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Hypertrophic osteoarthropathy : clubbing the digits

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SENIOR THESIS

Hypertrophic Osteoarthropathy

A Review of the Literature
and
Eight Cases of Clubbing
of the Digits

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A Review of the Literature

INTRODUCTION Since Hippocrates reported his observation on the occurrence of fusiform swelling of the terminal phalanges in persons with consumption this phenomenon has been noted repeatedly by physicians, who, though ignorant of the pathogenesis, nevertheless attached great significance to its appearance in wasting patients.[1] The French physician Pigeaux[2] wrote in 1832: "The secret and almost mysterious relationship between phthisis and the state of the nails evidently shows that older physicians were inclined to attach importance to small details which even in the 19th century represent elements of good diagnosis".

Interested in small details, physicians of the past overlooked, however, another detail, namely, that fusiform thickening of the phalanges sometimes accompanies a diffuse involvement of the skeleton. When similar widespread lesions were observed, they were not associated with the clubbed fingers and were not looked on as a sequellae of a visceral disease, such as a disease of the lungs or heart, but were considered as a malady Sui Generis. Indeed, to the latter part of the 19th century chronic pulmonary osteoarthropathy was confused with arthritis deformans, acromegaly, Paget's disease of the bones and leonthiasis ossea and even with osteomalacia, which was not rare in those years.[1]

Bamberger[3], in a brief presentation before the Wiener Medizinizinischer Gesellschaft in 1889, was the first to record the

observation that his patients with clubbed fingers also displayed thickening of the hands, wrists and legs. Moreover, he found the condition not only in tuberculosis, but in bronchiectasis, empyema and congenital heart diseases. At about the same time that Bamberger published his article, Marie[4] presented an article which was chiefly to clear away misconceptions. "I wish at first", wrote the French clinician, "to clear the field of acromegaly of facts not germane to it". He first reviewed a case of a condition reported by him previously as acromegaly and found it to be a separate entity. By analyzing this case and those with identical symptoms available in the literature he stressed that in all of them the skeletal deformity and the clinical features were not characteristic of acromegaly; also that they were invariably preceded and accompanied by a long-standing disease of the lungs. He then expressed the opinion that the peculiar overgrowth of the bones in these cases, which he labeled osteo-arthropathie hypertrophiante pneumique, resulted from a primary pulmonary disease. Bamberger, in another and more detailed paper, published in 1891, corroborated Marie's findings.

Many different names have been proposed for what we now know as clubbing and hypertrophic osteoarthropathy. The phenomenon of clubbing has been called Hippocratic fingers, drumstick fingers, parrot-beak nails, watch glass nails, and serpent's head fingers. Hypertrophic osteoarthropathy has been called pulmonary hypertrophic osteoarthropathy (originally by Marie), secondary hypertrophic osteoarthropathy, hyperplastic osteoarthropathy,

toxigenic ossifying osteoperiostitis, Marie-Bamberger's syndrome, and numerous other names. The terms now generally accepted are hypertrophic osteoarthropathy for the changes in the larger bones and joints and clubbing for the distal extremity changes in toes and fingers.

The syndrome of osteoarthropathy is important not only because of its curious occurrence in association with many widely dissimilar pathological processes but also, probably from a more practicle standpoint today because of its relationship to carcinoma of the lung. Osteoarthropathy in primary pulmonary carcinoma has been seen in a severe, disabling form months and even years before attention has been attracted to the chest by respiratory symptoms.[5]

Thus, the purpose of this paper is to attempt to review the salient points regarding the etiology and pathogenesis, clinical features, and possible diagnostic importance of hypertrophic osteoarthropathy and clubbing with particular emphasis on their relationship to malignancies of the lungs.

CLASSIFICATION Because of inadequate knowledge regarding the origin and development of chronic hypertrophic osteoarthropathy many synonyms have arisen which presumably represent stages of one clinical entity but which in all likelihood represent several different syndromes. It is to be hoped that further knowledge will separate these entities and regroup them in proper pathologic or etiologic relationships.[6] Thus, E. A. Locke and A. Grolman list a few of the synonyms in vogue: (1) clubbed finger, (2) Hippocratic fingers, (3) essential dactylmegaly, (4)hypertrophic

pulmonary osteoarthropathy, (5) pachyperiostosis, etc., etc.. They define the condition as being characterized by painless, general, symetrical clubbing of the fingers and toes, often associated with hypertrophy of the long bones of the forearms and legs. Often it is secondary to some chronic disease, particularly of the lungs. Mendelowitz[7] classifies the disease from the etiological standpoint into (1) the hereditary form (a rare, primary disease passed on as a Mendelian dominant type), (2) the idiopathic forms in which there is no evidence of primary disease and no hereditary factor (this may be the same as that described by Touraine and Galle), (3) the acquired form- (a) associated pulmonary conditions such as tuberculosis, empyema, bronchiectasis, abscess, etc., (b) secondary to cardiac conditions such as congenital heart disease with cyanosis and subacute bacterial endocarditis, (c) following hypertrophic biliary cirrhosis, (d) following such gastrointestinal conditions as ulcerative colitis, dysentery, etc., (e) in association with miscellaneous diseases such as Raynaud's disease, cystopyelitis, purpura and polycythemia. From the symptomatic standpoint Sternberg[8] classifies the disease into three types: (a) clubbing of the fingers and toes without changes in the long bones (this is the most common type, symptoms are absent), (b) Von Bamberger's type- clubbing of the fingers and toes associated with painful thickening of the long bones especially the forearms and lower legs, (c) Marie's type- deformities are markedly conspicuous, severe and painful, and overshadow the primary disease found.

