CRITIQUE ON THE INTER-RELATIONSHIPS OF THE OSTEOSTEOSARCOMAS

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For some time after a semblance of order had been brought into the diagnosis of the neoplastic diseases of soft tissues, the classification of bone tumors remained in a state of chaos. Although Virchow (1) interested himself in the field and did much toward its clarification, it was Ewing (2) who put it, essentially, into its present form. Only in recent years, however, has any far-reaching attempt been made to bring the new growths of bone into a phylogenetic system. In several papers and subsequently in a volume, Geschickter and Copeland (3) presented a wealth of painstakingly classified embryologic, pathologic, and clinical data. On the basis of this they developed some interesting theories. Hellner (4), in his book published in Germany, accepts and follows their system. Many references to it will be made in this essay.

To the writer, however, the inter-relationships of the tumors of the skeletal tissues seem never to have been put on a really logical and simple basis. In the course of study of the fairly comprehensive material in the laboratory of the Hospital for Joint Diseases, he has formulated certain opinions, which he presents here.

The histogenesis of the skeletal tissues takes place by the route

\[ \text{Mesenchyme cell—spindle cell—Cartilage.} \]

\[ \text{Mature fibrous connective tissue. Bone.} \]

The process is analogous for intramembranous, enchondral, and even heterotopic ossification. In the first case, the primitive cells of a young, actively growing, vascular connective tissue proliferate and differentiate, with the deposition of the characteristic matrix. In the second, a similar young, actively growing, vascular connective tissue invades and resorbs the definitive cartilage, using the latter for a framework and, presumably, for a supply of building materials, but producing bone with its own cells, just as in intramembranous ossification. In the last case, again, a tissue which has been rejuvenated and stimulated by injury goes through the same procedure. Cartilage similarly is the product of the differentiation of primitive connective tissue cells, whether of the embryo, of the perichondrium in the growth period, or of a stimulated metaplastic connective tissue in an ectopic location.

If there be thus no essential difference in the type or manner of bone formation in various parts of the skeleton, there should be no inexplicable difference in the tumor forms occurring throughout the skeletal system as regards either histogenesis, pathogenesis, or ultimate composition. In other words, the uniform histogenesis of the supportive tissues would seem to presuppose a unity
of their new growths, benign and malignant, and that this is in fact so is the thesis of this paper.

Only a few tissues come into question for their possible neoplastic activity. Bone itself consists of immured cells practically incapable either of normal or of pathological proliferation. We are concerned, then, with only four elements—the notochord, the relatively mature fibrous tissue, the skeletoblastic investing membranes (perichondrium, periosteum, and endosteum), and cartilage. Each of these behaves in a prescribed manner with limited variability, and it is upon their peculiarities of location that the multiplicity of tumors of bone depends. The notochordal growths are well understood and need no discussion here. They have been briefly reviewed by Chesky (5), and at greater length by Hass (6) and others.

The classification will be developed according to the following scheme.

**Tissue of Origin**

<table>
<thead>
<tr>
<th>Origin</th>
<th>Benign Tumor</th>
<th>Malignant Tumor</th>
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<tbody>
<tr>
<td>Notochord</td>
<td>Chordoma</td>
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<tr>
<td>Undifferentiated connective tissue</td>
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<td>Periosteum (fascicular layer)</td>
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<td>Medullary stroma</td>
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<td>Marrow fat</td>
<td>(Lipoma?)</td>
<td>Liposarcoma</td>
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<td>Cartilage</td>
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<tr>
<td>Growth zones</td>
<td>Enchondroma</td>
<td>Chondrosarcoma</td>
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<td>Skeletoblastic mesenchyme</td>
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<tr>
<td>Perichondrium</td>
<td>Ecchondrosis</td>
<td>Osteogenic sarcoma (chondroplastic type)</td>
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<tr>
<td>Periosteum of enchondral bones</td>
<td>Cartilaginous exostosis</td>
<td>Osteogenic sarcoma (variable type)</td>
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<tr>
<td>Periosteum of membranous bones</td>
<td>Ivory exostosis</td>
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<tr>
<td>Endosteum</td>
<td>Osteoid Osteoma</td>
<td>Osteogenic sarcoma (osteoplastic type)</td>
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<td>Giant cell tumor</td>
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**Tumors of Undifferentiated Connective Tissue**

*Periosteal Fibroma:* The outer layers of the skeletal investing membranes may be expected, as fibrous connective tissue, to manifest all of the reactions which characterize such tissue elsewhere. Among these reactions is benign neoplasia, with the production of fibroma, a tumor similar in origin, structure, and natural history to such tumors elsewhere in the body. The derivation and pathogenesis of fibroma have been adequately discussed, and its occurrence in the skeleton calls for no reiteration of accepted principles.
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Periosteal fibroma is often described, but its existence is unproved. Certainly there are fibromata in intimate connection with the periosteum; but adjacent connective tissues cannot be too dogmatically excluded from a causative relationship. Theoretically, however, at least occasional neoplastic activity would be expected from the cells of the periosteum (and perhaps of the perichondrium).

**Periosteal Fibrosarcoma:** Like the corresponding fibroma, periosteal fibrosarcoma is of questionable identity. Kolodny (7) deplores the use of the term and states that, "a well ascertained true example of a sarcoma originating from the outer layer of the periosteum is up to the present day unknown in the [Tumors of Bone] Registry material." Geschickter and Copeland accept tumors in this category, though with caution. Final judgment is difficult to pronounce.

**Central Fibroma:** The stroma of the marrow cavity has a marked reserve of potential activity. In fracture, infection, rickets, and a variety of other conditions it can proliferate and dominate the histologic picture. It would be surprising if this activity were not occasionally perverted to neoplasia, with a resultant fibroma. Reports of medullary fibromata of bones are rare in the medical literature, but there is reason to assume that the infrequency of the term is not a fair index of the incidence of the tumor. The term "myxoma" has achieved a more frequent and, the author believes, unfortunate use. It is employed, for instance, in connection with cartilaginous tumors, when the tissue so denominated is in all probability a dedifferentiated and primitive form of cartilage. Even when it refers to non-specialized connective-tissue elements alone, its propriety is still questionable. (Certain lesions of the umbilicus may represent an exception to the last statement.) The writer is in agreement with Stout (8), who speaks of "myxoma" as the "form of fibroma which grows with mucinous degeneration of the cytoplasm." As he states, it is to be differentiated from mucinous degeneration of chondromas, sarcomas, and other lesions.

If we include many of the so-called central myxomas under the heading fibroma, we have at once multiplied the incidence of the neoplasm several times. Bloodgood (9) has reported several examples in the small bones of hands and feet (although some of these may be enchondromata), and Ewing (10), probably employing stricter criteria, reports their occurrence in long tubular bones. Herfarth (11), too, has observed such a case.

Even with this inclusion, however, there is still probably an incomplete marshalling of these neoplasms. In soft tissue, a palpable mass discloses the presence of a fibroma, with a definite capsule, which can be excised by enucleation, to disclose a definite structure. In bone, however, the removal of a mass in this fashion is rarely possible. Diseased bone, except in the case of amputation of a frankly malignant tumor, is almost always removed piecemeal; under these circumstances the identity of a fibroma must almost inevitably be concealed under some such diagnosis as healing osteomyelitis, atypical giant-cell tumor, or the all-inclusive osteitis fibrosa. For this reason there is no considerable body of data to facilitate a statistical study. The tumor exists, and is presumably derived from the connective-tissue stroma of the marrow cavity.
Its morphology is essentially that of a fibroma elsewhere, subject to modification by its enclosure in a rigid capsule and by the characteristic giant-cell reaction of bone to so many different types of injury.

**Medullary Fibrosarcoma:** Malignant spindle-cell tumors of the stroma of the marrow cavity have been repeatedly observed, but, especially in the smaller bones (hands and feet), are extremely rare. Bufalini (12) has reported the only such instance in a metatarsal acceptable to the writer, who has himself seen one in a metacarpal.

It is probable that these tumors too are of more frequent occurrence than the literature would lead one to believe. Many of them have probably provoked enough reactive osteogenesis on the part of endosteum and periosteum to lead to the mistaken diagnosis of osteogenic sarcoma. It is possible that several of the cases reported by Geschickter and Copeland under the classification of osteolytic osteogenic sarcoma should be placed in this category. The pathogenesis presents no problem essentially different from fibrosarcomata in connective tissues elsewhere.

**Lipoma and Liposarcoma:** Fat is an inactive tissue, and the fat of bone marrow is no exception to this rule. It is not surprising, therefore, that few of its tumors are reported. A lipoma in this situation would almost certainly fail of recognition, even if the bone were removed and opened. Fatty islets in the vertebrae have been encountered, and denominated lipomata with questionable justification. Junghanns (13) finds them in 0.6 per cent of all autopsy subjects, but only in patients over fifty. Liposarcomata of bone, however, have been identified. Stewart (14) published the first cases and Rehbock and Hauser (15) have added two more. There have been rare reports in the interval.

