopathic osteoarthropathy have been recorded (Freund, 1938; Camp and Scanlan, 1948) one should hesitate in making such a diagnosis until a primary disease has been excluded. The fickleness of the syndrome is well illustrated by Locke's account of a patient who had osteoarthropathy for five years before a lung tumour became obvious. Such an experience was repeated in one of our series (Case 14); it was nine

months before there was radiological evidence of a lung tumour.

Craig (1937), Rottjer *et al.* (1946), Temple and Jaspin (1948), Pattison *et al.* (1951), and Ellman (1953) have all reported a small series of cases of bronchial carcinoma having joint symptoms as the presenting feature. The syndrome is seldom encountered by general physicians, and a possible reason is that the rapidly growing or oat-celled growth, common in the medical wards, does not produce osteoarthropathy. Conversely, in chest-unit patients the more chronic epidermoid variety predominates, and so it is difficult to estimate the frequency of the syndrome in all cases of lung cancer. Jack (1952) found three fully developed cases in 668 patients with bronchial carcinoma. Wierman *et al.* (1954) report an incidence of 5% in 481 resections for malignant lung

Summary of 24 Patients having Joint Symptoms Related to Lung Cancer and showing Clinical and Radiological Evidence of Hypertrophic Pulmonary Osteoarthropathy

Case No.	Age	Tumour Site	Histological Type of Tumour	Initial Symptoms and Signs	Duration of Joint Symptoms Before Correct Diagnosis Made	Treatment	Result (To November, 1954)
1	45	R.U.L.	Adenocarcinoma	Radiological shadow for 18 months	5 months	Pneumonectomy, 1947	Operation death
2	51	L.L.L.	Epidermoid	"Rheumatic fever"	7 "	Pneumonectomy, 1948	" "
3	47	R.U.L.	—	Stiffness and swelling of ankles and knees	5 "	Radiotherapy	Gold therapy produced a remission of joint symptoms. Died with metastases 4 months after start of treatment
4	64	R.L.L.	—	Stiffness, swelling, and pain in ankles and knees	5 "	"	No relief of joint symptoms. Died with metastases 3 months after start of treatment
5	47	R.L.L.	Epidermoid	Stiffness and pain both legs. Also haemoptysis	4 "	Pneumonectomy, 1949	Complete and immediate relief of joint symptoms. Died 3 months after operation with cerebral metastases
6	56	L.U.L.	Adenocarcinoma	Haemoptysis	3 "	Pneumonectomy, 1950	Complete relief of joint symptoms. Died 7 months after operation with cerebral metastases
7	53	R.L.L.	"	Pain and stiffness of knees	3 "	Lobectomy, 1949	Immediate relief of joint symptoms which, however, recurred with the appearance of osseous metastases. Died 8 months after operation
8	52	R.L.L.	Epidermoid	Pain and swelling of wrists, feet, and ankles	10 "	Pneumonectomy, 1949	Immediate and permanent relief of joint symptoms. Died 6 months after operation with local recurrence of tumour
9	59	R.L.L.	Adenocarcinoma	Haemoptysis	4 weeks	Pneumonectomy, May, 1951	Immediate relief of joint symptoms. Some residual stiffness of left shoulder and slight deformity of fingers. Has remained well since operation
10	59	R.L.L.	Epidermoid	Pains in legs and swelling of ankles and knees	5 months	Pneumonectomy, Sept., 1947	Has remained symptom-free since operation
11	38	L.U.L.	"	Stiffness of ankles and knees	6 "	Pneumonectomy, Jan., 1952	Immediate disappearance of joint symptoms. Died October, 1952, with local tumour recurrence
12	52	R.L.L.	"	Stiffness of arms and legs	2 years	Symptomatic	Died 2 months after first seen and diagnosed
13	41	R.U.L.	"	Stiffness, pain, and weakness of knees and ankles	5 months	Radiotherapy	Partial remission of joint symptoms and of chest pain. Died with cerebral metastases 12 months after diagnosis made
14	46	R.L.L.	"	Stiffness and swelling of knees	10 "	Pneumonectomy, April, 1952	Relief of stiffness and pain. "Weak joints" remained after operation. Ultimate complete rehabilitation. Died December, 1953, with cerebral metastases
15	54	L.U.L.	—	Left shoulder pain	3 weeks	Radiotherapy	Partial relief of joint symptoms with corticotrophin. Complete and permanent relief after radiotherapy. Died with local tumour extension 9 months after diagnosis made
16	50	R.U.L.	Epidermoid	Lassitude and weight loss	4 months	Symptomatic	Died 2 months after diagnosis made
17	48	R.L.L.	"	Haemoptysis	4 "	Lobectomy, Sept., 1952	Immediate relief of joint symptoms. Died with generalized metastases December, 1953. No recurrence of rheumatism
18	56	R.U.L.	"	Pain and stiffness left shoulder and cough	12 "	Thoracotomy, Oct., 1952	Partial spontaneous remission of joint symptoms before operation, and continued improvement after thoracotomy. Died April, 1953, with metastases
19	52	R.L.L.	"	Cough and chest pain	5 "	Thoracotomy, Feb., 1953	Spontaneous remission of joint symptoms preceded operation. No recurrence before death from metastases January, 1954
20	49	L.L.L.	"	Stiffness and pain in hips, knees, and wrists	6 weeks	Lobectomy, May, 1953	Immediate complete relief of joint symptoms. Has remained well to date
21	55	L.U.L.	"	Swelling and stiffness of ankles	6 months	Pneumonectomy, July, 1953	Relief of polyarthritis symptoms. Myocardial infarction with congestive failure during convalescence. Died with cerebral metastases March, 1954
22	57	L.L.L.	"	"Arthritis" left knee	16 "	Symptomatic	Admitted to hospital in terminal stages of illness with massive left pleural effusion. Died after 2 months' observation
23	62	R.U.L.	"	Generalized joint stiffness	3 "	Pneumonectomy, July, 1953	Immediate disappearance of joint symptoms. Died with metastases April, 1954
24	57	L.L.L.	"	Swelling of knees	3 "	Lobectomy, Nov., 1953	Had usual relief of "rheumatism" and has remained well to date