PATHOGENESIS While the etiologic relationship between the

pituitary gland and acromegaly is no longer contested, the causative factor of chronic pulmonary osteoarthropathy remains problematic.

The pathogenesis of diffuse osteoarthropathy occurring in chronic pulmonary diseases is as obscure today as it was when Marie described it. The conception of Pigeaux, postulated in 1832 for clubbed fingers, is thought to hold equally true for the disease as seen in the cases that were reviewed by Fried.[1] Pigeaux stated: "Three years of investigation have shown that the formation of curved nails is influenced by embarrassment in respiration and circulation; generally it occurs in all conditions affecting 'hematosis'". Marie in his original paper attributed the symptom complex to the selective absorption of toxins from the affected lung. Crump[9], from Erdheim's lab, stated: "There is an abnormal substance circulating in the blood which affects not only the periost, the bones, the joints, and the soft parts of the terminal phalanges but in the limbs throughout their entire length".

Observations indicate that not all bones are affected with equal intensity. The tibia and humerus are more intensely involved than other bones, and in the same bone the lesion is more severely involved in the diaphysis than in the epiphysis. As in all diseases of the skeletal system, the process involves both the bone and the periosteum. In the former, new bone formation (hyperostosis) is seen here and there. The picture, however, is dominated by osteoporosis; there is thinning out of the corticalis and the compacta. In the periost it manifests itself as a periostitis (osteophytosis).

The periost is normally composed of dense fibrous tissue. Whenever formation of new bone is called for and whenever there is destruction of bone a new layer, the cambium, is formed on the inner surface of the pre-existing periost. The cambium differs from the old periosteal layer in its poorer content of reticulum fibers, of cellular elements and of blood vessels. The cambium, and not the original periost, serves as matrix for newly formed bone. The intimate mechanism of the transformation of the cambium into bone is not understood. It may be ushered in by local or general conditions, by action of microbes (syphilis, osteomyelitis) or by a general disturbance as in the cases reported by Fried. It may by localized or it may be diffuse.

By studying different parts of the bone one finds different stages of the process, which has enabled investigators to reconstruct the life history of the disease. Thus it was established that the new periost is formed layer by layer, the new layer being superimposed on the one already existing, which gives to the newly formed structure a lamellary appearance visualized with the roentgen ray. Usually the new periost envelops the bone as the bark envelops a tree, its surface having a porous or wart-like appearance. It is significant that osteoporosis is also present in bones and in areas of bones where no new perosteum was formed. It is, then, even possible that the disease originates primarily not in the periosteum, as is universally believed, but in the bones. However that may be, the process is that of a hyperplastic porotic osteoperiostitis. As a result, the bones are considerably thickened and disfigured; they are not enlongated.

Not only the bones but the soft tissues as well are involved. There occurs a considerable thickening of the skin and subcutaneous tissue of the hands and feet, which produces the characteristic appearance of the extremities in chronic pulmonary osteoarthropathy. There is, then, a megalia cutis et ossium. The skin is soft and doughy but shows no pitting edema.

Hitherto pathologic changes of the nature described were said to be present uniquely in osteoarthropathies, occurring in lung tumors (primary or metastic) and in certain chronic purulent conditions of the lungs.

The French clinicians, Touraine and Galle[10] isolated a new entity under the name of "Pachydermie Plicaturee avec Pachyperiostose des Extremities". Patients affected with this malady show characteristic clubbing of the fingers and toes, squaring of the extremities, thickening of the skin and deformities of the long bones with lamellary deposits of the periost. Differing in some details from pulmonary osteoarthropathy, the condition is, on the whole, an exact counterpart of that in the cases presented by Fried. The pathologic and roentgen similarities of the skeletal and cutaneous systems in the two diseases are identical to the finest details. It is particularly significant that the malady does not develop on the basis of a cardio-respiratory or other visceral disease. The consensus is that the disease in these patients is of endocrine origin.

Prior to the isolation of this symptom complex by Touraine and his co-workers cases of this condition were reported under the designation of pseudoacromegaly or acromegalism, because of their close resemblance to acromegaly, the endocrine origin of

which today is firmly established.

It is well to stress that in acromegaly, as in pulmonary osteoarthropathy, the bones are enlarged (elongated), their increase in size being due to the increase both of the periosteal and the subcutaneous tissues. Microscopically, too, the structural changes in the two diseases are closely related. The tufting of the terminal phalanges of the fingers and toes, regarded by Cushing and others as an osteologic sign pathognomonic of acromegaly, is likewise present in the disease described by Touraine as well as in pulmonary osteoarthropathy. Tufting of the fingers and toes was pronounced in all four of Fried's patients. Generally the process in the three diseases affects the same system, the mesoderm. The pathologic changes may vary in degree, and their advance may differ in tempo, but qualitatively they are essentially of the same nature.[1]

Fried in his study of four cases favored the conception that diffuse osteoarthropathy found in neoplastic diseases of the lungs is in all probability caused not by toxins or by circulatory disturbances, as postulated more than a century ago, but by an endocrine imbalance akin to acromegaly and to pachydermia with pachyperiostosis.

That the lungs are endowed with function in addition to respiration has been stressed on many occasions. Various writers have attributed to the lungs a role in metabolism of lipids. This was suggested by the fact that absorbed albumins and carbohydrates pass directly into the liver while fatty substances

are transported by way of the lymphatics and the thoracic duct to the right side of the heart and to the lungs. Fort[11], in 1867, suggested that the lungs are characteristically secretory organs, and he used the term La Glande Pulmonaire- the pulmonary gland. In recent years Roger[12] and his associates, Aschoff[13] and others have ascribed to this conception.

