HETEROTOPIC OSSIFICATION IN INTESTINAL NEOPLASMS *

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The connective tissue stroma of epithelial neoplasms is a relatively uncommon site of heterotopic ossification. Previous reports have described its occurrence in benign and malignant tumors of widespread origin, including adenocarcinomas of the rectum, colon, appendix, ileum, stomach, gallbladder, uterus, breast, prostate and salivary glands, calcified "epitheliomas" of the skin, sweat gland adenomas, bronchial adenomas, and craniopharyngiomas.[1] Of these, intestinal adenocarcinomas in general, and rectal adenocarcinomas in particular, account for the majority of cases, although even in the latter group the incidence is extremely low, having been estimated at 0.4 per cent.[2]

Despite the interest in heterotopic ossification, as evinced by the abundant literature, its precise morphogenesis has remained obscure. Examination of 3 hitherto unreported cases of adenocarcinoma of the large intestine with stromal ossification has revealed certain features which appear to contribute to an understanding of the process.

REPORT OF CASES

Case 1

F. N. was a white male butcher, 43 years old, who first noticed blood in the stools in July, 1947. Exploratory laparotomy at another hospital established a diagnosis of carcinoma of the rectum and colostomy was performed. He was then referred to the Royal Cancer Hospital for definitive therapy. Here biopsy confirmed the diagnosis and an abdominoperineal excision of the rectum was done in September, 1947, at which time no metastases were evident. Gross examination of the surgical specimen disclosed in the distal rectum a large, fungating tumor measuring 6.0 cm. in diameter, which penetrated through the wall of the bowel. The postoperative course was stormy, being complicated by intestinal obstruction which necessitated laparotomy and by subsequent development of a perineal fecal fistula. Eventually the patient made a satisfactory recovery and was discharged in good health in December, 1947. He remained well and at work until February, 1952, when he complained of cough and hemoptysis. Multiple bilateral pulmonary opacities, considered to be metastases, were found in radiographs of the chest. Cytologic examination of aspirated pleural fluid confirmed the presence of malignant cells. Symptomatic therapy was instituted and three courses of an experimental chemotherapeutic agent were administered with some subjective improvement. The pulmonary metastases gradually increased in size and caused marked dyspnea. His general condition deteriorated and he died in this hospital in August, 1953, 6 years after the onset of rectal bleeding and 1½ years after the recognition of pulmonary metastases.

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Gross Findings

Necropsy was performed by one of us (J.W.W.) 80 hours after death. Examination of the thorax revealed complete obliteration of the right pleural cavity and partial obliteration of the left by firm adhesions; the patent portion of the latter contained blood-stained liquid. The parenchyma of both lungs was extensively replaced by necrotic, gelatinous, and partly gritty neoplastic tissue. The small gritty areas consisted of opaque, yellowish white, granular material mixed with minute, irregular, bony-hard, whitish spicules embedded in a translucent, gray, mucinous matrix. Gross permeation of large bronchi and blood vessels by tumor was visible in the right lower lobe and left upper lobe. The scanty non-involved lung tissue was poorly aerated due to multiple irregular areas of edema, pneumonic consolidation, and abscess formation. Copious thick, yellow, mucopurulent material was present in the trachea and bronchi. The hilar and other mediastinal lymph nodes were enlarged but showed no gross involvement by tumor. The thoracic duct and cisterna chyli were normal. There was bilateral slight enlargement and induration of axillary lymph nodes.

The pericardial sac was not invaded by tumor but contained a 100 cc. effusion of clear, straw-colored liquid. The heart weight was within normal limits and there was no gross cardiac abnormality. Minimal atherosclerosis was present in the coronary arteries and aorta.

In the abdomen were a few fibrous peritoneal adhesions but no tumor deposits. The liver, spleen, and kidneys, though slightly increased in weight due to passive congestion, were tumor-free. The pancreas, adrenal glands, and genito-urinary tract were normal. The esophagus, stomach, and intestine, which terminated in a patent colostomy, showed no lesions. The soft tissues of the pelvis and perineum revealed no residual tumor and the pelvic and abdominal lymph nodes were normal in size and consistency. Two right inguinal lymph nodes were slightly enlarged and indurated.

Within the right cerebral hemisphere were two discrete tumor nodules, the larger measuring 4.3 cm. in greatest diameter. They were soft and gelatinous throughout and contained no gritty areas. The pituitary gland appeared normal.

The remainder of the examination of the head and neck showed a normal thyroid gland and small, soft, cervical lymph nodes. The upper respiratory and alimentary passages were not remarkable.

There was no evidence of tumor growth in the skull, ribs, or lumbar

vertebral bodies. The skin and extremities showed no abnormality and the musculature was well developed.

Microscopic Findings

Sections of the surgical specimen showed a moderately well differentiated adenocarcinoma with focal mucinous areas. It had penetrated through the muscular wall of the rectum, but neither blood vessel invasion nor lymph node metastasis was present. There was no calcification or ossification.

Multiple sections of the extensive metastatic tumor deposits found in the lungs at necropsy disclosed numerous clumps of moderately well differentiated adenocarcinoma cells which lay in and around large pools of mucin and necrotic débris (Fig. 1). Tissue breakdown was indicated by the presence of nuclear débris, cholesterol clefts, and collections of foamy macrophages (Fig. 2). The malignant cells were identical in appearance with those of the primary rectal tumor. There was, however, considerably more mucin production and necrosis, so that there were large areas devoid of viable cells. Calcium deposition within such areas was extensive, varying from small, scattered, deeply basophilic granules to clumps and extensive irregular plaques (Fig. 3). Traversing many of the pools of mucin was a fine to coarse connective tissue network which contained proliferating fibroblastic cells and occasional capillaries but with a notable absence of inflammatory cells (Fig. 4). These fibrous trabeculae appeared to broaden with maturity and many had become densely fibrous and hyalinized, often incorporating calcified plaques.