**Tumors of Pre-formed Cartilage**

**Enchondroma:** Intramedullary cartilaginous lesions have been known for a long time, but their adequate study was impossible before they had been sharply demarcated from other cartilaginous growths and new growths. Today we have a fairly clear and distinct concept of enchondromatosis, even if general agreement as to its nature and origin is still lacking.

There are but two possible origins for enchondromata. They may conceivably be the result of a metaplastic differentiation of primitive connective-tissue cells, or they may be derived from remnants of the cartilage which precedes the osseous tissue in the construction of bone. Virchow considered an enchondroma the result of a metaplastic activity on the part of soft tissue. This is, however, somewhat difficult to reconcile with his discussion of rickets as a possible etiologic factor. The latter view would seem to incriminate faulty mechanics of epiphyseal plate development.

A theoretical objection to the metaplastic view of the origin of enchondromata from endosteum or medullary stroma may be drawn from consideration of the embryological development of a bone. The periosteum, being in most sites the derivative of the early perichondrium, had at one time the formation of cartilage as its function, and can in those sites readily resume that function
under such pathological stimuli as neoplasia, fracture, etc. The endosteum and connective-tissue stroma within the bone have a quite different history. This tissue invades the shaft from without at the onset of ossification, and from the very beginning produces bone directly, having nothing to do with cartilage save its destruction and resorption. In a variety of non-neoplastic diseases, in fact, in which the connective-tissue frame-work of the marrow cavity undergoes a process of proliferation and what appears to be metaplastic ossification independently of the endosteum (this can be observed in leukemic osteosclerosis, osteomyelitis, and other diseases), cartilage is never formed. Favoring some form of the metaplastic theory, on the other hand, is the occurrence of chondromas of the soft tissues—the implication of a generalized tendency toward chondroid change being suggestive.

A modified version of the metaplastic theory is presented by Geschickter and Copeland. These authors call attention to the fact that multiple enchondromata occur particularly in the sternum, ribs, hands and feet—regions of many joints. They observe that the joints are laid down by strands of primitive connective tissue, which they describe as cutting across the definitive, as yet purely cartilaginous, bones, and then undergoing mucoid regression. “Aberrant persistent strands which do not thus regress are responsible at a later date for the origin of cartilaginous islands in the bone, which form the chondromas and chondromyxomas.” The enchondromata, according to these authorities, “represent histogenetically supernumerary joint cartilages.” They make much of the “pure myxoma tissue” in such chondromas. A considerable body of evidence may be marshalled against this view. In the first place, the hypothesis of an attempt at ectopic joint formation seems, off-hand, purely arbitrary. In the second place, such a process, if it took place, would be expected to occur in closer proximity to the joints themselves—in other words, close to the ends of the tubular bones affected—whereas these lesions appear almost exclusively in the metaphyses. Thirdly, for multiplicity and complexity of joint formation, the carpus and tarsus are unapproached by any other region of the body; yet in these bones enchondromata are almost unknown. Fourthly, the tissue most characteristic of joints is the synovial membrane, but synoviomata in the bones do not occur. Fifthly, the “myxoid” stroma on which Geschickter and Copeland lay such stress has nothing specific about its architecture. It is much simpler to understand it as the result of a de-differentiation of cartilage cells undergoing metabolism in an abnormal site and under abnormal conditions. Lastly, the joint-forming tissue strands which the authors describe are just the opposite of chondroblastic. It is their function to resorb cartilage and to replace it by quite different matter—namely, the joint lining, space, and fluid. The joint cartilages represent the unresorbed ends of the bones, not the product of the invading mesenchyme.

A number of authorities refer the enchondromata to remnants of cartilage left behind by the advancing epiphyseal plate. Ollier (17) no doubt had this in mind when he described the disease as a new affection, dyschondroplasia, and assigned its etiology to “retardation and faulty ossification.”

Too much has been made of the unilaterality which, although not in the strictest form, characterized two of Ollier’s cases. Those who have followed
him have ascribed even more significance to the circumstance than did he himself, with the result that the term "Ollier's disease," though sometimes taken to mean the entity of multiple enchondromatosis with deformities, is often restricted to the unilateral form of the disorder. There is probably no warrant for the latter usage. The affection is sometimes symmetrical but more often displays varying degrees of asymmetry; complete restriction of pathology to one side is rare and probably fortuitous, as is doubtless true, also, of the one-sided exostotic affection also described by Ollier (18).

Anyone familiar with the microscopic architecture of a growing bone knows the picture of multiple small pieces of cartilage matrix, apparently non-viable, regularly invested by bone and persisting for some time in the normal metaphysis. That these islets may under certain circumstances be not only viable but capable of continued growth is the basis of the view that in the epiphyseal plate is to be found the origin of the enchondromata. It is unfortunately difficult to observe the process for the simple reason that enchondromatosis is a non-fatal disease. Bentzon (19), however, undertook to obtain experimental evidence. He was led thereto by observing that in a fifteen-year-old girl, in whom the affection was limited to one side, the distribution of lesions in the bone corresponded with that of the blood supply. His best results were obtained by injection of alcohol about the nutrient arteries of bones in rabbits, with the aim of putting their sympathetic nerves out of function. In a few cases he obtained lesions which were radiologically comparable with those of his patient. Only one of the bones was sectioned; the gross and microscopic architecture in this instance confirmed the radiologic impression of enchondroma. Bentzon concludes, therefore, that pathology in the autonomic nervous system is at once the cause of the disease and of its peculiarities of distribution.

Speiser (20) had the unusual opportunity of performing a complete autopsy upon a four-year-old boy who presented the affection (but whose family was free of it). He found narrow-stemmed, grape-like, inward projections of cartilage from the epiphyseal plate and from the periosteal surface of the bone. (In metacarpals and metatarsals these were found only at the growing, i.e. metaphyseal, ends.) In the older portions of the shafts typical enchondromata were seen.

At least some of the lesions, as Speiser's pictures clearly show, are referable to failure of resorption of portions of the cartilaginous plate that bounds the metaphysis. In other cartilaginous nodules in different positions (carpal and tarsal bones, and non-metaphyseal parts of tubular bones), a chondrifying activity of the cambial layer of the periosteum is apparent. These Speiser considers the results of a sort of metaplastic activity of the periosteum. He believes, indeed, that it is purely a matter of chance whether a cartilaginous growth appears on the outside or on the inside of a bone, depending solely on what part of the periosteum happens to undergo metaplastic change.

With the implication that a cartilaginous exostosis is the result of periosteal metaplasia, the writer is in agreement. As to the enchondromata, it may be true that they have a dual origin, from unresorbed cartilage and from periosteal activity. In a photomicrograph which Speiser presents, there is seen a typical
area of cartilage remote from the epiphysis and apparently derived from peri-
osteal metaplasia. It is clearly made up of two zones. The inner layer is
comparatively mature; the outer layer, fairly sharply demarcated from it, is
being deposited by the covering membrane of the bone. It is not inconceivable
that the inner mass represents an originally superficial bit of the epiphyseal
plate or original cartilaginous anlage which failed of resorption in the ossifying
process. Its perichondrium not unnaturally continues its chondroblastic ac-
tivity, subject only to osteoplastic encroachment from the metamorphosed
periosteum on both sides, producing eventually first the narrow-stemmed pro-
jections described by Speiser and ultimately complete investment by bone.

It is possible that the vascular-neurotrophic theory of causation applies
through some effect on the growth-plate.

The cartilage remnants would seldom come to clinical attention did they
not grow and produce the thin-shelled, spindle-shaped enlargement of bone
with which radiologists are familiar. To what extent this constitutes benign
neoplasia is a difficult question. In those cases which supervene or continue
after the growth-period, this process must be considered. According to Cüppers (21), one-third of 94 patients presented evidence of the disease before the
age of ten. Many cases reported elsewhere were first observed in the twenties,
thirties, or even later.

In 1930 a review by Dahl (22) appeared, in which four cases were pre-
sented. He found that the cartilaginous nodules are ultimately ossified and
disappear. He pleads for the identification with one another of the entities
which have been variously described as chondrodysplasia, multiple enchondro-
matosis, and Ollier's disease. In an excellent discussion of pathogenesis, he
quotes with approval Speiser's and Bentzon's work, and ascribes the lesions
to neurotrophic failure of blood vessels to remove the maturated cartilage and
replace it with bone. He rejects a neoplastic nature, but this, of course, is a
question of definition.

Insufficient attention has been paid to the last three contributions. Never-
theless, the developmental theory has been gaining ground. Jemma (23) ap-
parently believes in an epiphyseal plate derivation, as does Schramm (24).
The latter, however, includes the cartilage of the epiphys is proper in his hy-
pothesis. Leu (25) reviews the subject in connection with a case report of
his own, and comes to the conclusion that "enchondromatosis is a disease sui
generis, referable to embryonic faulty development. Other coincident new
growths, such as angiomata in Steudel's (26) case, or glioma, as in this case,
we consider parallel and significant at most of an increased tendency toward
neoplasia."