lesions, but these included patients with so-called "local osteoarthropathy" or simple clubbing. It is our impression that the frequency of the generalized form is in the region of 1-2%.

Clinical Manifestations of Osteoarthropathy

From the Table it will be seen that 16 patients had joint disability as the first evidence of disease. Case 12, for instance, had stiffness for a year before the first symptoms directly related to the lung tumour appeared. All 24 patients had experienced such "rheumatic" symptoms for an interval, varying from 3 weeks to 16 months, before the presence of a tumour was suspected. Stiffness and swelling of the large and small joints of the limbs were the usual complaints; pain may be severe or be present only with joint

may occur in certain types of chronic lung and congenital heart disease without evidence of periosteal reaction or joint disability. Clubbing therefore should not be considered synonymous with osteoarthropathy, nor even necessarily the earliest stage of it (Hansen, 1954).

There may be a low-grade pyrexia, and a raised erythrocyte sedimentation rate is invariable, but these, and especially the latter, are common findings with bronchial carcinoma. Swelling of the nipples occurred in two of our patients. Stephens (1928) reported an incidence of 7% with gynaecomastia in a series of 156 cases of bronchial carcinoma.

Response to Treatment

Remission of joint symptoms may occur spontaneously (Cases 18 and 19), and some relief may be obtained from nitrogen mustard (Case 8), gold therapy (Case 3), and corticotrophin (Cases 14 and 15). Some patients treated by deep x-ray therapy had partial or complete relief of "rheumatism," but the objective signs of osteoarthropathy were little altered.