There are many theories, none of which satisfactorily explains the entire picture. Von Bamberger placed material from a human lung abscess into the rectum of a rabbit; Compere, Adams and Compere[14] injected paraffin into the lungs of a dog and produced an abscess; Phemister[15] used various organisms intravenously while Harter and Churchill[16] tied off the bronchi in cats and monkeys. None of these experiments were successful in producing hypertrophic osteoarthropathy. Mendolowitz and Leslie[17] anastomosed the left pulmonary artery to the left auricular appendage in four dogs. One developed hypertrophic osteoarthropathy while three did not. In the animal developing hypertrophic osteoarthropathy, they were able to demonstrate an increased systemic blood flow. They thought that the chronic increase in blood flow with the increased periosteal nutrition was responsible for the proliferation of the subperiosteal new bone.

Other theories varied from toxic absorption of infection within the chest to alterations of acid-base equilibrium through decrease in aeration as a result of compression of pulmonary vessels, constriction of bronchi, lung compression or collapse.

Freund[18] reported a case of periosteal new bone formation without demonstrable pulmonary disease. He thought it was toxic in origin and a proteinogenic substance which was not destroyed in the liver.

Campbell, Sacasa and Camp[18] postulated that the transference of oxygen from the blood is dependent upon the oxygen tension in the blood being less effective where the circulation is slow, as it is in the hands and feet. This decrease in oxygen tension was brought about by faulty aeration of the blood which passed through the lungs. This toxemia leads to edema where the circulation is slow, namely to the extremities.

In nearly all cases there is no clinical evidence of obstruction to the venous return of the blood, but rather, according to Campbell, there is a "varying amount of lung tissue which has ceased to fulfill its proper function". This seems highly improbable in view of the fact that a circular or peripheral carcinoma of the lung, only 4 or 5 centimeters in diameter, is capable of producing marked bone and soft tissue changes, the symptoms of which can be promptly relieved by a pneumonectomy. It is obvious that there has been a marked reduction in the amount of lung tissue remaining following the operation when compared with the area involved by the tumor itself. It is, however, difficult to think that anything except immediate improvement of a circulatory condition could be responsible for such a rapid improvement in clinical symptoms. Temple and Jaspin[19] reported prompt and complete disappearance of the symptoms following pneumonectomy in one of

their cases, and disappearance of the symptoms following radiation therapy in two other patients. Van Hazel[20] reported prompt relief of symptoms in one of his patients who had been bed-ridden for six months, following the removal of a benign intra-thoracic neurofibroma. He also cited 12 cases from the literature where rapid improvement followed excision of a thoracic tumor, lobectomy or pneumonectomy. Several authors have expressed the opinion that at least two factors are necessary to produce the secondary osteoarthropathy, namely, a toxemia from long-standing disease and circulatory disturbances resulting from either cardiac or pulmonary involvement. Harter[21] believed that the condition was due to lack of oxygen, and called attention to somewhat similar changes found in some people living at high altitudes where oxygen is rare. This observation seems significant.[19]

Locke did not believe that uncomplicated heart disease was capable of producing periosteal new bone formation. He was unable to find any cases in the 144 that he described, his own and those reported from the literature. He stated that "in view of the high incidence of heart disease and the care with which it is studied throughout the world, it seems significant that no cases of uncomplicated heart disease with clubbed fingers have had periosteal new bone formation roentengographically demonstrated". He believes that "if the combination is not truly non-existent it must be at least rare". Holt and Hodges[22] state that pulmonary osteoarthropathy occurs more frequently in non-tuberculous patients and that they were unable to find a single instance of

its occurrence in uncomplicated pulmonary tuberculosis in the case records of the Michigan University Hospital.

More recently Mauer[23] again raised the hypothesis that local tissue anoxia is the predisposing factor leading to clubbing. His thesis is based on the fact that in patients who have a disease associated with clubbing, the erythrocytes are altered physically as evidenced by the increased sedimentation rate. The delivery and uptake of oxygen by the tissues are thus hindered by the altered physical state of the red blood cells and local anoxia results. It is known, however, that tissue anoxia alone does not cause clubbing as evidenced by the knowledge that clubbing does not occur with the slow rate of flow and cold finger tips of Raynaud's disease. Mauer postulated that the increased blood flow present in clubbing is secondary to the anoxia and that the rapid flow, the associated tissue warmth, and the rouleaux formation are all factors in the pathogenesis of clubbing. The exact mechanism by which circulatory changes produce the definite hypertrophy and hyperplasia seen pathologically is still unexplained. Thus, in spite of extensive study and voluminous literature, the pathogenesis of clubbing and hypertrophic osteoarthropathy remains conjectural.[24]

In the case described by Deutschberger, Maglione and Gill[25] the tumor was discovered 22 years before the operation, whereas the swelling of the extremities and the pains in the knees, ankles, and wrists developed only within the last 4 years at which time the intrathroacic tumor had reached considerable size. Therefore,

these authors conclude that with the presence of a benign intrathoracic tumor, the pathogenesis of hypertrophic osteoarthropathy may best be explained by an impairment of the pulmonary vessels due to mechanical pressure of the tumor which leads to a decreased oxygen tension and consequent poor oxygenation of the blood. These changes, however, take place in an advanced stage of the benign growth in which the symptoms and signs of the intrathoracic tumor have become apparent long before the development of the bone changes.

