TUMOR SEMINAR COLLECTION

SET III

Tumor Seminar, Columbia, 1947, Shields Warren

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Conducted by
SHIELDS WARREN, M.D.
BOSTON, MASSACHUSETTS

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TUMOR SEMINAR

Conducted by SHIELDS WARREN, M.D., *Boston, Massachusetts*

1. EMBRYONAL ADENOMA OF THE THYROID WITH BLOOD VESSEL INVASION

History (presented by J. Owen Blache, M.D., Homer Phillips Hospital, St. Louis).—For ten years previous to admission this 39 year old woman had noticed a non-painful mass in her neck which had increased in size during the year prior to admission. There were no subjective symptoms. The basal metabolic rate was +8. Physical examination was noncontributory. The mass was surgically removed for cosmetic reasons.

The specimen weighed 30 gms., measured 5 by 4 by 2 cm., and consisted of part of the thyroid gland, two thirds of which was apparently normal thyroid. The remaining one third was composed of an apparently well-circumscribed, encapsulated, grayish white, fairly firm mass. There was a break in the capsule of the mass and, on pressure, material similar to that of the tumor mass could be expressed.

SHIELDS WARREN, M.D.: The history is clearly presented and the gross shows a well delineated homogeneous grayish white tumor which is encapsulated and within the thyroid gland (fig. 1). With these adenomas, the appearance of areas of necrosis and degeneration is frequent. I would like to say that one of the many reasons that these are removed is that the patient comes in because of sudden increase in the size of the tumor and pain. In those instances, one finds considerable hemorrhage into the gland which is the cause of the pain. As this was thought by some to be a parathyroid adenoma, it should be pointed out that any tumor in the substance of the thyroid is practically never a parathyroid neoplasm. The cells of this embryonal adenoma are quite uniform, and one will note that there is a little hint of acinar arrangement occasionally, although true acini do not exist (fig. 2). The cords of the cells are well brought out in the arrangement of these nuclei and there is a hint that potential acini may appear later on. The cells are clear; there is no granulation or vacuolization in them.

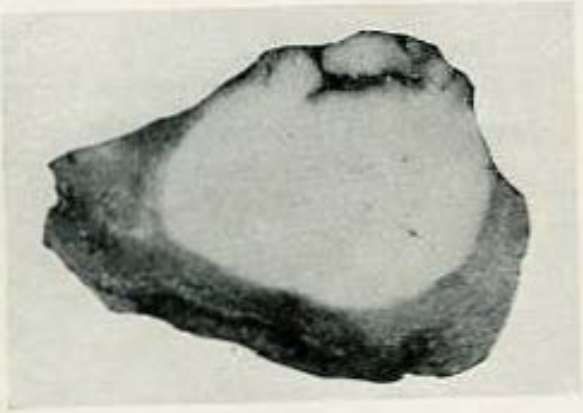

Fig. 1. Well delineated adenoma of the thyroid.

Now, in the parathyroid adenomas, one usually finds three types of cells: there may be oxyphil cells, there are practically always vacuolated cells sometimes going to the water-clear type of hyperplasia of the parathyroid, and also nonvacuolated solid cells. In the adenoma of the parathyroid, therefore, one would expect to find either some oxyphil cells which are not present here, or some vacuolated cells which I did not find here. The parathyroid adenoma without function is extraordinarily rare, just the reverse of the picture in the thyroid. Adenomas of the thyroid are rarely associated with hyperfunction. In the parathyroid they almost always are associated with hyperfunction. Here there is a carefully presented history which makes no mention of renal stone, repeated fractures, pain in the bones or anything that would suggest the characteristic syndrome associated with a functioning parathyroid tumor. So the weight of evidence, I believe in spite of the majority vote here, is against a parathyroid adenoma and

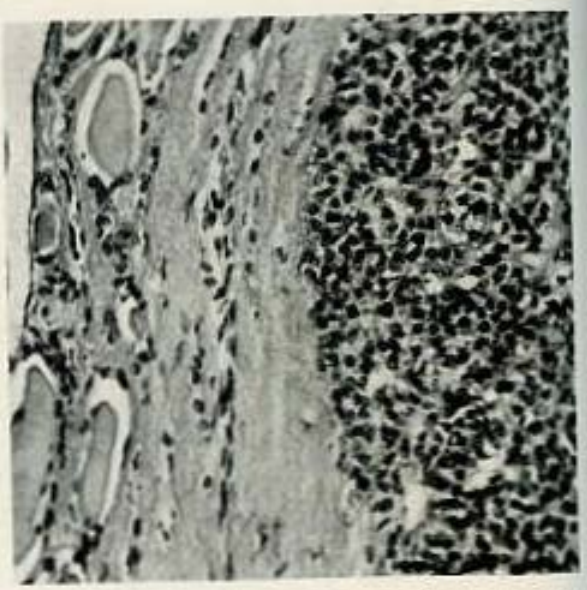

Fig. 2. Photomicrograph. Note sharp border between cellular tumor and fibrous capsule of adjacent collapsed thyroid. (Moderate enlargement.)

Assistant Professor in Pathology, Harvard University; Director, Division of Biology and Medicine, Atomic Energy Commission, Washington, D. C.