Superimposed on this background of organized and calcified mucinous tumor secretion were multiple scattered foci of intramembranous ossification. The heterotopic bone seemed to be formed in three slightly differing morphologic situations.

First, it appeared most commonly in apposition to masses of calcium, where it developed by metaplasia within the surrounding fibroblastic connective tissue (Figs. 5, 6, and 7). Numerous transitions were readily traced which demonstrated the rounding-up of the fibroblasts to osteoblasts and the acidophilic homogenization of the collagenous intercellular matrix to form osteoid (Figs. 5, 6, and 8). The connective tissue involved in this change tended to be immature and many of the cells in areas of osteoid formation retained a basophilic mantle of mucin. This produced a chondroid appearance in some areas (Figs. 3 and 5), but no true cartilage or evidence of endochondral bone

formation was recognized. The deposition of calcium salts and the incorporation of the osteoblasts as osteocytes advanced the process and the resultant new bony trabeculae, haphazardly arranged about the calcific deposits, were easily recognized. As a secondary change, the connective tissue between some of the trabeculae appeared loosened and myxomatous, and in it developed delicate thin-walled sinusoidal blood vessels (Fig. 7). The addition of a light infiltrate of histiocytes, lymphoid and plasma cells, simulating rudimentary hemopoietic tissue, completed the resemblance to cancellous bone. No haversian systems were detected, but the presence of occasional groups of osteoclasts indicated resorptive activity.

Second, small spicules of bone were seen in the fibrous trabeculae. These had doubtless been formed in a manner similar to that described in the preceding paragraph but were now not associated with calcium deposits (Fig. 8).

Third, many of the large, irregular, calcified plaques which lay in the mucinous lakes or were surrounded by fibrous tissue appeared to have incorporated a few connective tissue cells and then to have undergone direct transformation into poorly formed coarse bone, without the intervening appearance of osteoblasts or osteoid (Fig. 9). This type of ossification was most prominent in areas with excessive calcium deposition, and, at the same time, a paucity of proliferating fibroblastic tissue.

The relationship of viable tumor cells to the foci of ossification was inconstant, as can be seen in the series of photomicrographs. In a few places the bony trabeculae were aligned with their long axes parallel to adjacent rows of tumor cells (Fig. 8), but, in the main, they appeared to have a more frequent localization in the immediate neighborhood of calcium deposits (Figs. 5, 6, and 7). In addition, it was noted that the zones of osteoid and bone formation occurred in relatively avascular areas of the proliferating fibroblastic connective tissue, as was indicated by their distance from the accompanying blood capillaries. Due, undoubtedly, to progressive tumor growth and further circulatory changes, many of the bony trabeculae and surrounding fibrous tissue trabeculae had become secondarily necrotic.

Large bronchi were invaded and occluded by neoplastic tissue. Adjacent branches of the pulmonary arteries showed marked intimal fibrous thickening.

In the surrounding lung parenchyma there were areas of bronchopneumonia, with formation of small abscesses, and also diffuse chronic

inflammatory changes consistent with long-standing bronchial obstruction. The visceral pleura was the seat of marked fibrous thickening. A tracheobronchial lymph node contained microscopic deposits of metastatic tumor in which there was no calcification or ossification.

The cerebral metastases revealed both abundant formation of mucin and large zones of necrosis. As in the lung, the pools of mucinous and necrotic material showed early organization by a proliferative fibroblastic network but there was neither calcification in the mucin nor ossification in the immature fibrous stroma.

No significant histologic changes were found in the liver, kidneys, pituitary gland, or axillary lymph nodes.

Case 2

G. H., a white seaman, 46 years of age, had a partial left colectomy for carcinoma in December, 1948, at Capetown, South Africa. In August, 1950, a small nodule in the vicinity of the umbilicus was excised at another hospital and proved to be a secondary deposit of adenocarcinoma. He was first seen at the Royal Cancer Hospital in April, 1951, when he complained of a nodule in the operative scar below the umbilicus and of post-prandial abdominal pain, distention, nausea, and of being easily fatigued. The nodule was widely excised and exploration of the abdomen failed to disclose additional metastases. A barium enema and chest roentgenograms were non-contributory. The gross examination of the surgical specimen revealed a mass of grayish white neoplastic tissue, measuring 3.0 cm. in greatest diameter, involving skeletal muscle but not the overlying skin or subcutaneous tissue. He was discharged in good health to be followed as an out-patient. In February, 1954, he was well and apparently free of recurrent growth.

Microscopic Findings

Sections of the nodule showed infiltration of skeletal muscle and fascia by moderately well differentiated, mucin-secreting adenocarcinoma of intestinal type containing necrotic foci. Small pools of mucin contained granular calcific deposits and were frequently invaded by strands of proliferating fibroblasts from the surrounding abundant dense fibrous stroma. Bony metaplasia in the connective tissue in these areas (Fig. 10) showed nicely the transition phases through osteoblastic differentiation and osteoid formation to bony trabeculae as described in case 1. The location of the bony spicules demonstrated no specific relationship to either tumor epithelium or the calcific deposits, but tended to occur in relatively avascular areas devoid of inflammatory change. A section of the primary tumor was reviewed and no bone formation was found. The first recurrence in the abdominal wall, however, showed areas of mucin, calcification, and ossification, the bone having similar relationship to that in case 1.