Charr and Swenson[26] have demonstrated by infrared photographs of living persons and post-mortum arteriograms that the local vascular bed is increased and widened in cases of clubbing. This means that there is an increased peripheral flow of blood. The increased peripheral blood flow plus the reluctance of the erythrocytes to release their oxygen leads to arteriolar anoxia, low tissue oxygen tension and clubbing.[27]

Ray and Fisher[28] reported on 14 cases of osteoarthropathy associated with malignant disease of the lung. In 13 cases the tumor was located in the periphery of the lung. The size of the tumor and the types of malignant cells apparently played no role in the development of osteoarthropathy. It was also apparent that pulmonary infection had no part in the pathogenesis of osteoarthropathy associated with pulmonary malignant disease.

Bloom[29] presented a case in which there was metastasis to the pituitary gland. It is suggested that the metastatic lesions acted as a stimulant to excessive secretion of pituitary hormone,

giving rise to the osseous syndrome in much the same manner as acromegaly. In support of this concept, attention may be called to hypertrophy of the breasts associated with this disease as reported by Bamberger, Fried and present in the case of Bloom's. In addition, Fried's case also presented multiple cysts of the adrenal cortex. Rynearson and Sacasa[30] report the condition developing in a patient operated on for hyperthyroidism. This patient developed postoperative hypothyroidism with progressive exophthalmos. There were no lung lesions. Thomas[31] described a similar case without lung lesions. Both of these cases are in many ways similar to the syndrome described by Touraine and Galle and implicate the pituitary gland.

PATHOLOGY On the basis of various reports in the literature, the pathologic changes appear to consist cheifly of hypertrophy and hyperplasia. There is increased porliferation of all the tissues of the finger tip, especially in the fibrous elastic portion of the nail bed and in the fatty connective tissue of the ball of the finger. Corresponding with the increase in the underlying substance, there is an increase in the cross-sectional area of the nail. Newly formed capillaries have been observed, as well as dilatation and increased thickness in the walls of the small blood vessels in the end of the finger. The terminal phalanx may show increased thickness of its periosteum and of the ungual process itself or, in advanced cases, complete resorption of the bone.

In hypertrophic osteoarthropathy there is calcification of

the periosteum, and islands of new-formed periosteal bone may be found along the shaft of the long bones, thickest in the region of the peripheral epiphysis and at the points of musculo-tendinous insertions. There is thinning of the cortex of the original bone and osteoporosis of the cancellous portion. Bone resorption may extend to the new periosteal bone, leaving a thin trabeculated space between the cortex and the periosteum. In patients with exacerbations and remissions, one sees multiple laminations suggestive of tree-trunk layers. Pathologic fractures may occur if thinning and osteoporosis exceed the capacities of the reparative process. With the joint involvement, the joint capsule and synovial membrane occasionally are thickened and there may be fluid collection with the joint capsule. Proliferation of the subsynovial granulation tissue associated with lymphocytosis and fibrinoid degeneration of the synovial membrane has been reported, resulting in pannus formation. Pressure from the pannus can produce degeration of the cartilage with erosion; if this occurs, the process may terminate in ankylosis.[24]

According to Temple and Jaspin[19], grossly, the process is essentially one of chronic proliferative subperiosteal osteitis surrounding the shaft of the bone, viz., tibia, fibula, radius, ulna, less frequently the humerus and femur or proximal portion of the scapulae or vertebrae may be involved. The new bone formation is from 1-7 millimeters thick and has a thin cortex surrounding the new cancellous bone which fills in the space between this new thin cortex just beneath the periosteum and the old

cortex, which appears intact. This new bone formation is extremely vascular and there are recorded attempts at biopsy which have resulted in excessive hemorrhage and the necessity of packing before bleeding is controlled. The clubbing of the fingers is said to be due, by most authorities, to soft tissue changes and there is no bone involvement. This consists of connective tissue thickening. Weens and Brown[32], however, reported that absorption of the terminal phalanges may occur, and that these changes are preceded by hypertrophic changes.

In 1915 Locke[33] drew the following conclusions after reviewing the cases of secondary hypertrophic osteoarthropathy to that date: the evidence is overwhelming that hypertrophic osteoarthropathy is always a secondary disease. Among the primary diseases, pulmonary tuberculosis is probably the most important though rarely inducing the extreme degree of bone and joint changes seen with bronchiectasis. There is a very definite correspondence between the characteristic clinical course of the disease and the process in the bones. During the periods of exacerbation in the primary disease, the pain, tenderness and swelling in the soft parts are not only increased, but the precess in the bones is also more active. On the other hand, during the quiescent periods associated with cure or relief of the condition responsible for the bone and joint changes, the process in the bones is stationary and in rare instances actual resorption takes place. The new subperiosteal bone, which is at first sharply marked off from

the old shaft, later becomes (usually after a period of some years) a more compact, dense layer, closely fused with the underlying old bone. In the late stages of the most progressive type of cases there is evidence of wide-spread halisteresis in the affected long bones. Occasionally the process in the bones and joints once established may progress even after actual cure of the primary disease. The ungual phalanges as a rule show proliferative changes. They consist mainly in an irregular burr-like expansion of the distal half. More rarely small osteophytes are found at the proximal ends near the line of the joint cartilage. The epiphyses of the affected long bones are to some extent always involved, but the new osseous tissue is much more irregular in outline and the ossification is less complete. The proliferation in the long bones in advanced cases is more general than has been recognized, often affecting nearly the entire skeleton. Changes in the joints are a constant and important feature of the disease. While the early changes are confined largely to the periarticular tissues, in the later stages, erosion of the cartilage, lipping about the joint, and even a moderate degree of ankylosis are common lesions. A considerable percentage of so-called Hippocratic fingers show by means of skiagrams early proliferative changes in the periosteum of some of the long bones of the forearm and lower legs of exactly the same type as seen in hypertrophic osteoarthropathy.