Stocks (27) has made a particularly extensive study of enchondromatosis
from a genetic point of view. In his series of 125 single enchondromata un-
associated with other bone tumors, not one had a hereditary history. Of 121
so-called enchondromata which were multiple or allegedly associated with exos-
toses, on the other hand, 38 presented obvious evidence of heredity.

As far as the associated exostoses are concerned, they will be discussed only
to be ruled out of consideration in a succeeding section of this paper. The
case for hereditary transmission of pure enchondromatosis is equally insecure.
The writer has found no example that will bear scrutiny. Steudel (26), under
the title of multiple enchondromata, mentions two brothers, one of whom had what can be identified with certainty as multiple cartilaginous exostoses and died probably from chondrosarcomatous degeneration of one of the lesions with generalized metastases; the other had died at the age of twelve with neither biopsy nor necropsy to determine the nature of two cherry-sized tumors of the toes. Kienböck's (28) evidence is even flimsier; it concerns a mother with multiple cartilaginous exostoses or ecchondroses, and a daughter with a solitary lesion shown by resection to be a "round-cell sarcoma."

Among Stocks' non-hereditary single cases the bones were involved in the following order: hand, 32 cases; pelvis, 21; ribs and tibia, 8. (One suspects that many of the pelvic cases, especially, are exostotic interlopers; Geschickter and Copeland's series contains no example from this region.) Among the hereditary cases the order was: ribs, 7; femur, 5; humerus and pelvis, 4 each. There were of course other localizations in smaller numbers, but the hand is not prominently represented. The hereditary lesions are evidently cartilaginous exostoses, or, when occurring on the costal cartilages, ecchondroses. The femur and humerus are sites of common occurrence for cartilaginous exostoses.

The distribution of the tumors remains to be accounted for. One wonders whether, if the nodules occurred in many bones throughout the body, the heavy cortices of the larger bones, built to resist enormous pressures and tensions, might offer considerable resistance to growth of cartilage and might favor its degeneration and disappearance; whereas the much more delicate framework of the hands, fingers, and sternum might more readily be ballooned out by the expansile force of the developing cartilage cells. Keith (29) notes that the phalanges, metacarpals and metatarsals are "peculiar in their order of ossification; the periosteal sheath of bone is laid down almost before the cartilage core has commenced to ossify. This may be significant in the developmental mechanics."

Most enchondromata become quiescent and may undergo regression and bony replacement, but some, during or after the physiological period of cartilage growth, can undergo true benign or malignant neoplasia. Typically and essentially, however, enchondromatosis is, in the author's opinion, a dystrophic and not a neoplastic disease.

The foregoing discussion has, in the main, concerned itself with multiple, rather than solitary, enchondromatosis. In the genesis of the former disorder, there must presumably be a mechanism more central than the bones themselves to bring about the appearance of the lesions in widely scattered positions. Bentzon has been quoted as referring the etiology to a disturbance in the autonomic nervous system. Presumably a solitary tumor would be the result of such a malfunction occurring further down the line—perhaps at the plate itself. The earliest stage of a solitary enchondroma does not come to observation for obvious reasons. It is believed that it, too, is the result of a failure of absorption of part of the cartilage growth-plate.

Chondrosarcoma: A number of attempts have been made in the past to subdivide the sarcomata of the skeletal tissues on the basis either of their site of origin or of their histology. Most of these were based upon untenable hypotheses or inadequate data. Kolodny (7), surveying the material available in the Registry of Bone Tumors, despaired of being able to effect a valid classi-
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fication, but believed it possible that the accumulation of additional information might make such a proceeding possible in the future. Geschickter and Copeland mention five kinds of osteogenic sarcoma. Although the writer believes that they have introduced unnecessary complexities and unwarranted assumptions into their system, he has availed himself of their wealth of data.

Cartilage is a self-proliferating tissue, and wherever cartilage exists the possible occurrence of a tumor must be considered. The growth-plates of the long bones come most naturally to mind, and they do in fact furnish pure cartilaginous malignant tumors, or chondrosarcomata.

The distribution of the chondrosarcomata, as of other bone tumors, is determined largely by the differential of activity, and it is not surprising that the region of the knee and the upper end of the humerus, the most sensitive and rapidly growing parts of the skeleton, furnish the largest number of examples. In those cases seen at the Hospital for Joint Diseases, the relationship of the neoplasm to the growth cartilage was very striking, and led one to feel that such an origin could be assigned with a high degree of probability. The articular cartilage was relatively uninvolved until late in the disease. These are the sarcomata which, beginning as benign or relatively benign tumors, are often incompletely eradicated. They change both in histology and behavior in the direction of greater malignancy with each operative intervention, metastasize, and terminate fatally.

It is this group which Geschickter and Copeland characterize as chondroblastic sarcoma. As they point out, it is the cartilage cells themselves that are the active agents in, and not the passive results of, the neoplasia. The myxoid stroma, which becomes more and more prominent in the course of the disease, is the result of a dedifferentiation of malignant cartilage, not its precursor. These tumors are not to be confused with osteogenic sarcoma of the chondroplastic type arising in the periosteum, in which spindle-cells are the active element of the neoplasm and the cartilage is their product.

Bergstrand's (30) position, that this tumor has no connection with the formation of cartilage but is vascular in origin, does not seem tenable in view of the embryonic cartilage cells that make it up. He was probably misled by atypical manifestations.

Cartilage is cartilage, and its malignant tumors cannot vary greatly. The writer sees no reason for retaining Geschickter and Copeland's separate category of "secondary chondrosarcoma," in which they include malignant tumors arising in cartilage of pathological origin, with special reference to enchondromata and the cartilaginous caps of exostoses. This cartilage, too, is liable to progression from a benign tumor state to a malignant one. When this occurs, the histologic picture is like that of chondrosarcoma elsewhere, showing abnormal cartilage cells, sometimes in a state of dedifferentiation. The same progressively fatal course is observed, often through the same gradual modifications. The age incidence of these neoplasms is, as would be expected, later than that of tumors of the growth cartilage. The former persist throughout life, whereas the latter have commonly, though not invariably, disappeared before the end of the third decade. In the vertebrae, the growth cartilages are retained as the intervertebral articular cartilages, while, as Jacobson and Driver (31) have shown, remnants of the sacral and even the coccygeal carti-
lages commonly persist to an advanced age, contrary to the statements of the text-books. It is perhaps significant that the vertebrae and the sacrum are not unusual sites of chondroma and chondrosarcoma.

The articular cartilages, inactive though they are, could also theoretically give rise to chondrosarcomata, although the writer knows of no such case. The costal cartilages are more active, and cartilaginous tumors have certainly arisen from this site. Which of them arose through a perversion of metabolism of normal cells, and which through a malignant degeneration of pre-existing ecchondroses, is somewhat difficult to decide.

To summarize, the writer believes that we can form a category of malignant tumors under the designation chondrosarcoma. These tumors are distinct and uniform in their pathogenesis, in that they are derived directly from pre-existing non-malignant cartilage cells. They are distinct and uniform in their histology, in that they are composed of malignant cartilage cells proliferating as the active elements of the tumor and accompanied only incidentally and inconstantly by mesenchyme-like cells as a product of dedifferentiation. They are distinct and may be uniform in their behavior—incomplete data necessitate caution in generalizing—in that they exhibit a gradual exacerbation of clinical and anatomical signs of malignancy. The name "chondrosarcoma" might well be limited to them, to the exclusion of other chondroplastic tumors.

**Tumors of Skeletoblastic Mesenchyme**

*Ecchondroses:* Perichondrium, like any other primitive skeletal tissue, may be activated to proliferate and differentiate in neoplastic fashion. This is true whether the perichondrium be the covering of a not yet ossified bone or the limiting membrane of such normally persistent structures as the costal cartilages or the symphysis pubis. The membrane may participate in the generalized diathesis that produces multiple exostoses, or may be subject to such adventitious stimuli as elsewhere evoke a sporadic exostotic response. In either case, the cambial mesenchyme proliferates, differentiates, and produces a pure cartilaginous tumor on the skeletal surface.

The looseness of terminology in the literature makes it impossible satisfactorily to separate the confusing case reports of cartilaginous exostoses, ecchondroses, chondromata, and enchondromata. At the present time it is possible to state of ecchondroses only that they exist, and that apparently they may be either part of the picture of multiple osteochondromatosis, or of sporadic occurrence. They presumably arise from perichondrium in the same way that exostoses are produced by periosteum, but descriptions of the stages are lacking. Their relative rarity reduces the question to secondary importance.

Virchow knew of the existence of the ecchondroses. Ewing (10) is one of the few modern writers to differentiate them from enchondromata. He illustrates the origin of a group of cartilage cells in the skeletal investing membrane. He apparently considers this the same as the entity, "cartilaginous exostosis," which practically it is. The only difference lies in the fact that ecchondroses abut on cartilage and fail to undergo ossification. Stout refers to them but briefly. Most writers on bone tumors ignore them or group them with other cartilaginous nodules.
The perichondrium of extra-skeletal cartilage shares in this property of neoplastic proliferation. The tumors occur on the thyroid and cricoid cartilage, on the tracheal rings, and in the bronchi. Whether the nodules on arthritic joint cartilages are to be considered neoplastic is more than doubtful.