Case 3

A. B., a white male, 58 years old, developed rectal bleeding, and, at laparotomy in June, 1951, at another hospital, was found to have an inoperable carcinoma of the sigmoid colon associated with a pelvic abscess. A colostomy was performed in August, 1951. His general condition remained good for over a year and for this reason he was referred to Mr. A. Lawrence Abel for consideration of further therapy. He was admitted to the Princess Beatrice Hospital in June, 1952, where physical examination and a barium enema confirmed the diagnosis. An abdominoperineal resection of the rectum was carried out in conjunction with removal of a loop of adherent small bowel and the colostomy was revised. Multiple hepatic metastases were found at operation. The surgical specimen, examined at the Royal Cancer Hospital, disclosed to the naked eye an ulcerated, constricting tumor encircling the rectum at the line of peritoneal reflection and penetrating through its wall to invade an adherent loop of small intestine to the depth of its submucosa. No lymph node metastases were found.

Postoperative recovery was satisfactory except for persistence of a perineal sinus. This was scraped in June, 1953, and histologic examination of the material removed showed inflammatory tissue with no evidence of tumor. In February, 1954, his condition was fair with occasional bouts of upper abdominal pain but without weight loss.

Microscopic Findings

A section through the base of the carcinomatous ulcer in the rectum revealed a moderately well differentiated, partly mucinous adenocarcinoma which penetrated through the muscular wall and invaded the serosal aspect of the adherent loop of small intestine. Considerable necrosis of tumor was present and small pools of secreted mucin lay in a dense fibrous stroma. Small deposits of calcium were seen frequently within the necrotic débris and pools of mucin (Fig. 11). Little tendency to fibroblastic organization was apparent, and no ossification was evident at this site. However, in the portion of tumor invading the small bowel there were numerous bony spicules within the proliferating connective tissue stroma and lying between columns of tumor cells (Fig. 12). In contrast to cases 1 and 2, the ossification in this location did not appear in zones of mucinous infiltration nor in close relationship to calcific deposits, although, as mentioned, both of these features were noted nearby.

Discussion

A brief consideration of the histogenesis of heterotopic ossification in general seems pertinent. Leriche and Policard[3] discussed it at considerable length in their monograph on the pathophysiology of bone. They stated that the essential features of this process are the existence of an ossifiable connective tissue medium and the presence of a calcific deposit in the vicinity. The ossifiable medium is described as a connective tissue which, because of inadequate blood supply, has become

edematous and has reverted to an "embryonic" state. This involves swelling and multiplication of elementary collagenous fibrils followed by infiltration with "pre-osseous substance" (osteoid). The simultaneous resorption of nearby organically fixed calcium salts produces a "local calcific surcharge" whereupon ossification takes place by the usual processes.

Their interpretation is strongly supported by the structural features of the majority of the more common instances of bony metaplasia in fibrous tissue surrounding non-neoplastic lesions which contain calcified necrotic or degenerate tissue, such as caseous tuberculous foci, atheromatous plaques, and thyroid nodules. It is also supported by the finding that the bone resulting from heterotopic ossification contains calcium and phosphorus in the same proportion as does normal skeletal bone.[4]

Contrary opinions are, however, also based on considerable pathologic and experimental evidence, as Willis[1] has pointed out in his admirable monograph on the subject of metaplasia. For instance, in many examples of heterotopic ossification as seen in laparotomy scars and myositis ossificans, no local calcific deposits are demonstrable by the usual histologic methods. Furthermore, experimentally transplanted epithelium of the urinary bladder, proliferating in contact with connective tissue in certain situations, induces in it bony metaplasia without associated calcification.[5,6] The transplantation of gallbladder and gastric mucosa has produced similar results,[7] but the mechanism of this inductive effect is far from clear.[8] In addition, the experimental introduction of calcium in various forms into the tissues of laboratory animals in an attempt to induce osteogenesis has led to conflicting results.[3,6,8] Apart from the recognition that zones of osteoblastic activity are constantly rich in alkaline phosphatase,[8,9] enzyme studies have not clarified the problem. Thus it appears that the morphologic criteria enumerated by Leriche and Policard[3] as essential to heterotopic ossification are present frequently but not constantly.

Although differing over the nature of the stimulus to osteogenesis, most recent writers have agreed that it is manifested through metaplasia *in situ* of the pre-existing fibroblastic connective tissue.[1,3] Keith,[10] however, proposed that the earliest osteoblastic cells were derived from proliferating vascular endothelium. The occasional subsequent development of bone marrow containing hemopoietic elements affirms the validity of the concept of the pluripotentiality of proliferating mesenchymal tissues.[1]