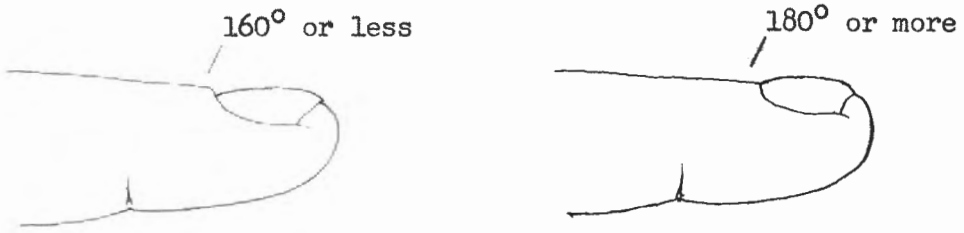
Recently Gall Bennett and Bauer[34] presented a very complete pathologic study of osteoarthropathy. Their findings showed the

distal third of the long bones to be involved initially, with the progression toward the proximal portions of these bones. Later they found involvement of the shafts of the metacarpals and metatarsals. It was also their experience that the periosteal changes were greater on the dorsal and medial surfaces.

CLINICAL FEATURES The symptoms of clubbing are most entirely objective, particularly in cases which are developing slowly; usually the patient is not aware of the deformity until it is brought to his attention.

Early clubbing is important to detect because of its diagnostic implications. On the other hand, clubbing in its early stages may at times be confused with other abnormalities of the fingers. Early clubbing should be differentiated from: (a) simple "curving" of the nail, which is seen normally- especially in the negro; (b) chronic paronychia, where the soft tissues at the base of the nail are swollen and no change occurs in the nail bed itself; (c) Heberden's nodes, which lie more proximally and rarely cause diagnostic difficulty; (d) chronic infectious arthritis, in which the swelling is periarticular and no change is apparent in the nail bed; and (e) felons where there is associated pain and absence of changes in the other fingers. Early in the process of clubbing, thickening of the fibro-elastic tissue of the nail bed produces a definite firm transverse ridge at the root of the nail, best observed on the dorsal aspect of the finger. Lovibond[35] noted this "profile sign". When one views the finger from the side, one sees an obtuse angle of about 160 degrees, normally,

between the base of the nail and the adjacent dorsal surface of the terminal phalanx. This angle is referred to as the "base angle" and is clearly demonstrated in the normal thumb. In early clubbing the base angle is obliterated and it becomes 180 degrees or greater. This "profile sign" is one of the best means of detecting the beginning stage of true clubbing.



Clubbing usually occurs first in the thumb and index finger, spreading to the other digits later. In the advanced stage there is an increase in all tissues of the finger tips, the soft tissues as well as the nails, so that the ends of the fingers assume a bulbous appearance the overlying skin as well as the volar pads are smooth, shiny and bright pink in color. The vascular bed gives a lilac or cyanotic hue to the nail. Witherspoon[36] pointed out that the return of color following slight pressure on the finger nail is characteristically slower than normal. The base of the nail may be elevated so that its outline is seen beneath the skin's surface. The nail can be rocked back and forth as if it were floating on a soft edematous pad. Patients may complain

of excessive sweating, a feeling of warmth, or a burning sensation in the finger tips; pain is rare but may occur in cases of very acute clubbing. There is an accelerated rate of growth of the nails. Hang-nails form readily, due to the rapid growth of the cuticle, resulting frequently in acute and chronic paronychia. In long standing cases, particularly in congenital heart disease, dorsi-flexion with hyperextensibility of the distal phalangeal joints may be present. Hypertrophic osteoarthropathy should always be sought for in the presence of clubbing. Locke stated, "Every case of hypertrophic osteoarthropathy so far recorded has shown well developed clubbing of the fingers and toes, and it is regarded as an absolute sign of the disease.[24]

The most common symptoms of hypertrophic osteoarthropathy in carconoma of the chest are aching pains and tenderness in joints and along the shafts of the long bones, transient increase in joint fluid usually not associated with the local inflammatory sign, muscular weakness, edema and hypertrophy of the subcutaneous tissues of the extremities, burning sensations and increased sweating of the hands and feet, gynecomastia, and other evidence of endocrine imbalance. The one important feature of this condition in its relation to pulmonary neoplasm is that it usually precedes the pulmonary symptoms by a period of time sufficient to allow successful surgical removal of the malignant lesion. This is in rather marked contrast with the chronic suppurative conditions of the chest in which the diagnosis is made long before the appearance of hypertrophic osteoarthropathy.[26]

ROENTGEN FINDINGS The roentgenologic changes are variable and depend upon the intensity and the duration of the pathologic process. In early clubbing there is usually no evidence of radiologic alteration. Later there is often (but not always) an increased flare of the ungual process, also described as a burr-like proliferation of the tuft of the terminal phalanx. In long-standing cases of clubbing atrophic changes occur ranging from simple osteoporosis to complete resorption. Erosion of the terminal tufts is rare; not infrequently, however, there is atrophy and spindling of the terminal, and sometimes of the other phalanges and of the metacarpals and metatarsals. The development of new-formed periosteal bone in the terminal phalanges has been reported only rarely. It should be pointed out that the roentgen diagnosis of hypertrophic osteoarthropathy is doubtful in the absence of definite periosteal proliferation.[24]

Of the numerous cases of clinical description of clubbing of the fingers, very few are recorded of actual flaring or mushroom appearance of the terminal tuft. After careful review of the literature, Temple and Jaspin felt that there are no bone changes in the terminal phalanges in this condition, and that the findings of lateral projection of the tuft can be seen in normal patients. These authors were unable to demonstrate the findings reported by Weens and Brown.