**Cartilaginous Exostoses:** The benign osteochondral bodies upon bone have played their part in the general confusion which surrounds the growth disorders of this tissue. They are hereditary and non-hereditary, single and multiple. Most of the extensive literature concerns itself with their multiple appearance, and much of the rest is so confused that it is impossible to tell whether the solitary, the multiple, or both forms are under discussion. Although Virchow discussed the single and the multiple growths as different entities, not every one has followed his example; even in modern times Meyerding (32) draws no distinction between them. A distinction there is, however, and in this article hereditary multiple cartilaginous exostoses will be segregated as one dystrophy, and reference will subsequently be made to solitary osteochondroma as a separate entity.

There is no reason why confusion should exist between the true osteochondromata and osteomata, and the osteophytes called forth by a variety of insults. The coincidence of a true osteochondroma, in point of location, with the calcaneal spurs of a neisserian infection is no indication of any kinship between the two disorders. Nor does the occasional appearance of a true osteochondroma on a terminal phalanx, where traumata and infections are common and osteophytes frequently develop, justify the formation of a pathological entity of subungual exostosis, much less its inclusion with the osteochondromata. Virchow held these growths to be non-cartilaginous. Paget was familiar with both types, as were Cornil and Coudray (33), who found the cartilage usually absent. Johnson and Lawrence (34), however, seem to have fallen into the prevalent confusion and accept the entity of subungual exostosis as identical in structure with the other cancellous exostoses.

There are several reasons for demarcating the multiple form of the lesion from the single. Of these the most obvious is the hereditary character of the former. Of multiple exostoses there are 765 cases (65 per cent) with and 409 (35 per cent) without a familial history, reported by Stocks. It is entirely possible that many—perhaps all—of the latter group would have been included in the former had more adequate family records been available. The disease can skip at least two generations in the female line. Of the solitary cartilaginous exostoses, on the other hand, only 57 (10 per cent) out of 563 cases were known to be hereditary. It is likely that this 10 per cent really falls into the category of the usually multiple growths, representing a minimal development of the disease.

Age furnishes another differential point. Of 248 multiple cases, only 6 appeared after the age of twenty. Of 100 solitary exostoses, 36 appeared after the twentieth year.

Multiple cartilaginous exostosis or hereditary deforming chondrodysplasia, as the multiple form of the disorder has been styled, is frequently associated with other structural anomalies. Of 70 patients, only 2 males and 1 female, after the period of growth had passed, were above the normal height; shortness of stature was a usual observation. Forearm deformities are frequent.
Keith states that dislocation of the radius occurred in one-third of the reported cases. Other forearm deformities have been found in large numbers. Genu valgum occurs in about 20 per cent of cases for the arm and 10 per cent for the leg. Other associated deformities are scoliosis, kyphosis, talipes valgus, curving of tibia and fibula, flat foot, enlargements of metacarpals and phalanges, deflexion and shortening of phalanges, anomalous epiphyses of proximal phalanges and metacarpals, distortion of the scapula, deformity and asymmetry of the pelvis, rachetoid deformity of thorax, and displacement or asymmetry of the patellae. Jenny's (35) interesting case involved especially (though not quite exclusively) the trunk and right side; there were growth repressions and stimuli of various bones, enlargement of the right ear and of the right half of the tongue, pigmentation, multiple fibromata, lipomata, and telangiectasias. Solitary osteochondroma, on the other hand, is not accompanied by other skeletal malformation with any undue frequency.

Speculations as to the pathogenesis of the tumors fall into several categories. Attempts have been made to refer the exostoses to a considerable number of precedent diseases. Syphilis has been cited since the days of Astruc (36). Ackermann (37) led the procession of those who sought to incriminate thyroid dysfunction. Vix (38) and subsequent observers discovered an associated rickets, and some have made much of this. Cholewa's (39) and Bourdillat's (40) patients had cranial tumors, which caused insanity and epilepsy. Some authors have tried to reverse this relationship. Lortat-Jacob writing with Aubourg (41) and with Sabareanu (42), as well as Pissavy (43) and others, incriminated tuberculosis. None of these theories has stood the test of time.

Virchow, as stated, differentiated between the single and the multiple lesions. The solitary osteochondroma he considered a maldevelopment, but he is not too definite about the mechanism. Braune (44) falls back on the inviting but unsupported "rest" hypothesis of Cohnheim.

Trauma, while cited without warrant in most cases, may possibly be justly ascribed an etiological rôle in 14 per cent of Stocks' solitary osteochondromata. Gallois and Japiot (45), who favor a traumatic origin, point out that the tumors are not to be found in Egyptian mummies. This they ascribe to the circumstance that among the ancient Egyptians only the well-to-do, unexposed to industrial accidents, were so well embalmed that their remains are still available for examination. Their descriptions, however, lack preciseness; they may have been studying non-cartilaginous exostoses of the osteophytic type.

Bisgard (46) supports the traumatic theory with an interesting and significant experiment. He removed segments from the shafts of radii of rabbits. Partial or complete separation and displacement of the distal epiphyses ensued spontaneously, followed, again spontaneously, by complete or nearly complete replacement. In 7 out of 12 instances cartilaginous exostoses developed, apparently from avulsed fragments of epiphyseal cartilage. "So it is suggested," he writes, "that some of these tumors in man (particularly the solitary ones) may have a similar etiology . . . but it seems unlikely or impossible to explain the multiple and familial types of the disease on this basis alone."

All of these views have in common the fact that they conceive of multiple exostosis as a disease due to a superimposed or external factor and not as a
simple neoplasia or inherent growth anomaly. Some of them may be dismissed
by a consideration of such cases as one of Ehrenfried's (47), in which the con-
dition was congenital.

Pels-Leusden (48) presents 10 cases, and takes occasion to reject Bessel-
Hagen's (49) views on the relationship between the exostoses and other asso-
ciated deformities. But he too regards the disease as a non-neoplastic growth
disturbance. He thinks it may be due to faulty vascular development, and
quotes v. Recklinghausen and Nehrnorn to the same effect. He believes that
trauma may be responsible in some cases.

One group of writers look upon irregularities in growth of the intermediary
cartilage as the factor responsible for exostoses. Bessel-Hagen (49), who
published a comprehensive review of the subject in 1891, emphasized the
skeletal anomalies which he found accompanying the multiple cartilaginous
exostoses in every one of his 11 carefully described cases, including 3 skeletons.
In one case, previously described by Drescher (50), the tumors were said to
have occurred also on the articular surfaces of the femoral heads. (As in
many of the cases, these are purely adventitious findings of arthritic manifesta-
tions secondary to altered static factors resulting from anomalies of the legs.)
It is concluded that multiple cartilaginous exostosis is "a distinct disease, a
growth disturbance of the intermediary cartilage, caused by an originally faulty
anlage."

Broca (51) comes out definitely and emphatically for a derivation of the
exostoses from the growth cartilages by a sort of exuberance of production:
"This cartilage lays down bone at one or several points of its circumference
in quantity more than sufficient for the growth in length of a bone." Edington
(52) discusses the single and multiple types separately, but concludes that
both are derived from non-resorbed or sequestrated portions of the epiphyseal
plate. This theory has been echoed in America. Johnson and Lawrence
(34), writing in 1923, express themselves regarding the osteochondromas in
similar terms. More recently, von Kress (53) has espoused this point of
view, going on to plead for the recognition of these structures as true neoplasms.

Keith (29) calls attention to the widened metaphysis. He holds that in
the organogenesis of a long bone, the periosteum and its derivatives resorb and
model the shaft, and that failure of the periosteal growth ring causes the ir-
regularity. Actually, the periosteum is by no means the sole agent in the
Umbau of the cortex. Endosteum of marrow space and of canals plays an
active rôle. Keith suspects that the "primary disturbance may prove to lie
in the growth behavior of the cartilage cells." He thinks that the cartilage-
formed bone outgrows the periosteally formed bone in the metaphyses, pro-
ducing the deformities. He would relate the disease to achondroplasia and
suggests an endocrine origin—probably thyrogenic. It is to him that we owe
the term "diaphysial aclasis." Cornil and Coudray (33), while agreeing in
the main with the theory of overproduction by the growth plate, do not deny
a subsidiary rôle to the periosteum.

Faulty periosteal function at the ends of the bones is responsible according
to Jansen (54), also. He considers the deformity of the metaphysis to be the
result of a "total retardation of tubulation," and the exostoses of "partial re-
tardation of tubulation."
Geschickter and Copeland separate the solitary from the multiple tumors. They regard as the mother cells of the solitary lesions the small cells in the ends of tendons, which they consider cartilaginous. Their view of the pathogenesis of the sporadic tumors may be abstracted as follows: "Since in normal bones the growth centers at the epiphyseal line contain neither proliferating fibrous tissue nor foetal cartilage cells but derivatives in a higher state of differentiation, it is evident that the osteochondromas are not related histogenetically to the bone proper nor to the epiphyseal line, as so often stated. . . . If the periosteum surmounts only the outgrowth of the underlying bone and fails to blend with the fibrous attachment of the tendon, the growth of the cartilaginous center in the fibrous attachment of the muscle will not be properly limited, and a tumor results. . . . Histogenetically, these tumors are considered to be an exaggeration of a normal bony protuberance intended for the anchoring of an important tendon." Incidentally, 30 per cent of their cases were observed in persons above the age of thirty years, when growth and reshaping have long since been completed.