As to the more specific problem of heterotopic ossification in the

stroma of intestinal adenocarcinomas, published reports fail to give a clear account of its morphogenesis. Most of the histologic features described in our 3 cases have been mentioned by previous authors, but none has noted the striking appearance of massive calcification in the tumor-secreted mucin shown in case 1, and to a lesser extent in cases 2 and 3. In an attempt to interpret the over-all importance of this feature as a stimulus or localizing factor in the osteogenesis under consideration, we have re-examined the histologic material from the 3 cases previously reported from this hospital by Christie,[11] and 2 other cases with bone formation in metastases of rectal adenocarcinomas referred here for consultation. In none of these cases were significant calcific deposits demonstrable in the material available for study, although necrosis and mucin production were seen in varying degree. Two cases of transitional cell carcinoma of urinary tract epithelium, containing metaplastic stromal bone, one from the bladder and the other from the pelvis "in the position of the urachus," were studied. Neither contained mucin but one case revealed extensive necrosis with focal areas of calcification. Finally, a case of recurrent malignant "mixed" tumor of the parotid gland showed metaplastic ossification of its stroma without obvious necrosis, calcification, or mucin production. To complete the picture, examination was made of the material from several cases of rectal adenocarcinoma, including both primary and secondary lesions, in which there was extensive calcification, but no bone formation. In the main, the calcium salts were deposited in areas of coagulative necrosis of tumor tissue rather than in secreted mucin, but in one section an occasional focus of calcification was found in a pool of mucin surrounded by proliferating fibroblastic tissue. Thus the stage would seem to have been set for bone formation. To explain its absence, we can only assume that the local circulatory status was not conducive to ossification or that a time factor is involved, insufficient time having elapsed for bone to have appeared.

It appears clear from the study of this additional material that the presence of calcification in mucin is by no means a constant feature of the development of bone in the stroma of epithelial neoplasms, although obviously an important one in the 3 cases which have been described. Conversely, as might be expected, its presence is not inevitably associated with bone formation as far as can be determined from the material examined. In the case of recurrent rectal adenocarcinoma reported by Senturia, Schechter, and Hulbert,[12] heterotopic bone predominated in areas of necrosis and mucinous degeneration,

and in some of these areas scattered calcium granules were observed. Although their illustrations do not demonstrate recognizable calcification in mucin, it appears likely that the morphologic features were essentially similar to our 3 cases. A closer resemblance obtains in the case of a mucocele of the appendix reported by Juvara and Borcescu[7] in which extensive ossification appeared in areas of calcification and necrosis separated by granulation tissue from islands of epithelium in the presence of mucoid impregnation of the whole structure. Christeller and Mayer[13] illustrated a similar case in which bone formation in the wall of an appendicular mucocele was associated with calcification and mucinous infiltration. However, the majority of writers[1,2,11,14,15] have failed to find calcium deposits in their material and have, therefore, tended to reject the previously mentioned theory of histogenesis advanced by Leriche and Policard[3] which requires among its essential factors the presence of a local calcium deposit.

The hypothesis most frequently offered in its place postulates the existence of a specific stimulus to stromal osseous metaplasia derived from some property peculiar to the epithelium of the particular tumor and presumably related to enzymes or metabolites produced by the tumor cells.[1,11,14,15] We are not aware of the application of any histochemical studies which support or deny this hypothesis, although the final step-by-step elucidation of the whole problem probably lies in that field of investigation. Thus, while a categorical denial of the existence of such an epithelial stimulus is not called for, it is equally clear that the validity of this concept remains to be established, and, at the same time, there are a number of anatomical facts which challenge it. First, no one has been able to detect any histologic difference between the malignant cells of tumors which form bone in their stroma and those of the (commoner) tumors which do not form bone. Second, the cases we have described show that in at least some instances the presence of calcification adjacent to proliferating immature connective tissue is associated with heterotopic bone formation. Third, in the cases recorded, the occasional occurrence of bone formation in recurrent or metastatic lesions, with no evidence of its presence in the primary tumor, seems difficult to understand on the suggested basis of a specific epithelial stimulus, as also is, fourth, the unexpectedly frequent localization of these secondary lesions in the anterior abdominal wall. Fifth, the well known tendency of necrotic tissue to undergo calcification lends support to the impression that diligent examination of bone-containing adenocarcinomas, almost all of which will disclose necrosis to some degree, might reveal the presence of calcium deposi-

tion more often than has been noted in the literature. Indeed, as Leriche and Policard[3] have stated, "If one takes into account the frequency of zones of necrosis in these new growths, one need not be astonished that there can be points of calcification in them, and the latter are probably the origin of the bone plates found in such tumours."

On the basis of our 3 cases, the additional material examined, and the cases recorded in the literature, we would prefer to take the middle road and support a histogenetic theory based on the osseous metaplasia of proliferating mesenchymal tissue which is stimulated by the interaction of local physicochemical factors. The deposition of calcium salts in accumulations of mucin represents one such factor to be considered of importance in the cases in which it is present. In those cases in which apparently it is absent, we do not agree that it is necessary to postulate the existence of a peculiar epithelial property which stimulates osteogenesis. It may rather be that some morphologically undetected factor is operating locally to produce a "calcific surcharge."

Necrosis has been suggested by some as playing a part.[2,16] However, as almost all adenocarcinomas of the intestine will show some necrosis, it is in itself unacceptable as a significant factor, although probably playing an indirect rôle by predisposing to calcification.

The secretion of mucin by tumor cells, usually in minimal amount, has been present in many of the cases reported. This can be recognized, however, in a large percentage of ordinary intestinal adenocarcinomas, particularly if special stains for mucin are carried out. Furthermore, in those with abundant mucin production, there does not appear to be an increased incidence of heterotopic bone formation. In our material mucin appears to play its part by providing an avascular medium susceptible to calcification and organization by embryonic connective tissue. This seems a more significant factor than necrosis. Whether the mucin may have any chemical contribution to the osteogenic process is at present conjectural.