LABORATORY TESTS The most common abnormal laboratory finding is an elevated sedimentation rate. In addition, various other altered laboratory tests may occur in association with the

underlying disease processes. Since the concentration in the blood of phosphorus and of alkaline phosphatase may be elevated during destruction and repair of bone, these determinations may also be changed in hypertrophic osteoarthropathy. This bears further study.[24]

MEDICAL IMPORTANCE Of the 144 cases of hypertrophic osteoarthropathy reported by Locke, 113 (78 per cent) were associated with diseases of the respiratory tract. Review of more recent published reports indicates that between 75 and 80 per cent of cases with clubbing and hypertrophic osteoarthropathy are associated with diseases of the pulmonary system; 10 to 15 per cent occur with diseases of the cardiovascular system; 5 to 10 per cent are associated with the gastro-intestinal tract, including the liver; and another 5 to 10 per cent fall into the miscellaneous group. Of the individual pulmonary diseases reported by Locke, tuberculosis (20 per cent), bronchiectasis (19 per cent), malignancy (7 per cent), and empyema (5 per cent) occurred most frequently. Poppe[37] reviewed 129 cases in which lobectomy was done at the Barnes Hospital for bronchiectasis or chronic lung abscess. Of these 103 cases or 79 per cent had clubbing varying degrees. Of 276 tuberculous patients at the Koch Hospital surveyed by Poppe, 71 or 25 per cent revealed evidence of clubbing. In the cardiovascular group of diseases, clubbed fingers were present in cyanotic heart disease in 132 or 13 per cent of Abbott's[38] 1000 cases. Friedberg[39] noted clubbing in about 66 per cent of fatal cases of subacute bacterial endocarditis, whereas

Blumer[40] reported the incidence of clubbed fingers in subacute bacterial endocarditis to be 18 out of 48 cases or 36 per cent.

The various diseases that should be suspected in the presence of clubbing or hypertrophic osteoarthropathy are:

(1) Pulmonary group: bronchiectasis; primary and secondary tumors of the lung, bronchus, mediastinum, thymus and chest wall; chronic empyema; lung agscess; fibroid pulmonary tuberculosis with excavation; chronic pneumonitis; emphysema; pneumonconiosis; atelectasis; cystic disease of the lung; chest deformities; syphilis of the lung; actinomycosis; Hodgkin's disease of the lung or mediastinum; pulmonary hemangioma; and aortic aneurysm with compression of the lung.

(2) Cardiac group: cyanotic congenital heart disease with a venous-arterial shunt (right to left heart); subacute bacterial endocarditis; chronic congestive heart failure; and cardiac tumors.

(3) Hepatic group: cholangiolytic or Hanot's type of cirrhosis; obstructive biliary cirrhosis secondary to bile duct obstruction; cirrhosis associated with chronic malaria; and, rarely, in portal cirrhosis.

(4) Gastro-intestinal group: chronic ulcerative colitis; regional enteritis; intestinal tuberculosis; chronic bacillary and amebic dysentery; sprue; ascaris infestation; multiple polyposis of the colon; abdominal Hodgkin's disease; pyloric obstruction and gastrectasia associated with carcinoma of the pylorus or duodenal ulcer; and, rarely, in carcinoma of the colon.

(5) Mixed group: idiopathic; hereditary; post-thyroidectomy; nasopharyngeal tumors; generalized lymphosarcomotosis; chronic mountain sickness (Monge's disease); chronic osteomyelitis with amyloidosis; and pseudo-hypertrophic muscular dystrophy.

(6) Miscellaneous group: unilateral clubbing may be present in aneurysm of the subclavian artery, innominate artery or arch of the aorta; lymphangitis; brachial arterio-venou aneurysm; and superior sulcus tumor (Pancoast tumor).

REVIEW OF CASES Thirty-four cases of pulmonary malignancy brought to autopsy at the University of Nebraska Hospital were reviewed in an attempt to correlelate the relationship between clubbing of the digits, hypertrophic osteoarthropathy and pulmonary malignancy. Unfortunately, hypertrophic osteoarthropathy was not demonstrated roentgenographically in any of the cases reviewed.

Of the 34 cases reviewed, 8 or 23½ per cent revealed clubbing of the fingers and /or toes. Of these 8, 2 records revealed the presence of clubbing from 4-6 months prior to admission to the University Hospital. The remaining 6 cases presented clubbing of the digits when examined, but the records did not reveal the length of time that the clubbing had existed. Of these 8 cases, clubbing occurred in the fingers in 5 cases and the fingers and toes in 3. There were no cases of clubbing of the toes only. The average age of the 8 cases was 48.

In reviewing the autopsy records it was found that the portions of the lungs involved with neoplastic tissue were: left upper lobe main bronchus (2); left main bronchus (1); entire right upper lobe (1); lingular bronchi left lung (1); small bronchi right upper lobe (2); right main bronchus (2); superior mediastinum (1); left upper lobe (1); right lower lobe (1). The size of the lesions varied from 3 centimeters to involvement of the entire right upper lobe. The location of the lesions in these cases followed no definite pattern, though the bronchi were involved in 5 instances.