The most dramatic, immediate, and complete relief of joint symptoms is produced by operative removal of the lung tumour. In all 13 patients who survived tumour resection, joint mobility was increased within hours of the operation, and the patients who had been bedridden with "arthritis" for weeks or months were walking normally within a few days. It is no exaggeration to state that these patients were dumbfounded at the relief, and more than once we found them the morning after operation studying the increased mobility of their fingers and arms in utter amazement. Just as rapidly,

they remarked that their hands and feet felt more cool, and objectively we could no longer find evidence of increased peripheral blood flow. Joint swelling subsided in a matter of days; in a few weeks, thickening of the skin of the face and around the joints had disappeared and clubbing subsided (Figs. 1 and 2). After a few months, radiological examination showed absorption of subperiosteal new bone (Fig. 3) and disappearance of osteoporosis in the wrist bones.

movement, or it may be absent. Four of the patients were completely crippled and confined to bed. Sensations of warmth or burning and increased moisture of the hands and feet were sometimes volunteered.

Skin around the affected joints may show thickening and brawny oedema. A similar change is sometimes found on the face, producing rather a characteristic coarse, furrowed appearance (Fig. 1), already observed by Fried (1943).

The hands may have a rheumatoid appearance or be spade-like as in acromegaly (Fig. 2). Hands and feet are warm and moist, and pulsation may be felt in the palms and fingers and heard with a stethoscope on the brachial or femoral artery. Capillary pulsation, however, is not a feature.

Finger-clubbing is almost invariably associated with osteoarthropathy, and occasionally is the most obvious feature clinically; on the other hand, it may be very mild in degree. Conversely, it is known that advanced clubbing

FIG. 1.—Clinical photographs of Case 14, illustrating (left) the furrowed and coarse features sometimes seen with osteoarthropathy, and (right) the same patient four months after right pneumonectomy.

FIG. 2.—Case 14. Patient's right hand (A) before operation, showing the spade-like deformity, with clubbing and thickening around the wrist- and finger-joints. Same hand (B) seven months after pneumonectomy.

FIG. 3.—Case 10. Right radius and ulna before operation (A): note the marked subperiosteal proliferation. Film (B), three months after pneumonectomy shows considerable absorption of this new bone.

One patient (Case 7), who had obtained the usual relief from lung resection, had a relapse of "arthritis" associated with the appearance of metastases: however, this was an exception, as other patients who died from local tumour recurrence or from metastases had no such relapse before death.

Death was invariably related to tumour spread and there was little evidence that these tumours behaved differently from the more usual case of slowly growing epidermoid carcinoma. Indeed, operative results have been disappointing, only 4 out of 15 patients treated by resection being alive.

Biochemical Findings

In common with previous observers, we have found essentially normal results in most estimations carried out for the study of metabolic bone disease. An exception was the serum phosphorus level, which was found elevated in four severe cases studied. Excretion of F.S.H. (follicle-stimulating hormone) was normal, but this test brought to light a finding which may be of practical importance: in two cases the patient's urine, extracted for the hormone, appeared to contain an unidentified substance which was lethal to laboratory mice.

Arteriovenous oxygen difference was found to be very low in two patients, and in one other the figure rose abruptly after operation. This finding and increased peripheral blood flow, along with absent capillary pulsation, suggest the presence of arteriovenous shunts by-passing the capillary bed.

Skeletal and Articular Changes

The bone changes of osteoarthropathy have been adequately described by past observers (Compere *et al.*, 1935; Gall *et al.*, 1951). There is a proliferative periostitis, characterized by lymphocytic and plasma-cell infiltration, subperiosteal new bone formation, and the production of a pseudo-cortex, 1 to 5 mm. thick, which ultimately fuses with and expands the cortex. It particularly affects the lower ends of the forearm and leg bones, metacarpals, and metatarsals. In extreme cases, clavicles, ribs, pelvic bones, scapulae, and malar bones may be involved. Radiologically (Fig. 3) the picture is quite characteristic, and is perhaps most like a yaws periostitis, showing an irregular but symmetrical osteoid sheathing of the long bones. Joints in involved extremities show extra-articular thickening, but may be the seat of mild to moderately severe chronic synovitis, associated with non-specific degenerative changes in the articular cartilages. In advanced cases, deformities and even subluxations may occur. Changes in the carpus and tarsus are of an osteoporotic character.