An early observation on the rôle of local circulation in the formation of heterotopic bone is attributed[3,6] to von Recklinghausen who observed that slowing of the lymphatic current is a condition necessary for calcification. Leriche and Policard[3] noted that zones of preosseous edema and osteoid formation tend to appear in relatively avascular areas of the ossifiable connective tissue medium, as indicated by their distance from the accompanying blood capillaries. We found a fairly impressive relationship of this sort in cases 1 and 2, but it was difficult to confirm in the remainder of the material studied. Binkley and Stewart[17] also have considered that local tissue anoxia resulting

from stagnation of blood flow is a factor of prime importance in the development of calcification and ossification in a hyalinized connective tissue, but, as morphologic evidence for this viewpoint, they referred to the nearby presence of thin-walled cavernous vessels which, they believed, result from obstructive dilatation. Scheidegger[15] went so far as to call the heterotopic bone in his 2 cases of rectal adenocarcinoma "angiogenic" bone, because he observed its formation in the vicinity of blood vessels.

This discrepancy of opinion with regard to the relationship of heterotopic bone formation to blood vessels can be resolved if the appearance of the thin-walled sinusoidal vessels lying adjacent to and between well formed bony trabeculae is considered to be a secondary change; namely, a manifestation of the architectural reorganization of the newly formed bone and of its contained connective tissue. The formation of a distinct periosteal limiting layer about the trabeculae, lacunar osteoclastic resorption, and the appearance of fat cells and hemopoietic elements in the connective tissue spaces represent other secondary changes which may develop in the heterotopic bone.[1,3,11] These changes are analogous to those seen in the reorganization of newly formed skeletal bone. This similarity of biologic development reinforces the concept that the respective histogenetic mechanisms are also alike.

In his analysis of 4 cases of rectal adenocarcinoma containing metaplastic stromal bone, Dukes[2] suggested that a tendency to slow growth, as was indicated by the clinical course and the histologic appearances, represented a common feature. More recent reports,[11,12] however, have failed to confirm this contention, inasmuch as several of the cases have shown rapid growth with early and wide dissemination leading to death in 1 to 2 years following the onset of symptoms. Our case 1, with a total survival of 6 years, is probably best considered of long average duration, as is case 2 with a survival of over 5 years at the time of writing; whereas the follow-up in case 3 is too short for consideration. Our cases contribute little to this question, but we feel that no significant difference has been established in the biologic behavior of these bone-containing tumors as compared with intestinal adenocarcinomas in general.

Finally, it is interesting to note that in at least 3 of the recorded cases of intestinal adenocarcinoma containing bone, of which we have found a total of 19,[2,11,12,14-16,18-20] with inclusion of our 3, the bone has developed in the stroma of secondary tumor deposits within surgical scars in the anterior abdominal wall as described in Clark's case,[18]

Christie's[11] case 2, and our case 2. This frequency of osseous metaplasia in metastases in the abdominal wall seems disproportionately high and suggests that it may share a common factor with another well known instance of heterotopic ossification, namely, that occurring in laparotomy scars. Only one of our cases, case 2, falls into this group, and its histologic examination does not clarify the nature of this association. It might be thought possible that the tumor deposits in these 3 cases are simply metastases to heterotopic bone within incisional scars, but we consider it far more likely on morphologic grounds that the bone formation is similar in its origin to that occurring in the other tumors described. It may be that the peculiar susceptibility of the proliferating fascia of the anterior abdominal wall to undergo heterotopic ossification[6] represents an addition to the local factors responsible in these cases for osteogenesis.

Summary and Conclusions

Three cases of intestinal adenocarcinoma with heterotopic stromal ossification are reported. The histologic features are described and illustrated and the predominating morphologic features are discussed in relation to the mechanism of this bone formation and to its previous interpretations. It is concluded that calcium deposits play an important rôle in the induction and localization of metaplastic ossification in the stroma of some mucin-secreting intestinal adenocarcinomas.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

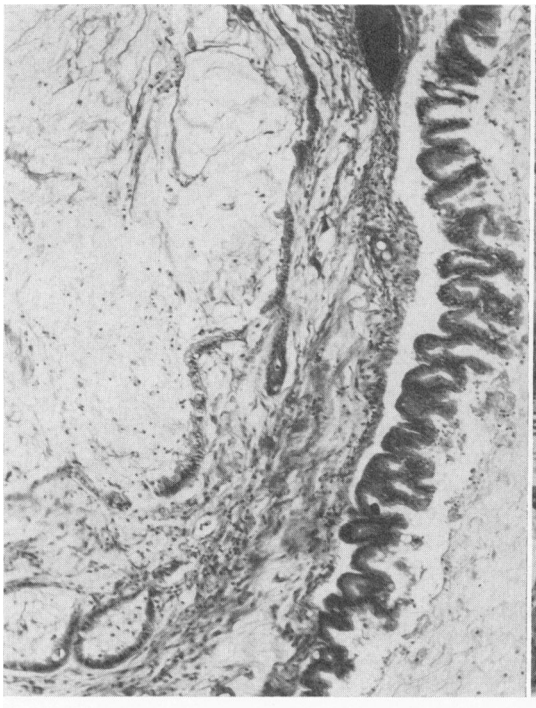
All sections illustrated were fixed in 10 per cent formalin and stained with hematoxylin and eosin.