A careful study of the microscopic morphology of the osteochondroma yields some slight support for that view of its histogenesis which is favored by Geschickter and Copeland. The present writer follows them to some extent, in ascribing the primary activity to the connective-tissue envelope which surrounds the bone. Cells may be seen feebly proliferating in the basic layers of the membrane which encloses an osteochondroma and dips into the crevices dividing its lobules. As it proliferates, its lower portion possibly differentiates into cartilage of a fairly mature type. This in turn in its deeper layers undergoes the same type of ossification, albeit more slowly and less regularly, as does the epiphyseal plate.

Without categorically denying its possibility, we cannot, however, unreservedly accept the view that this new growth is the work of embryonic cartilage cells in the tendons. The cells described by Geschickter and Copeland are indeed to be seen, but their assignment to the category of cartilage rather than to that of a less differentiated connective tissue appears to be an assumption which can neither be supported nor contradicted on the basis of existing histologic methods. To many, certainly, the matrix and cells of the envelope of an osteochondroma have the appearance of non-specialized connective tissue or mesenchyme. It also seems extremely doubtful that the absence of a continuous well defined periosteal sheath is of importance in permitting the formation of these tumors. Bone does not and cannot, of itself, spread outward; on the contrary, it is the passive result of the activity of its surrounding periosteum and enclosed endosteum. An intact soft membrane, moreover, can prevent the invasion and passage of a benign tumor, not its formation and growth. The relative rarity of this disease in the carpus and tarsus, where periosteal discontinuities are numerous and tendinous attachments not wanting, would seem to militate against this portion of the hypothesis.

Elsewhere in their book, speaking of the multiple osteochondromata, Geschickter and Copeland reaffirm the theory of unequal growth. They assign to the nodules a derivation from foci of perichondrium presumably persisting in the periosteum. (The involvement of the pericranium, with the production of ivory exostoses, in some generalized forms of the disease is certainly not
favorable to this point of view.) Failure or lag of periosteal development is assumed by them to cause insufficient thickness of the cortex. "In addition, the envelope formed by the periosteum is insufficient, resulting in a failure to act as an efficient limiting membrane to growth of bone. Failure in this function leads to widening of the metaphysis and irregular protrusions through points of defect in the periosteum."

So far as the writer is aware, there is no particular warrant for ascribing a growth-limiting function to the periosteum. Indeed, it is difficult to see how the periosteum, being a non-rigid tissue, could oppose unlimited bone growth—even were it not known that one, at least, of its functions is the promotion of bone growth rather than its repression. As remarked above, tumors may fail to penetrate a membrane, but they grow nevertheless, pushing the membrane before them.

It is difficult to understand how the observations of Müller (55), published in 1913, have failed to occupy the prominent place which is their due. He performed a complete autopsy upon a twenty-six-year-old male with multiple tumors and a familial history of the disorder. He describes and beautifully illustrates in colors many islets of cartilage formation in and by the periosteum, the deeper layers of which separate them from the cortex. Intraperiosteal ossification is proceeding at the same time and closely related in space. Transitional zones between spindle cell and cartilage, spindle cell and bone, and cartilage and bone, are seen. Müller stresses the point that marked anomalies of the epiphyseal plate are not recorded in these cases, thus indicating that they could not have given rise to the tumors. More decisively, he calls attention to the appearance of tumors before the onset of ossification—even congenitally—thus definitely ruling out the irregularities at the proliferating plate. He regards the origin of the disease therefore as being in the periosteum—at least, so far as the tumors are concerned. Conclusively, he calls attention to the presence of tumors even at the non-epiphyseal ends of metacarpals, metatarsals, and phalanges in his own and others' cases.

It must be admitted that there is one feature of Müller's presentation which is at first sight difficult to reconcile with the rest. Upon the metaphyseal cortices he describes some very long, thin layers of cartilage, which are not typical of the disease. Chiari (56) reports similar formations in groove-like depressions of the cortical surfaces. They could, however, have arisen in periosteum like Müller's other nodes, and have been subsequently outgrown by the adjacent surfaces of the expanding shafts.

Ehrenfried (57) has come forward with a resected epiphysis of a more typical case. In this, "the process of cartilage cell proliferation, instead of being orderly, with an orderly zone of calcification, is exceedingly irregular. The growth of cartilage is excessive. . . . Scattered along in the thickened and hyperactive periosteum of the end of the shaft are to be found clumps or nests of cartilage cells, persisting uncalcified where they were left in the process of growth. These groups may develop later into cartilaginous exostoses or chondromas." Were these cell nests the remains of epiphyseal growth, as he implies, or were they a heterotopic formation, like those of Müller and, probably, Chiari? And could not the irregularity of growth in the plate have been the result of altered statics in a deformed shaft? In a photomicrograph, a
subperiosteal mass of cartilage is seen flush with the surface of bone and apparently without trabeculated fibrous tissue within itself. Some completely intracortical nodules are seen. Despite what he observes in the periosteum, Ehrenfried believes that enchondral ossification alone is involved, and that the membranous bones are always unaffected. Stocks, however, gives several cases to the contrary.

Before elaborating a comprehensive theory of the pathogenesis of multiple osteochondromatosis, it may be advisable to eliminate a serious stumbling-block. Reference is made to the enchondromata which are not infrequently reported to be present in cases of multiple cartilaginous exostoses. As early as 1907 Pels-Leusden expressed himself as follows: “At any rate Ollier's growth disturbance and multiple cartilaginous exostoses are related diseases. In the former, cartilage production outstrips ossification; the cartilage offers abnormal resistance to the advancing marrow tissue.” The etiology was sought in faulty vascular development.

Jansen (54) went further than Pels-Leusden and considered enchondromata and multiple cartilaginous exostoses a single disease. Their genetics as analyzed show an intimate relationship. This phenomenon has been summarized by Stocks (27) in the following rules.

1. Multiple chondromatosis is a definite entity.
2. It is frequently associated with multiple exostoses.
3. This association is much more frequent in hereditary cases.
4. Hereditary association between the two diseases is so close that any admixture or cross-inheritance is possible.
5. Pure multiple enchondromata may be inherited, as such, through at least three generations.

As the writer has shown, in all cases of alleged hereditary enchondromata exostoses were associated either in the same person (in four-fifths of the cases) or in other members of the family. This would seem to speak strongly for the unity of the two processes. In 208 recorded cases of enchondromata without hereditary history, 58 presented exostoses also. The explanation for this is not as formidable as may appear. The fact is, that this supposed association is probably based on error. In none of the case reports which the author analyzed could he substantiate the presence of enchondromata in persons suffering from cartilaginous exostoses, the term “enchondroma” here being taken to mean a mass of cartilage within a marrow cavity, not attached to the epiphyseal plate. If this definition be accepted, the association of these tumors with cartilaginous exostoses in the same patient may readily be disproved. In some cases, such as that of McGavin (58), the simple assertion of their presence is made, without picture, description, or submission of other evidence. In other instances, such as those recorded by Griffiths (59), Tuffier (60), and Turner (61), a careful study of the descriptions leads to the conclusion that the so-called enchondromata were in point of fact merely additional osteochondromata. The lesion in Braune’s case is rather difficult to interpret. It was certainly not an enchondroma, but may possibly have been a chondroma of the lower epiphyseal plate of the tibia. The cases of Fischer (62) and of Gangolphe and Gabourd (63) were actually ecchondroses or ecchondromata—that
INTER-RELATIONSHIPS OF THE OSTE_GENIC TUMORS

is, cartilaginous tumors arising from the perichondrium of the ribs. The
tumor referred to by Marle (64), studied and described after an autopsy by
Virchow, was reported as an enchondroma, but not by the latter. The carti-
laginous mass lay within and slightly raised above the surface of the cortex
of the humerus. This is evidently the same structure as found by Chiari and
referred to above.

The case for the existence of enchondromata and exostoses in different indi-
viduals of the same line of inheritance rests on no better evidence. Fischer
and Langmead, it is true, reported the occurrence of enchondromatosis in per-
sons with a familial history of exostoses. But in Fischer's (62) case the al-
leged enchondromata, of the fingers, "were movable, and could have originated
in the tendons." He had "no more exact data. An operation was not per-
formed." It seems fairly clear that whatever else these lesions may have
been, they were certainly not enchondromata. Langmead (65), in discussing
a paper of Turner's, spoke of the son and two nephews of a patient with exos-
toses as being afflicted with enchondromata. The exostoses, pictured by
Pepper, were certainly genuine; the reference to enchondromata, however, is
supported by no description and doubtless represents the loose diction of a
careless moment.