Lung Tumour Features

Most of our patients had bulky, circumscribed peripheral neoplasms. Of these studied histologically, 17 were of epidermoid type and four were adenocarcinoma. Central necrosis was a feature in all operation and necropsy specimens. The tumours were present in the right upper lobe (6), right lower lobe (10), left upper lobe (4), and left lower lobe (4). As this type of neoplasm rarely produces atelectasis or invasion of neighbouring structures in the earlier stages, clinical silence is the rule, and yet the patient may be a helpless cripple from his associated arthropathy.

Illustrative Case Histories

Case 7.—An electrical engineer aged 53 was admitted to hospital in January, 1949, complaining of pain in his left chest for a month, pain and stiffness of his knees and swelling of the finger ends for three months, and swelling of the ankles and feet for one month. X-ray examination showed a circumscribed dense homogeneous shadow in the posterior basal segment of the right lower lobe and the changes of osteoarthropathy in the long bones. There was marked clubbing of the fingers and toes and tender extra-articular thickening around both knee-joints. Bronchoscopy showed tumour tissue in the orifice of the right posterior basic

segment orifice (histologically adenocarcinoma). He had a right lower lobectomy on March 1, 1949, and the following day his knees and ankles were much less stiff. Convalescence was uneventful and the joint symptoms disappeared completely. Six months later, however, he developed pain in his left elbow, and x-ray examination showed a metastasis in the lower end of the humerus. From then until his death in November he had a marked exacerbation of the joint symptoms. Two weeks before death he was almost unable to move his arms and legs because of joint swelling, pain, and stiffness.

Case 8.—A married woman (the only female in the series), an accountant aged 52, developed pain and swelling of the feet and ankles in November, 1948. A month later her knees became swollen and stiff, and in January, 1949, she noticed that the ends of her fingers were swollen. Five months later she had to stop work because of pain and stiffness in her hands, wrists, and elbows. The only other symptoms at this time were listlessness and "catarrh." In August, 1949, she was admitted to hospital with gastroenteritis. Generalized osteoarthropathy roused interest, and an x-ray film of the chest showed a large circumscribed shadow in the right mid-zone. She was transferred to a thoracic unit in October. By this time she was in poor general condition. She looked old and wizened, with deep facial furrows, marked swelling of joints, and clubbing of fingers and toes. X-ray examination showed a massive shadow in the right lower chest and radiological signs of advanced osteoarthropathy. In November she was given a four-day course of nitrogen mustard (total 19 mg.), which produced some relief of joint stiffness. On December 6, as her general condition had improved, a right pneumonectomy was performed with dramatic and immediate relief of her joint pains. Histology of the tumour showed an epidermoid carcinoma. She died six months later with local recurrence of the tumour, but without recurrence of joint symptoms.

Case 10.—A blacksmith aged 59 (the longest survivor) began to have pains in his legs with swelling of the ankles and knees in March, 1947. The following month he could not get out of bed because of joint stiffness. When admitted to hospital in August he had lost 2½ st. (15.9 kg.) in weight. He was investigated as a case of infective rheumatism. The blood sedimentation rate was 65 mm. in the first hour (Westergren). Clubbing of his fingers was noted, and an x-ray film showed a round shadow in the apex of the right lower lobe. Bronchoscopy confirmed the presence of an epidermoid carcinoma protruding from the apical segment orifice. He had a right pneumonectomy in September, some six months after the onset of his joint symptoms. The day after operation he was surprised at the relief of pain and joint stiffness and the improvement was progressive. Three weeks after the operation he was walking well. Four months later, x-ray examination showed marked diminution in periosteal new bone formation round the radius and ulna (Fig. 3). His progress was uneventful, and he is alive and working more than seven years after the beginning of his symptoms.