	Number	Sex	Age	Onset of Clubbing	Extent	Location of the lesions	Size
1.	62813	M	38	unknown duration	fingers	left upper lobe main bronchus; right lower lobe	3 cm.
2.	76190	M	38	unknown duration	fingers & toes	left main bronchus	nearly occluding lumen
3.	105441	M	55	4 months before admission	fingers & toes	infiltration of entire upper lobe, rt.	
4.	107517	M	61	unknown duration	fingers & toes	obstruction lingular bronchi lt. lung with consolidation of lingular division	
5.	78362	F	66	unknown duration	fingers	small bronchi rt. upper lobe; numerous pinhead nodules same lobe	3 cm.
6.	75046	M	48	6 months before admission	fingers	narrowing of rt. main bronchus; also rt. upper, middle and lower lobes adherent on lateral surfaces	
7.	94108	M	45	unknown duration	fingers	irregular nodular mass filling superior mediastinum and encircling trachea and esophagus; nodules in rt. upper lobe; compression of rt. main bronchus	
8.	75792	M	35	unknown duration	fingers	large ulcerating tumor of left upper main bronchus obliterating lumen	

Portions of the lungs involved:

1. left upper lobe bronchus (2)
2. left main bronchus (1)
3. lingular bronchus left lung (1)
4. right main bronchus (2)
5. small bronchi right upper lobe (2)
6. entire right upper lobe (1)
7. left upper lobe (1)
8. right lower lobe (1)
9. superior mediastinum (1)

CONCLUSIONS It is true that the pathogenesis of diffuse osteoarthropathy and clubbing of the digits in chronic pulmonary disease is as obscure today as it was when Marie described it. However, most authorities agree with Pigeaux, in that the formation of curved nails is influenced by embarrassment in respiration and circulation in one way or another.

Various theories for the pathogenesis of this disease have been proposed, among them being abnormal circulating substances; endocrine disturbance (pituitary); abnormal secretory substances from the lungs; chronic increase in systemic blood flow; alterations in acid-base equilibrium through decrease in aeration as a result of compression of pulmonary vessels, constriction of bronchi, lung compression or collapse; decreased oxygen tension brought about by faulty aeration of the blood which passes through the lungs; and physical alteration of the erythrocytes resulting in local tissue anoxia. In only two instances were definite experimental conclusions reached. In one, Mendelowitz and Leslie successfully developed hypertrophic osteoarthropathy in a dog after anastomosing the left pulmonary artery to the left auricular appendage. In the other case, Charr and Swenson demonstrated by infra-red photographs of living persons and postmortum arteriograms that the local vascular bed is increased and widened in cases of clubbing. They concluded that this means an increased peripheral flow of blood. The increased peripheral blood flow plus the reluctance of the erythrocytes to release their oxygen leads to arteriolar anoxia, low tissue oxygen tension

and clubbing.

thus, in spite of extensive study and voluminous literature, the pathogenesis of clubbing and hypertrophic osteoarthropathy remains conjectural.

The various authors are in close agreement on the pathology of hypertrophic osteoarthropathy and clubbing. In the former, it appears to consist chiefly of hypertrophy and hyperplasia secondary to chronic proliferative subperiosteal osteitis; while in the latter, most authorities agree that it is due to soft tissue changes and no bone involvement.

The symptoms of clubbing are most entirely objective. It is for this reason that, in the absence of cardiovascular abnormalities, evidence of clubbing to the examining physician should direct his thinking towards the respiratory system and the possible existence of a pulmonary malignancy. In the review of the 8 cases at the University Hospital, 2 of the 8 cases revealed clubbing between 4 and 6 months before admission, while the others probably had clubbing of the digits for a comparable time. From these findings, one should become more aware of the diagnostic implications of clubbing in relation to pulmonary malignancy.

There appears to be minimal aid to the diagnosis of clubbing and hypertrophic osteoarthropathy from laboratory studies, though the sedimentation rate is elevated in the latter in most cases. Since the concentration in the blood of phosphorus and alkaline phosphatase may be elevated during destruction and

repair of bone, these determinations may also be changed in hypertrophic osteoarthropathy. This bears further study.

The roentgenologic changes are variable and depend upon the intensity and the duration of the pathologic process. In early clubbing there is usually no evidence of radiologic alteration. It should be pointed out that the roentgen diagnosis of hypertrophic osteoarthropathy is doubtful in the absence of definite periosteal proliferation.

Ray and Fisher, in reviewing 14 cases of carcinoma of the lung revealing clubbing, found that in 13 cases the lesion was located in the periphery. These findings could not be corroborated in the cases reviewed in this paper. In fact, the findings revealed that the lesions predominately effected the bronchial system, and in no case was a peripheral lesion alone demonstrated.

BIBLIOGRAPHY

1. Fried, B. M.: Chronic Pulmonary Osteoarthropathy; Dispituitarism as a Probable Cause, Arch. Int. Med., 72:565-80, Nov., 1943.