It is Müller's report that gives most insight into the pathogenesis of the
lesions. They may be considered as the result of a congenital hereditary
diathesis, by virtue of which periosteum has a tendency to differentiate and
produce islets of cartilage on the basis, presumably, of a return to its em-
byronic function, and bone on the basis of its ripened activity. Where this
embryonic function is not found—as in the case of many of the bones of the
skull—cartilage is not produced. Here bone alone appears.

Throughout the growing years the osseous and cartilaginous tissues of the
body are subjected to the influence of growth hormones and react accordingly.
This would understandably be as true of the heterotopic islets of bone and
cartilage just described as of the more normal structures of the same composi-
tion. We see, accordingly, the active growth of these tumors in youth and
their quiescence in adult life. In the later years they may undergo resorption,
in accordance with Wolfe's (66) law, or malignant change like any other ec-
topic tissue.

The next problem to be solved is that of the architecture of the lesions.
Their remarkable mimicry of epiphyseal growth has been the chief argument of
those who derive them from that structure. The morphology, however, is
otherwise explainable. It has been shown by Jacobson (67) that the same pic-
ture can appear in fracture callus remote from any epiphysis. He was also able
to produce it experimentally on a metaplastic basis by transplanting urinary
mucosa into rectus muscles of dogs. Bone and cartilage made their appear-
ance, and sometimes enchondral ossification was demonstrable, leading to the
conclusion that the epiphyseal plate morphology, characteristic of osteochondro-
mata, is not specific to these structures. It was suggested that the alignment
of cartilage cells with reference to a cartilage-bone interface, and the resorp-
tion and replacement of cartilage by adjacent bone, represent a mutual reaction
of these two tissues, invoked whenever they are actively proliferating in close
juxtaposition. If this theory be correct, it explains how the islets of cartilage
and bone forming in the periosteum, as described by Müller, can grow and assume the characteristic architecture of an osteochondroma under the influence of the metabolic stimuli of youth.

Some writers who espouse the growth plate theory make much of the fact that most of these tumors occur toward the ends of shafts, on the metaphyses. In fact, the gradient of activity applies even more exactly. The ends of a long bone grow with different speed, and the frequency of osteochondromatous involvement follows this proportionate activity fairly closely. Digby, quoted by Stocks, states that for the humerus the percentages of growth are, for upper and lower ends, 81 and 19 respectively. The corresponding incidence of exostoses is approximately 83 and 17. For the radius the figures for growth are 75 and 25 per cent; for exostoses, 83.3 and 16.7. In the ulna the growth figures are 81 and 19 per cent; those for exostoses 71.3 and 28.7. The femur, tibia, and fibula are not assigned any figures for growth, but they are known to grow most actively at the knee. The percentages of affection at the knee are 75.6, 60.7 and 47.2 respectively. The fibula behaves anomalously in many ways. While these figures are given for the generalized type of the disease, the solitary osteochondromata show a similar distribution.

This point, however, constitutes inadequate evidence for epiphyseal derivation. The distribution of the lesion can be accounted for by a simple law. It has been shown by Jaffe (68) that bone tissue is not uniform in its metabolic characteristics, but that it responds unequally to the application of generalized stimuli. Thus the metaphyseal regions react far more strongly than do epiphyses, diaphyses, or the round bones of carpus and tarsus. In hyperparathyroidism, nutritional osteoporosis, phosphorus osteosclerosis, or acidotic decalcification, for instance, the fastest growing areas may be the only, and are always the most severely, affected ones. It would be very natural, therefore, for a diathesis toward such a periosteal dysplasia as has here been hypothecated to reach its maximal expression in the most rapidly growing and metabolizing regions.

Whether or not these exostoses are to be considered neoplasms is largely a matter of definition. Some of them, even in the multiple form of the disorder, make their appearance after the period of active growth. This certainly suggests neoplastic behavior. Others again, regardless of their time of establishment, will suddenly embark upon a growth venture that may even carry them into frank malignancy. It would seem, as pointed out in a previous section, that we are justified in considering sporadic and solitary osteochondroma as an entity quite distinct from multiple hereditary osteochondromatosis, with, possibly, a different etiology and pathogenesis. The occurrence of the isolated lesions does not coincide so generally with the growth period of the host. While this observation is open to some question, there are nevertheless indications that, despite a striking similarity to the multiple lesions, different factors may be involved.

The solitary osteochondroma may occur at any point in the skeleton with the exception of the membranous bones. If, however, its distribution were an even one, it would constitute a violation of the rule which has been stated above as applying to the activity of bone; in point of fact its distribution is in excellent correspondence with that rule. Among 262 cases of this disease re-
ported by Geschickter and Copeland, the great majority affected the meta-
ephysial region, one third of all being at the knee-joint. There were none in
carpus or tarsus, with the exception of three cases affecting the calcaneus, and
these cannot be considered tarsal within the meaning of the foregoing rule,
since the calcaneus is in its developmental history a long, rather than a round,
bone—that is to say, it develops as a shaft with a metaphysis and a separate
epiphyseal.

Meyerding reports 265 osteochondromata in 232 patients—the vast ma-
jority thus obviously solitary tumors, though his data do not permit the dis-
tinction. There were four in the diaphyses of long bones, 4 in the carpus, 26
in the “foot,” and 12 in the facial bones. The rest, except for 2 in the ver-
tebreae, were in the metaphyseal-epiphyseal regions (he does not discriminate).
Edington reports 7 cases, all metaphyseal.

For the solitary tumors, Bisgard’s experimental production of osteochon-
dromata is very suggestive. Besides this, Stocks refers to Latour (69) as
quoting Dor to the effect that the latter succeeded in producing such lesions
experimentally and concluded that some of these tumors are of inflammatory
origin. Neither of the latter papers was available to the present writer.

It is certainly difficult to deny that some of the isolated lesions which ap-
pear in childhood may be traumatic derivatives of the epiphyseal plate, but
this hypothesis will not adequately account for those which occur in later life.
Here we must fall back, provisionally at least, on the hypothesis of a neoplastic
proliferation of a focus in the periosteum with subsequent differentiation into
cartilage and bone, and ensuing growth.

Ivory Exostoses (Osteomata): In the case of the bones which owe their
origin to a process of intramembranous ossification, the activated periosteum,
even when neoplastic, pursues its embryonic function and forms bone through
the intermediation of fibrous and osteoid tissue rather than cartilage. The
osteomata of the skull are properly so-called, being devoid of cartilaginous ele-
ments; whereas the corresponding lesions of the endochondrally formed skele-
ton are rarely completely osseous, and then only at a very late stage, after
complete replacement of the original cartilaginous cap. Even in the skull,
only those bones and portions of bones which are of membranous origin give
rise to true osteomata, the other bones and parts of bones being the seat of
osteochondromatous tumors. Of 771 osteomata of the skull tabulated in
Stocks’ monumental work, 86 per cent were solitary. None of the patients in
the series had any relatives similarly affected.

Virchow quoted Boerhaave and Pallas as holding that some non-carti-
laginous exostoses are formed by the bone lamellae proper. He was willing
to grant that a minority could be so formed, but regarded the periosteum as
their main source. We know today that only the latter hypothesis is possible.
It is not quite definite just what growths Virchow had in mind, since in a
separate section he referred to the solitary ivory exostosis of the skull.

The ivory exostoses usually appear in childhood, when the periosteum of
calvarium and facial bones is still subject to the influence of the growth hor-
mone. No histological descriptions in the stage of inception are known to the
writer. Whether the lesions arise as subperiosteal or intraperiosteal condensa-
tions is a matter of conjecture.
It is surprising that the periosteum of the non-membranous bones does not more frequently form non-cartilaginous exostoses. In point of fact, however, they are exceedingly rare. Cobbold (70) mentions one of ivory consistency on the tibia. This is in connection with a case of alleged hereditary enchondromatosis. The non-cartilaginous nature of the tumor, however, is doubtful, at least at the time of its origin.

**Osteoid Osteoma:** The endosteum of the marrow cavities of bones is, like periosteum, possessed of proliferative, and therefore of neoplastic, power. Virchow discussed enostotic bony tumors extensively. He pictured one in the tibia of a young child, and quoted other cases but stated that they were rare. Many bony tumors of the orbit are included by him under the heading exostoses. Cornil and Coudray described what they considered a medullary osteoma in the lower end of the humerus. They published no photomicrographs, but to judge from their description they were certainly dealing with some sort of ossifying nodule and not with giant-cell tumor. Some of the cases described by Phemister and Grimson (71) as "fibrous osteoma of the jaws" probably belong with this group. Their description, however, does not permit us to differentiate with certainty between external (periosteal) and internal (endosteal) tumors.