Discussion

Although simple clubbing of the fingers is a common phenomenon, true osteoarthropathy is relatively rare, and in this seven-year period we have not witnessed a case related to disease other than lung cancer. As stated recently (*British Medical Journal*, 1954), bronchial carcinoma would seem now to predominate as the chief cause, although Price-Thomas (1953) has stated that no condition is associated with osteoarthropathy as constantly as fibroma of the visceral pleura. This, however, is a rare tumour. It seems possible that many cases of arthropathy previously reported as associated with empyema and lung abscess were suffering from carcinomatous lung abscess or empyema secondary to unrecognized lung cancer.

Mendlowitz (1942), reviewing the "welter of hypotheses" advanced to explain the phenomenon, found them unconvincing. These included the theories of toxæmia, anoxæmia,

capillary stasis, lymph stasis, endocrine disturbance, and autonomic nervous upset. He concluded, however, that increased blood supply must form the cornerstone of any theory of production of osteoarthropathy, and certainly we have found increased peripheral blood flow a constant feature and one which disappears within two or three hours after removal of the lung tumour.

Hypertrophy and hyperplasia from circulatory changes can be observed in arteriovenous fistulae in the limbs. The increased growth of the limb was thought by Sir Thomas Lewis to result from the more rapid flow of blood distal to the arteriovenous shunt. Cross and Wilson (1952) record a case of axillary arteriovenous aneurysm with unilateral clubbing in which increased blood flow to the hand was the only demonstrable circulatory abnormality. Increased peripheral circulation was regarded by Wilson (1952) as an essential feature in acquired clubbing. He demonstrated that blood flow through clubbed fingers was greater than normal, and showed that vasomotor nerves were probably not responsible for this. Lovell (1950) found an excess of fibrous tissue in the distal segments and increase in the calibre of the digital arteries in clubbed fingers. There were abundant characteristic local arteriovenous anastomoses in the distal finger segments, near the junction of the dermis and subcutaneous tissue. He thought that the excess of blood reaching the finger-tip was mainly through these anastomoses and that the by-pass of blood away from the capillary bed might be responsible for the proliferative changes. Mauer (1947), attempting to explain the aetiology of clubbing in both cyanotic and hypervascular states, elaborated this theme. He introduced the interesting concept of peripheral tissue anoxia produced by combination of accelerated peripheral blood flow and raised erythrocyte sedimentation rate; thus erythrocytes, moving rapidly in rouleaux formation through capillaries or arteriovenous shunts, do not have an opportunity for adequate gaseous exchange. It is worthy of note that in our patients both hyperaemia and raised E.S.R. approached normal limits immediately following tumour resection.

The exact mechanism by which increased blood flow produces hypertrophy is unexplained, but from the postulations of Leriche and Policarde (1928) and of Greig (1931) it seems just possible that hyperaemia alone may be the responsible factor in osteoarthropathy. It is acknowledged that new bone is normally restrained by the periosteum, and that a bone cannot exceed its normal limits unless this membrane be removed or raised. Possibly, in this disease, subperiosteal new bone may be deposited as a result of raising of the membrane by serous effusion, an invariable accompaniment of the oedema and cellular proliferation of periosteal hyperaemia. Similar vascular changes may explain the associated subcutaneous tissue and joint involvement. Increase of periarticular circulation modifies synovial fluid both in quantity and in quality and stimulates proliferation of all connective-tissue cells.

Before considering any theory on the mode of production of osteoarthropathy by bronchial carcinoma we must bear in mind the following facts. Osteoarthropathy is produced by only a small proportion of bronchial cancers, most of which are peripheral, grow slowly and concentrically, and show marked central necrosis. There is invariable and immediate relief when such a tumour is resected. Similar relief has been reported to follow ligation of the pulmonary artery on the side of the tumour (Wyburn-Mason 1948) and also denervation of the lung hilum when the tumour could not be removed (Brea, 1948). We have witnessed remission of symptoms occurring spontaneously, following certain drugs, and also after thoracotomy. It must also be remembered that osteoarthropathy can be produced by many other tumours both within and without the thorax. Three hypotheses might be considered.