FIG. 1. Case 1. Pulmonary metastasis. Early dissolution of tumor cells at periphery of pools of accumulated mucinous secretion. × 75.

FIG. 2. Case 1. Pulmonary metastasis. Necrosis and mucinous infiltration with proliferation of stroma from surviving nests of tumor. × 75.

FIG. 3. Case 1. Pulmonary metastasis. Calcium deposits in mucin. A few connective tissue cells incorporated at lower right resemble cartilage cells. × 125.

FIG. 4. Case 1. Pulmonary metastasis. Fibroblastic organization of mucin. × 75.



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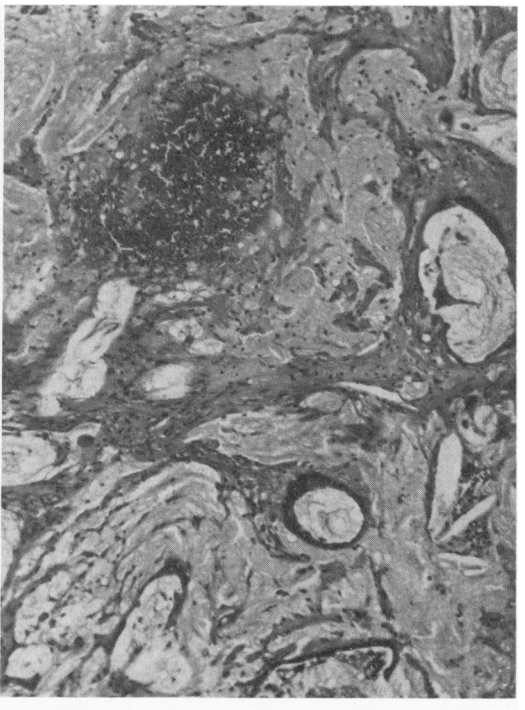

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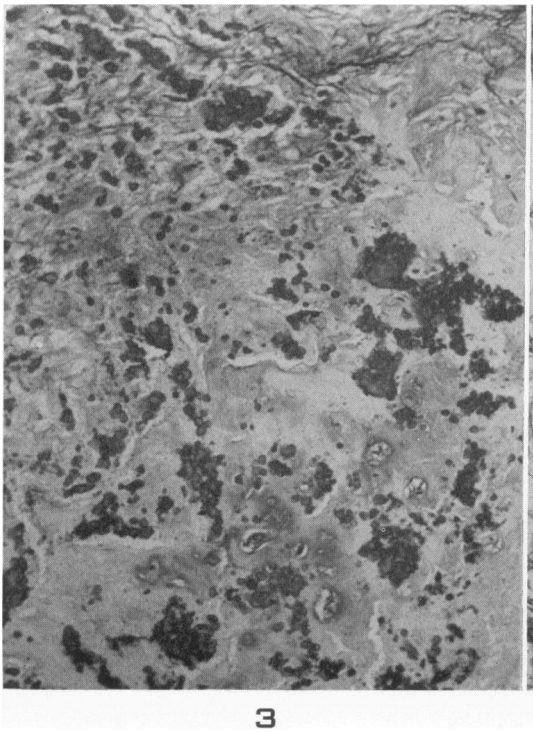

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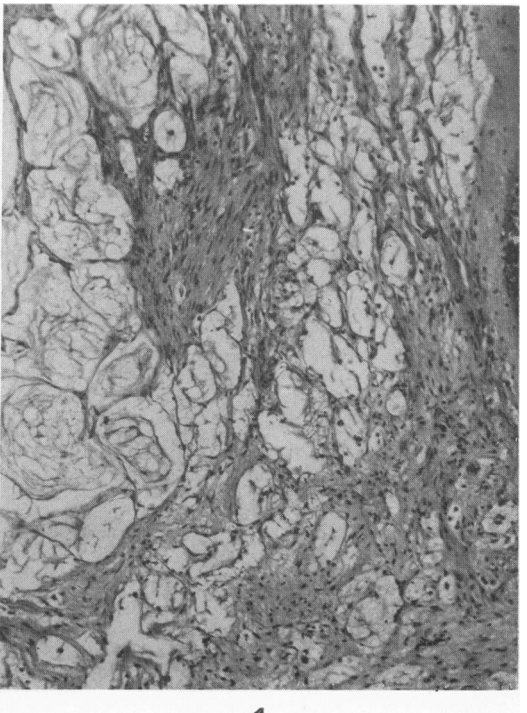

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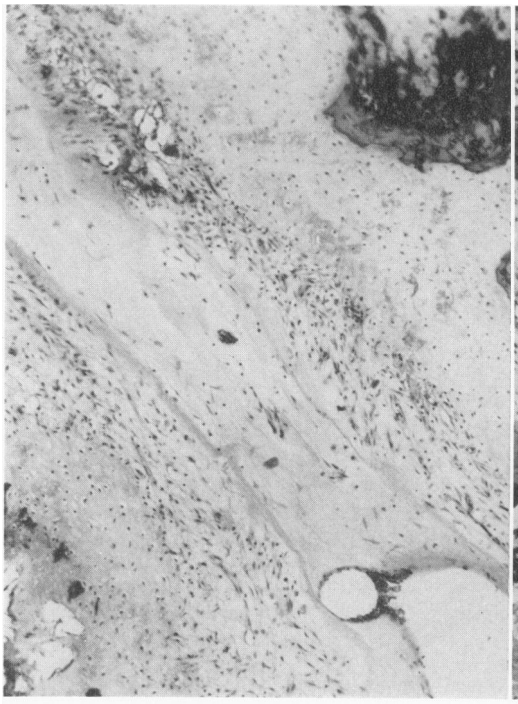
FIG. 5. Case 1. Pulmonary metastasis. Osteoid tissue at lower left and upper right where it surrounds a calcific plaque. A narrow rim of bone lies in apposition to the lower edge of the plaque. The faint stippling around some of the osteoblasts represents a residue of mucin and imparts a chondroid appearance. There is relative avascularity of zones of ossification compared with the non-ossifying connective tissue centrally. × 75.