The appearance of Jaffe's (72) paper in 1935 made it evident that the existence of an important and not infrequent tumor had, except for a few observations such as those mentioned above, been completely overlooked. He presented a series of lesions arising within bones. These manifested activity and proliferation of spindle-shaped cells, accompanied by cells of the epulis type, with the production of osteoid tissue and of bone. The tumors were in all cases benign and usually occurred in young people. Subsequent work on the part of Jaffe (1940) disclosed that the disease was even more frequent than he had at first thought and that, interestingly enough, it lay at the basis of most, or possibly all, cases diagnosed as Garré's sclerosing osteomyelitis. The lesion obviously follows the embryonic course of endosteal activity, and the endosteum almost inevitably appears as its parent tissue. It is conceivable that a metaplastic tumor of the medullary stroma may sometimes be involved.

**Osteogenic Sarcoma:** According to the varying potentials of the skeletoblastic mesenchyme, its tumors theoretically may differentiate into cartilage, bone, or both. Accordingly, three types can be expected.

1) Chondroplastic Type: In a few sites perichondrium persists throughout life. Such perichondrium has never had ossification for its function; if it forms a malignant tumor, therefore, only spindle-cells and cartilage result from its activity. The articular cartilages have only a low power of proliferation; if they have produced malignant tumors, this is unknown to the writer. The costal cartilages are more active and may be the site of benign and malignant cartilaginous tumors. The reports in the literature are for the most part not clear, and it is difficult to tell whether the latter cases represent chondrosarcoma arising from cartilage cells directly or an osteogenic sarcoma of the cambium layer of the perichondrium. In the former case cartilage cells should be the essential constituents of the tumor; in the latter, these would be the relatively inactive products of spindle-cell proliferation and differentiation. Descrip-
tions of cancerous tumors of this region generally speak only of cartilage cells as against spindle cells; and indeed these tumors seem generally to be secondary to benign cartilaginous growths. A spindle-cell chondroplastic sarcoma of perichondrium is not easy to identify in the literature. Histologic findings cannot be accepted at face value; many writers are prone to characterize the more primitive cartilage cells of chondrosarcoma with the careless designation "spindle cells." Most do not go into such detail. Even published photomicrographs are seldom clear enough to permit the differentiation. Such tumors as here discussed are probably rare.

(2) Variable Type: The investing membrane of the enchondrally formed bones appears in fetal life as perichondrium and fulfils a function of chondrogenesis for a variable period of time. Thereafter, and for most of the growth period of the individual, it is known as periosteum and produces bone. Inherently, then, its cambium layer has this double potential, but ordinarily chondrogenesis is inhibited. With a stimulus, such as fracture, which brings about a recrudescence of more primitive functional demands, both cartilage and bone formation may occur. Neoplasia represents a still more primitive state. (That a few cells have retained their embryonic character from the first, is conceivable; but why then would we lack signs of their activity in such rapid proliferative processes as periostitis, subperiosteal hemorrhage, etc.?) It is to be expected, therefore, that in these tumors at least three kinds of cells might occur. These are (a) the unmodified spindle cells, (b) cartilage, and (c) bone. The first, being the active element of the tumor, proliferating and differentiating, would necessarily appear in any case. The other two might appear separately or in variable combinations.

In point of fact, this is exactly the condition that is found to obtain. In all osteogenic sarcomata of the enchondrally formed bones, spindle cells form the substrate of the tumor and constitute the basis of its histological diagnosis. In addition, some of these neoplasms manifest ossification, some chondrification, and some a combination of both processes.

Here again Geschickter and Copeland seem to complicate the situation unnecessarily. They present two entities—a "primary chondrosarcoma" and a "sclerosing sarcoma," an osteoplastic or mixed tumor. The former they somewhat arbitrarily derive from the same hypothetical embryonic cartilage cells which they incriminate in the histogenesis of osteochondroma. They concede the periosteal origin of the second. On the basis of their own data, there is little reason to separate these types. In both, as against chondrosarcoma, the spindle cell is the essential and constant constituent, and the parent of the other two. The curves of the age incidence can be superimposed with remarkable exactness, the anatomical distribution is almost identical, and the clinical courses are similar. The only observable difference is in the end-results—6 five-year cures among 52 pure cartilaginous tumors and 17 among 65 of the mixed or pure bony type. This is not outside the limits of probable error, and seems significant, at most, of a greater tendency to malignancy in those cases whose morphology follows the more primitive pattern.

In the experience of the writer it is difficult to exclude sharply the osteoplastic from the chondroplastic varieties of periosteal malignancy. Different areas of the same neoplasm show different pictures, and the impression is
gained that the osteogenic sarcomata will fall into a continuously graded series rather than into two sharply demarcated types.

Other writers who have surveyed fairly extensive material—Kolodny, Ewing, Stout, Sabrazès, Jeanneney and Mathey-Cornat (73)—have apparently not been able to segregate a group of purely cartilage-producing spindle-cell sarcomata of periosteal origin.

(3) Osteoplastic Type: The endosteum of the enchondrally formed bones and both the endosteum and the periosteum of the bones of intramembranous ossification have never, at any stage of ontogenesis of the individual, had any chondroblastic function. Their histogenetic ability in neoplasia is therefore restricted to ossification.

Kolodny feels that the assignment of central versus periosteal origin to a bone sarcoma rests on very uncertain grounds. He may be a little overcautious; if so, he errs on the right side. On the other hand, there are amputated specimens which give a very definite impression of periosteal or of central origin.

Again referring to Geschickter and Copeland's compilation of material, one cannot but be impressed by the fact that none of their cases of "osteolytic sarcoma" manifests chondrogenesis. This speaks well for the validity of their distinction between these and the periosteal tumors. It is supported on the theoretical basis outlined above. On the other hand, the writer is not disposed to accept all of their cases in this category. It may be that they overemphasize the resorptive functions of the endosteum, forgetting that it produces much of the bony substance. They overlook, also, the remarkable power of proliferation and even differentiation of the stroma of the marrow cavity. It is impossible to be dogmatic about individual cases. It would seem, however, that some of their undifferentiated spindle-cell tumors of central origin probably arose in the delicate connective-tissue frame-work of the marrow and are perhaps to be considered medullary fibrosarcomata. Those growths that were noticeably osteoblastic are fairly assignable to the endosteum.

The age incidence of this class of tumors agrees well with that of the other osteogenic sarcomata. As with them, the curve has its peak in the fourth five-year period of life, but declines less sharply during the years thereafter. An explanation for this is to be found in normal anatomy and physiology. With cessation of growth the work of the periosteum is largely done. Only in response to a considerable insult does it resume activity. The endosteum of marrow cavity and canals, however, is to a much greater extent continuously on the "qui vive." It is constantly resorbing and rebuilding in response to subtle metabolic stimuli. The stimuli—whatever they may be—to malignant neoplasia would not unnaturally awaken a sharper response in an active than in a resting tissue.

Osteoplastic sarcoma of the endosteum favors the same bones and the same parts thereof as do the other osteogenic sarcomata, in obedience to the same gradient of activity.

The investing membranes, inner and outer, of the cranial bones are in analogous case to endosteum elsewhere. Only in the enchondrally formed parts of the skull can cartilage be expected, on theoretical grounds, to appear; and in practice it meets this expectation. Elsewhere in the skull malignant neo-
plasia of the skeletoblastic mesenchyme results in an osteogenic sarcoma of spindle cells and bone, but not cartilage. This tumor, embryologically and histologically identical with the last, is included in the same group. Its age incidence agrees well with theirs. Its prognosis and course are similar.

Giant-Cell Tumor: In the epiphysis, the most active tumor ordinarily encountered is the so-called giant-cell tumor. This entity and morphologically similar ones have long been a storm center among oncologists. Some have maintained, and others as stoutly denied, that the disease is deservedly classed with the neoplasms.

Konjetzny (74) speaks eloquently for the proponents of the dystrophic theory. He first presents cases of localized intraosseous hemorrhage. Microscopic studies show that giant cells of the epulis type are part of the reactive picture. He believes that such cells result wherever hemorrhage occurs in bone, and from this point goes on to develop the genesis of bone cyst. He thinks that an original hemorrhage, secondary even to an inconsiderable trauma, causes pressure due to the presence of effused fluid in a confined space, with erosion of bone. Further hemorrhage and further resorption ensue. The characteristic expansile thin-walled cyst results. Konjetzny's illustrations strongly support his view that the epulis cells are of endothelial origin. He then turns his attention to giant-cell tumor, which he regards as a variant of the same lesion, characterized by somewhat more reaction. He protests vigorously against the view that such lesions are blastomatous. Had he used the adjective malignant, instead, his arguments would carry more weight; for it is the criteria of malignancy which, he points out, are lacking in the giant-cell tumor.

An authoritative pronouncement on the neoplastic nature of the giant-cell tumor is extremely difficult. As Lubarsch has stated, there is no adequate definition of a neoplasm. Even if Konjetzny's hypothesis as to the etiology of the growth be accepted, that does not automatically exclude it from the category of the tumors. If the disease were a mere response to trauma, we would expect it to preponderate among males, who are more exposed than females to industrial accidents. Actually, the incidence is slightly higher among the latter. Mallory's comparison of the enlarging propensities of giant-cell tumor to those of an aortic aneurysm would more appropriately apply to the expansile characteristics of large bone cyst. This the writer considers a relatively passive response of bone to hemorrhage and resorption, and quite distinct from typical giant-cell tumor.