1. *Tumour affects indirectly the endocrine balance.*—Such a theory is supported slenderly by the production of bone growth and soft-tissue changes in acromegaly and by Selye's

work showing that D.C.A. can produce polyarthritides in adrenalectomized animals (Selye *et al.*, 1944). Thomas (1933) described osteoarthropathy occurring after subtotal thyroidectomy. Bariéty and Coury (1950) obtained relief of arthralgia by giving synthetic oestrogen to a patient with inoperable lung cancer. Fried (1943) reported four cases with bronchial carcinoma and osteoarthropathy, all of which showed variable clinical and pathological evidence of endocrine upset. (These changes included an acromegalic appearance, tufting of terminal phalanges, testicular atrophy, hirsutism, macroglossia, and gynaecomastia.) We have already commented on the reversible coarse facial features, and would point out that gynaecomastia (present in two of our patients) must not be accepted as certain evidence of an endocrine aetiology; it has been described in severe starvation and in hepatic cirrhosis, and we have noted it occasionally with bronchial carcinoma in the absence of arthropathy. We have not found testicular atrophy, hirsutism, or macroglossia in our patients. We have not detected any pituitary cortical or thyroid adenomatous changes in the course of three necropsies. Our biochemical investigations lend little support to this endocrine theory, and the dramatic response to removal of the tumour suggests to us a much more direct connexion between the neoplasm and the osteoarthropathy.

2. *Tumour secretes a specific chemical substance, responsible for the change.*—The rapid disappearance of symptoms and signs of osteoarthropathy after tumour resection favours such a theory and also suggests that this substance, possibly of hormonal nature, is destroyed or excreted rapidly. It seems just possible that, excreted in the urine of patients, it might even account for the severe reaction in mice found during our F.S.H. studies. Its effect could be an indirect one through the medium of hyperaemia. On the other hand, the tumour has no special cytological features which would single it out for such a secretory role. A toxic product of tumour necrosis, however, might be absorbed into the blood stream and produce such an effect. While such a theory could explain the relief following pulmonary artery ligation it could not account for the relief after hilar denervation, nor for the occurrence of osteoarthropathy in conditions other than neoplasm.

3. *Theory of an autonomic pulmonary-systemic vascular reflex.*—Cudkowicz and Armstrong (1953a, 1953b) have found precapillary broncho-pulmonary anastomoses in the lungs of patients with variable degrees of finger-clubbing and osteoarthropathy. They were unable to demonstrate such anastomoses in normal lungs or in cases of bronchial carcinoma in which no clubbing was present. The anastomoses in cases of tumour, bronchiectasis, and empyema were seen only in the affected lobes, and there was occlusion of the pulmonary artery proximal to the anastomoses with a variable degree of recanalization. Cockett and Vass (1951) suggest that thrombosis of a pulmonary artery branch may be a stimulus to the development of these anastomoses. Gilroy *et al.* (1951) found arterial blood in the pulmonary arteries of collapsed lobes at operation, strongly suggesting the presence of bronchial arterial blood in the pulmonary circulation. Accompanying this diversion of bronchial artery blood, Cudkowicz and Armstrong demonstrated hyperplasia of the walls and narrowing of the lumina of the smaller peripheral bronchial artery branches, suggesting a state of spasm and reduced function. They suggest that impulses from the peripheral nerve fibres of the lung, rendered ischaemic by the deviation of bronchial arterial blood flow, reflexly influence the formation of the systemic arteriovenous anastomoses in the limbs, described by Lovell. Such an autonomic reflex theory could explain the occurrence of osteoarthropathy in a variety of thoracic lesions, its absence in most lung tumours, and the relief given by tumour removal, pulmonary artery ligation, hilum denervation, and vagus resection (Hansen, 1954).

All three theories have defects, but their further study will probably furnish a conclusive explanation of the syndrome. Investigations by inoculation of animals with

tumour and urine extracts, vascular studies of resected lungs, and autonomic block are all possible keys to the solution of this fascinating problem.