FIG. 6. Case 1. Pulmonary metastasis. Metaplastic bone formation within proliferating fibroblastic connective tissue adjacent to large focus of calcification in pool of mucin below. Smaller accumulations of mucin in spaces above. × 75.

FIG. 7. Case 1. Pulmonary metastasis. Similar to Figure 6, showing bone formation about calcific deposits. There are large sinusoidal blood vessels lying in loose connective tissue between the bony trabeculae in the upper portion of the field. × 75.

FIG. 8. Case 1. Pulmonary metastasis. A calcified bony spicule lies parallel to a row of tumor cells on either side. Osteoid tissue above and below is surrounded by a layer of plump osteoblasts. × 75.



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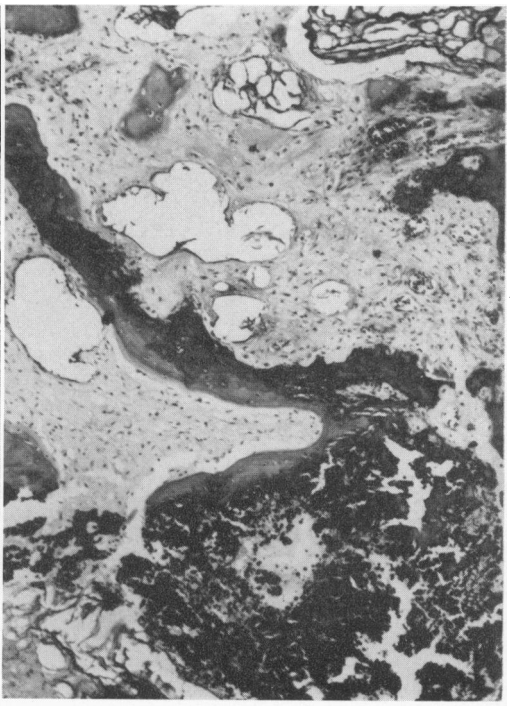

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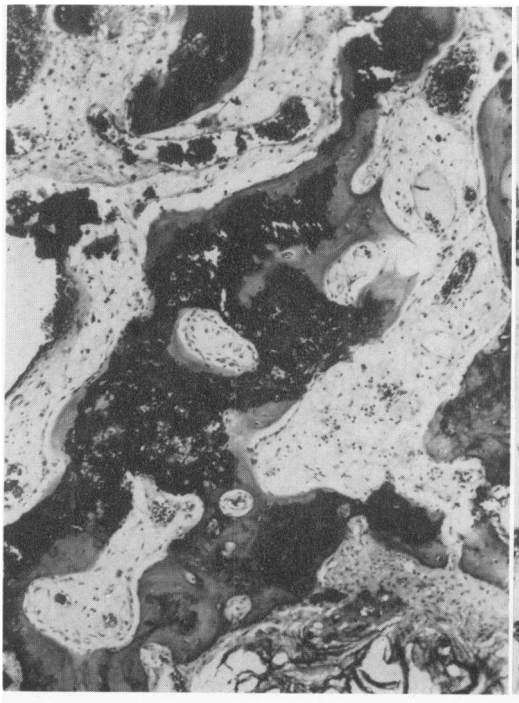

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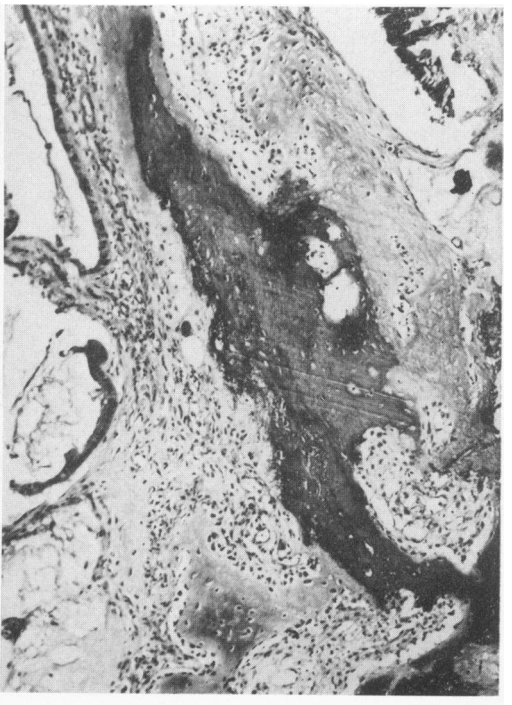