Pommer (75) has a different point of view. To him, the giant cell is the essential constituent of the lesion; and this he derives from the osteoclast. Geschickter and Copeland, admitting this to the role of the new growths of bone, follow Pommer and conclude that "the giant-cell tumor and the related lesion of bone cyst are the result of an abnormal hyperplasia of osteoclasts."

This concept would seem unsatisfactory on several grounds. First, the identification of the epulis type of giant cell with the osteoclast has nothing to recommend it beyond their common possession of a plurality of nuclei and their consequent larger size than mononuclear cells—characteristics which they share with several other and presumably unrelated cell types. Otherwise, the epulis cell is much larger and rounder than the osteoclast, and possesses far
more nuclei (15 to 200, often, as against a usual 6 or 8). The two are quite
dissimilar under the microscope. Nor is any convincing evidence presented
to support Geschickter and Copeland's contention that the epiphyseal osteo-
clasts have come through the cortical shell, even if some have done so. On
the contrary, there is not an area in the skeleton where osteoclasts may not
be observed to arise in large numbers in response to functional demand. In-
deed, they occur physiologically in the metaphyses on a large scale. Never-
theless, giant-cell tumor is more or less sharply restricted to the epiphyses.
Furthermore, if this be a unique neoplasm of the giant cells, how explain their
frequent occurrence and, in places, even dominance of the field, in such other
entities as osteogenic sarcoma, hyperparathyroidism etc.? Finally, the ascrip-
tion of paramount function in even pathological histogenesis to a giant cell
does not altogether coincide with the pathologist's concept of the nature and
fate of such structures. True, we no longer believe—thanks to the work of
Levine (76) and others—that the giant cell is to be regarded as a degenerative
manifestation, incapable of mitosis; as Levine himself states, however, division
of a giant cell has not been observed, and the epulis cells certainly do not con-
spicuously reproduce. To their assumption of the basic rôle in normal or
malignant histogenesis, a rôle usually played by a more or less embryonic type
of cell, is still a far cry.

Goforth (77), probably nearer the truth, regards the giant-cell tumors as
true neoplasms of fibroblasts. If we substitute for the word fibroblasts,
"spindle-cells," which in general usage is practically its equivalent, we have
characterized osteoid-osteoma, osteogenic sarcoma, and giant-cell tumor with a
single expression. Goforth too, incidentally, falls into what is here regarded
as the error of seeing the giant cells as osteoclasts, anatomically and func-
tionally. He does not regard them as neoplastic cells, however.

According to the thesis enunciated in the first part of this communication,
it would seem that the same tumor should occur wherever its parent cell is
found. This is not to say, however, that it cannot be modified by local factors.
And in fact, as we have mentioned above, there are inherent local factors whose
influence upon the activity of bone tissue is most profound. It would be most
surprising if the tumor known in the epiphysis as giant-cell tumor showed
the same degree of activity outside of that area; or if a different degree of
activity were not accompanied by altered gross and microscopic anatomical
manifestations.

The writer believes that the neoplastic manifestations of the endosteum
may be arranged in a graded series. Entirely benign is the osteoid-osteoma.
The more malignant developments are composed of the same elements—
spindle-cells, osteoblasts, osteoid, bone, and giant cells. If the lesion arises
in a region of low metabolic activity, such as the epiphysis, it appears in rela-
tively restrained form as giant-cell tumor; if in a region of high metabolic
activity, such as the metaphysis, the frank malignancy of an osteogenic sar-
coma is the result.

There seems to be a transition from giant-cell tumor to osteoid-osteoma.
Under the general heading of giant-cell tumor variants a number of lesions
have been reported—one in Geschickter and Copeland's textbook, one (the
last) in Pommer's series—which perhaps belong near, if not in, the latter group.
Let us assume an endosteal tumor which is more active and somewhat less completely self-limited than osteoid-osteoma. Its essence would be the spindle cell. More primitive than the other, it would have less tendency to differentiate into osteoid and bone. Being more active, it would be more invasive and destructive, and would evoke much more hemorrhage; in fact, in the enclosed trabecular mesh of an epiphysis, the hemorrhage and the reaction thereto might come to dominate the picture. At the same time, being in and of the relatively sluggish epiphysis, the tumor would not break through the cortex and exhibit the unrestrained proliferation and wild histopathology of an osteogenic sarcoma.

The giant-cell tumor possesses the self-same cellular constituents—spindle cells, bone cells, small ovoid cells which have been likened to osteoblasts, and giant cells of the epulis type—as does the osteogenic sarcoma. In osteogenic sarcoma we may have the predominance of spindle cells, of giant cells, or of bone, and differing degrees of vascularity; in giant-cell tumor we may have, in identical fashion, the predominance of spindle cells, of giant cells, or of bone, as Pommer's admirably graded series, or Kolodny's, demonstrates. The differential diagnosis between them, so far as their histopathology is concerned, rests on only one criterion, namely, the relatively benign or relatively malignant appearance of the spindle-cells. It is urged, therefore, that the two tumors are manifestations of the same disturbance, modified by the differing levels of metabolic activity prevailing at different sites of bone formation. As Renner (78) points out, even the ossification in giant-cell tumor can be shown to be true tumor formation, and not such purely reactive bone formation as almost any soft tissue may stimulate in bone.

The difference, moreover, is not absolute. All transitions and intermediate forms between the two neoplasms occur; not only is the experienced pathologist occasionally hard put to it to assign a new growth to one or the other category, but accounts of so-called malignant giant-cell tumor, long regarded with skepticism, can no longer be ignored. They have been published by King (79), Freeman, Kinney and Moore (80), Korchow (81) and others. The writer has seen two or more neoplasms which he has been compelled to admit to this status. Furthermore, tumors of the shaft occur which partake of the nature of giant-cell tumor. Konjetzny himself includes a case of what is clinically and anatomically giant-cell tumor arising in the shaft of the fibula. (The fibula, it is true, is a somewhat anomalous bone in its behavior, being in some respects less reactive than others). Other observers have found giant-cell tumors in a metaphyseal location.

In the reaction against the name and conception of "giant-cell sarcoma," the idea of benignity of this neoplasm has been somewhat overdone. The tumors grow slowly and continuously, with destruction of the organ of origin. Many cases at least may be considered locally malignant. They have certainly more claim to that appellation than basal-cell carcinoma, for instance, being responsible for far more mutilations and deaths. Metastases have been known, as pointed out above, and aside from this, the neoplasm almost regularly shows a progressive growth in which it compares very unfavorably with definitely benign lesions. If it be objected that the more malignant tumor should not show more osseous differentiation than the less, it can be pointed
out that osteogenic sarcoma of apparently central origin has a relatively poor osteoplastic tendency while in that location.

The non-appearance of giant-cell tumor in the calvarium is an argument against his theory which the writer cannot answer.

The epulides of the jaw are likewise a most interesting group. Although many have considered them inflammatory granulomas, their appearance is in favor of a close relationship to the foregoing class. Geschickter and Copeland, indeed, consider them identical, and, carrying out their prior point, attempt to show that only such parts of the skull give rise to epulis as are of enchondral, rather than intramembranous, ossification. With the concept of the identity of the two tumors the present writer is in hearty agreement.

**Bony and Cartilaginous Tumors of Soft Tissue**

Our theme may be pursued still further through the supportive tissues of the body. The same osteoplastic and chondroplastic potentialities in kind characterize extra-skeletal connective tissues, but the potential here is of very low degree. It comes to expression in the formation of a parosteal callus and in the various metaplastic productions of cartilage and bone. Seldom do heterotopic ossification (or chondrification) and neoplasia coincide, but when they do, a tumor of the same general characteristics results.

At one end of the series are those which are morphologically and clinically similar to osteogenic sarcoma, such as Greenspan's (82) osteoid chondrosarcoma of the lung or Broders and Pemberton's (83) osteogenic sarcoma of the thyroid. (The former of these might in a sense be considered, with reference to the cartilaginous framework of the bronchi, not truly heterotopic.) After these may be ranged the more malignant appearing, and perhaps truly neoplastic, cases of myositis ossificans. The osteoblastomas of Rhoads and Blumgart (84), Ferrero (85), Speciale (86), Marziani (87), and Pecco (88), all in soft tissue, but not that of Lubarsch (89) in the tibial marrow, probably come within this classification, as do the bony and cartilaginous mammary tumors reported by Jaki (90) and others, which are so common among bitches. Two giant-cell tumors of the cervix uteri (one of which should be considered a sarcoma, since it metastasized to the lung) came under the observation of Kotzian (91), while two others of more benign type, corresponding to giant-cell tumor and osteoid-osteoma, in the muscles, were seen by Jacobson (92). Leiner (93) published a case of osteochondral tumor of the back. The author has also seen large chondromas, simple and recurrent, of the ankle and of the gluteal muscles.

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