Summary

Bronchial carcinoma may now be regarded as the chief cause of generalized hypertrophic pulmonary osteoarthropathy. A review of 24 patients with this syndrome encountered during the past seven years is presented.

The pathogenesis of osteoarthropathy has been reviewed in the light of our clinical studies, past experimental work, and the dramatic and invariable "cure" effected by tumour removal.

Such patients are often treated for rheumatism or rheumatoid arthritis for many months, and may become bedridden cripples before the presence of a silent lung tumour is suspected.

Fifteen of the patients were submitted to lung resection. Only four are alive. Operative results in this type of tumour might be expected to improve when the significance of such joint symptoms becomes more generally appreciated.

We wish to thank Mr. Bruce Dick for his ever-helpful co-operation and stimulation; Dr. Angus Scott (Cases 3, 4, and 15) and Professor Sir John McNee (Case 16) for permission to record their respective patients; Mr. R. S. Barclay and Mr. Kenneth Fraser for surgical assistance and advice; and Dr. Ian Anderson for biochemical determinations. For the photographic reproduction we are indebted to Mr. H. C. Gray, of the clinical photographic department, Victoria Infirmary, Glasgow.

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CARCINOMA OF BRONCHUS IN ASSOCIATION WITH ACTIVE PULMONARY TUBERCULOSIS

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Both pulmonary tuberculosis and carcinoma of the bronchus are common diseases, and it is not a matter of surprise that the two conditions should at times be encountered together. It is generally accepted that there has been, in recent years, an absolute increase in the incidence of bronchial carcinoma, a disease more common in middle-aged and elderly males. With modern methods of treatment, the mortality from pulmonary tuberculosis has shown a dramatic fall, and this implies that more tuberculous patients are surviving into the cancer age. In addition, more cases of active pulmonary tuberculosis are being found in the older men. It is to be expected, therefore, that the two diseases will be encountered more and more in association. For this reason it is of interest to describe the following six cases with the dual pathology. They were all seen during the past three years, the diagnosis being made during life and confirmed at necropsy. They demonstrate the various problems which arise in the diagnosis of these conditions when associated, and their possible interrelationship.

Case 1

A plasterer aged 50 was found, in 1935, to be suffering from bilateral fibrocavernous tuberculosis, the left upper lobe being chiefly affected. He spent two years in a sanatorium, at the end of which time his sputum still contained tubercle bacilli, but his condition was improved. He remained well and at work for the next 10 years in a stable chronic condition. When seen in 1950 he was bothered by a wheezy bronchitis, but for two years there had been no change in the radiological appearances of his lungs, which showed many calcified foci on the right side, while on the left there was some fibrotic disease of the upper lobe.

In October, 1951, he began to deteriorate. There was some staining of the phlegm, he became easily fatigued, but there was little loss of weight. He was forced to give up his work. Radiologically there was a coalescence of the opacities present in the left upper lobe. In February, 1952, streptomycin and P.A.S. were administered to him at home, with little benefit, and in May it was necessary to admit him to hospital. Tomograms of the left upper lung showed a number of large cavities, those lying posteriorly having a fairly regular outline, but there was one anteriorly which had a very irregular wall. This appearance suggested the possibility of a carcinoma having supervened on his chronic pulmonary tuberculosis. He was too ill for bronchoscopy. Despite the administration of further streptomycin, together with isoniazid, his condition deteriorated. In October the sputum still contained tubercle bacilli, but thereafter all sputa were reported as negative for tubercle bacilli on direct smear. Radiologically there was the gradual development of a large dense opacity in the left upper lung, and the left hemidiaphragm became paralysed. No radical therapy was possible, and in March, 1953, he died.

Necropsy revealed the presence of chronic fibrosis and cavity formation of a tuberculous nature in the apices of both lungs, but in the left lung there was also a round necrotic mass (7.5 cm. in diameter), macroscopically a carcinoma, lying mainly in the upper lobe, against the hilum and the aorta.

Histology showed the carcinoma to be of the epidermoid type, arranged in solid masses, with a little differentiation