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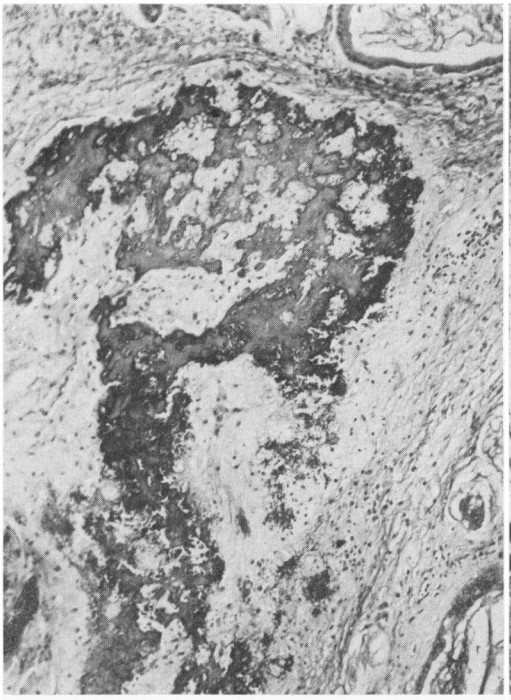
FIG. 9. Case 1. Pulmonary metastasis. Large calcific plaque, lying in partially organized mucinous matrix, has undergone in its upper portion direct transformation into imperfect bone by the incorporation of a few connective tissue cells. × 75.

FIG. 10. Case 2. Secondary adenocarcinoma in scar of abdominal wall. Large calcium deposit at upper left lies in mucinous secretion which is being infiltrated by proliferating fibroblasts. Two small bony spicules at lower center. × 125.

FIG. 11. Case 3. Primary adenocarcinoma of rectum. Nests of degenerative mucin-secreting tumor cells within dense fibrous stroma in ulcerated base of primary lesion. Small irregular calcium deposits are seen in mucin, necrotic tumor, and stroma. × 75.

FIG. 12. Case 3. Adenocarcinoma invading small bowel by direct extension from rectal primary. A group of small bony spicules lies in the tumor stroma. × 125.



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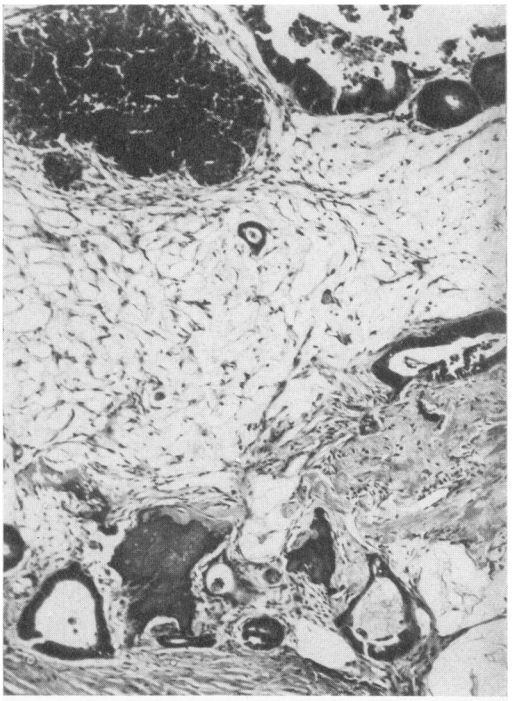

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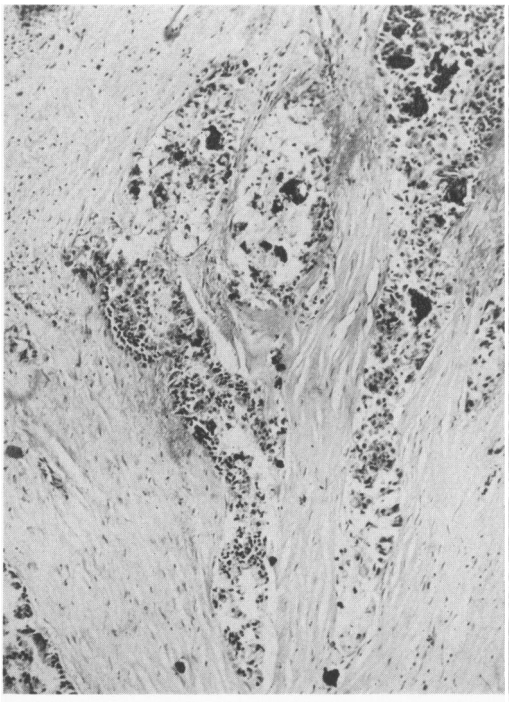

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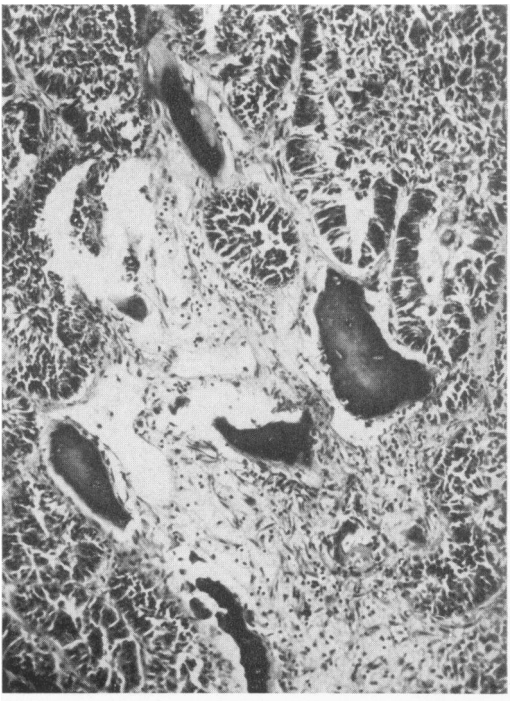

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