2. Pigeaux: Reference source not listed.

3. Bamberger: Reference source not listed.

4. Marie, P.: De L'osteoarthropathic Hypertrophiante Pneumonique, Rev. de Med., Paris, 10: 1-36, 1890.

5. Camp, J. D., Scanlan, R. L., Chronic Idiopathic Hypertrophic Osteoarthropathy, Radiology, 50: 687-700, 1948.

6. Bloom, W.: Pituitary Implications in Hypertrophic Pulmonary Osteoarthropathy, Ann. Int. Med., 29: 361-70, 1948.

7. Mendelowitz, M.: Clubbing and Hypertrophic Osteoarthropathy, Med., 21: 269-306, 1942.

8. Sternberg, S.: Quoted by MacBryde, C. H., Signs and Symptoms, Phila, J. B. Lippincott, 1952, p. 203-216.

9. Crump, J. D.: Quoted by MacBryde, C. H., Signs and Symptoms, Phila, J. B. Lippincott, 1952, p. 203-216.

10. Touraine, R., Galle, A.: Quoted by Fried, B. M., Chronic Pulmonary Osteoarthropathy; Dispituitarism as a Probable Cause, Arch. Int. Med., 72: 565-80, Nov., 1943.

11. Forte, A. J. A.: Anatomie et Physiologie du Pouman Considere Comme Organ de Secretion, Paris, A. Delahaye, 1867.

12. Roger, G. H., Binet, L.: Physiology of the Lung, Rev de Med., 42: 1-20, 1945.

13. Aschoff, L.: Physiology of the Lung Tissue, Zlschr. f. d. Ges. Exper. Med., 50: 52-63, 1926.

14. Compere, E. L., Adams, W. E., Compere, C. L.: Generalized Hypertrophic Osteoarthropathy; Experimental and Clinical Study with Report of Two Cases; Surgery, Gynec. and Ob., 61: 312-323, Sept, 1935.

15. Phemister, C. F.: Quoted by Temple, H. L., Jaspin, G. Hypertrophic Osteoarthropathy, Amer. J. of Roent., 60: 232-45, 1948.

16. Harter, J. S., Churchell, E. D.: Quoted by Compere, E. L. Adams, W. E., Compere, C. L., Generalized Hypertrophic Hypertrophic Osteoarthropathy, Surg. Gynec. & Obst., 61: 312-23, 1935.

17. Mendlowitz and Leslie: Quoted by Temple, Jaspin; see #19.

18. Campbell, D. C., Sacasa, C. F., Camp, J. D.: Chronic Hypertrophic Osteoarthropathy, Proc. Staff Meetings Mayo Clinic, 13: 708-13, Nov. 1938.

19. Temple, H. L., Jaspin, G.: Hypertrophic Osteoarthropathy, Amer. J. of Roent., 60: 232-45, 1948.

20. Van Hazel, W.: Joint Manifestations Associated with Intrathoracic Tumors, F. Thoracic Surgery, 9: 495-505, 1940.

21. Harter, J. S.: Quoted by Temple and Jaspin, see #19.

22. Holt, D. E., Hodges, A. L.: Quoted by Temple and Jaspin, see #19.

23. Mauer, E. F.: Etiology of Clubbed Fingers, Amer. Ht. J., 34: 852, 1947.

24. Mac Bryde, C. H.: Signs and Symptoms, Phila., J. B. Lippincott, 1952, pp. 203-16.

25. Deutschberger, O., Maglione, A. A., Gill, J. J.: An Unusual Case of Intrathoracic Fibroma Associated with Pulmonary Hypertrophic Osteoarthropathy, Am. J. of Roent., 69.2: 738-744, 1953.

26. Charr, R., Swenson, P. C.: Clubbed Fingers, Am. J. Roent., 55: 325, 1946.

27. Pattison, J. D., Jr., Beck, E., Miller, W. B.: Hypertrophic Osteoarthropathy in Carcinoma of the Lung, J. A. M. A., 146: 783-87, June 30, 1951.

28. Ray, E. S., Fisher, H. P.: Hypertrophic Osteoarthropathy in Pulmonary Malignancies; Annals Int. Med., 38.1: 239-46, 1951.

29. Bloom, W.: Pituitary Implications in Hypertrophic Pulmonary Osteoarthropathy, Annals Int. Med., 29: 361-70, 1948.

30. Rynearson and Sacasa: Proceedings Staff Meet. Mayo Clinic, xvi, 353, 1941.

31. Thomas, H. M., Jr.: Acropachy; Secondary Subperiosteal New Bone Formation, Arch. Int. Med., Li, 571-88, 1933.

32. Weens, H. S., Brown, C. E.: Atrophy of the Terminal Phalanges in Clubbing and Hypertrophic Osteoarthropathy, Radiology, 45: 27-30, 1945.

33. Locke, E. A.: Secondary Hypertrophic Osteoarthropathy and Its Relationship to Simple Clubbed Fingers, Arch. Int. Med., 15: 659-713, 1915.

34. Gall, E. A, Bennett, G. A., Bauer, W.: Generalized Hypertrophic Osteoarthropathy, Amer. J. of Path., 27: 349, 1951.

35. Lovibond, J. L.: The Diagnosis of Blubbed Fingers, Lancet, 1: 363, 1938.

36. Witherspoon, J. T.: Congenital and Familial Clubbing of the Fingers, Toes, with a Possibly Inherited Tendency, Arch. Int. Med., 57: 18, 1936.

37. Poppe, J. K.: Diagnostic Significance of Clubbed Fingers, Dis. of the Chest, 13: 658, 1947.

38. Abbott, M. E.: Atlas of Congenital Heart Disease, New York, Amer. Ht. Assoc., 1936.

39. Friedberg, C. K.: Diseases of the Heart, Phila., Saunders, 1949.

40. Blumer, G.: Sub-acute Bacterial Endocarditis, Medicine, 2: 105, 1923.