The Seminar was under the auspices of the St. Louis Pathological Society and held at the Ellis Fischel State Cancer Hospital, Columbia, November 22.

in favor of a thyroid adenoma. Assuming that it is a thyroid adenoma, one has to consider what type. There is practically no colloid formation anywhere in the tumor. I did not find any mitotic figures, which is in favor of an adenoma. The capsule seemed to me to be relatively intact. There are one or two places where it is thinned a bit, but not actual evidence of invasion. There are a number of large thin-walled blood vessels present, none of which show invasion, and I am extremely loathe to make the diagnosis without finding blood vessel invasion. I think that clue which Allen Graham emphasized is the most valuable single thing that one can have, and I am always worried about diagnosing a thyroid tumor as a malignant tumor unless I can find evidence of blood vessel invasion. The thyroid tumor always looks worse than it is. In fact, a hyperplastic thyroid looks much worse than it is, and a good many people have made the mistake of calling a hyperplastic thyroid a malignancy; but that is one of the places where many have laid themselves open to the attacks of individuals like Astwood who, thoroughly competent in their own field, have considered themselves competent to judge problems entirely outside their field. I think Astwood is doing little service to the clinicians of the country when he is as outspoken as he is about the relatively rare existence of malignancies of the thyroid because, if these cases of malignancy of the thyroid are not recognized and treated, one is going to lose a number of patients who otherwise could be saved. In this case there is not a question of malignancy. I believe that I would classify this tumor as an embryonal adenoma of thyroid origin.

DR. ACKERMAN: In this case, I think I misinformed you because multiple sections of the thyroid through the capsule revealed evidence of blood vessel invasion, although I believe there was no evidence of this invasion in the sections which were made for the Seminar. In view of this finding, would you mind commenting on the importance of blood vessel invasion regarding the future outlook of this patient.

DR. WARREN: In that case, the prognosis of an embryonal adenoma with blood vessel invasion is uncertain. This is a benign neoplasm which has become potentially malignant. I recall a tumor of the thyroid designated as potentially malignant, but twelve years after removal the patient had skeletal metastases. This proved that it actually was a malignant tumor originally. As far as one can tell from a ten year follow-up, 10 per cent of these tumors with blood vessel invasion metastasize. A considerable number of that group had had irradiation postoperatively. I think the chances are great that there is no tumor remaining in the neck of this patient, and I would say that irradiation is not indicated. If the capsule is not intact, and if there is a suggestion of penetration outside or adherence of the tumor to underlying structures, or thickened irregularity of the tissues in the region of the tumor, then I would say that the patient should receive postoperative irradiation.

DR. PLATT, Louisville, Ky.: I would like to ask Dr. Warren about the criteria of blood vessel invasion.

DR. WARREN: I am glad that you brought up that point. I feel that the tumor cells should be attached to the vessel wall by definite fibrin strands or be closely adherent to the intima. The mere finding of scattered cells or even clusters of cells is not sound evidence of blood vessel invasion. Not infrequently veins will be distended to the size of the little finger for a distance of 2 or 3 cm. away from the tumor. The parable of the soil applies definitely to the establishment of metastases. A good many of the tumor cells that are scattered around the body fall upon stony ground or are picked up by the vultures of the air, so to speak; that is, fibrin clot will form around them, there will be inadequate local aeration and the cells will die.

DR. JENKINS, Omaha, Neb.: Do you have the data, Dr. Warren, on how frequently there is malignant change in an adenoma. In other words, if you have 100 people with an adenoma, how often do you think they become malignant?

DR. WARREN: The only clear picture that I have is one that came from some rather old statistics which I am not sure are up to date; that was 0.3 per cent. That is a pretty low incidence and I am not at all sure whether that is right. I feel that every single nodule of the thyroid should be removed, first, second and third, because even an adenoma does not do anyone any particular good, and the operative risk is so slight that I think it is well warranted to remove any of these single nodules. It is stated that 95 per cent of thyroid cancers come from preexisting adenomas. How in the world that figure was arrived at I have never been able to find, and all I can say is that the majority of thyroid cancers which I have seen give a history of a preexisting nodule for a number of years.

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2. GIANT CELL CARCINOMA OF THE THYROID

History (presented by Shields Warren, M.D., New England Deaconess Hospital, Boston).—This 52 year old woman was admitted to the hospital on January 19, 1935, with a diagnosis of a malignant tumor of the thyroid. There had been rapid growth of the mass for two weeks previous to hospitalization, and physical examination at the time of admission revealed a greatly enlarged, stony hard thyroid. These changes were most prominent in the right lobe. The patient could speak only in a hoarse whisper, there was considerable stridor and she complained of difficulty in breathing. Roentgenogram on January 17, 1945, showed a 7 cm. mass in the region of the thyroid which occupied the anterior mediastinum, extended substernally and displaced the trachea and esophagus posteriorly and to the left. There was a marked degree of compression of the trachea, the narrowest point being at the level of the second thoracic vertebra. There was some calcification of the tumor. The findings were those of substernal thyroid with marked compression of the trachea. On January 21, at 9:15 p. m. she became unable to breathe and her color was poor. She was prepared immediately for operation and an emergency tracheotomy was performed. However, she expired at 10:19 p. m. the same evening.

The tumor weighed 300 gms. and was composed of yellowish gray tissue subdivided into lobules by fibrous trabeculae. In some zones it was homogeneous, smooth and shiny, and, in others, rather opaque yellowish white as though necrosis had occurred. A small amount of calcification was also present in the central portion, and only a remnant of normal thyroid tissue remained on the right. On the left, about half of the lobe was still present superiorly. No definite encapsulation was seen although externally the tumor mass was rather well circumscribed. No circumscription was noted in areas in which the mass infiltrated the thyroid tissue.

DR. WARREN: All are agreed that this is a malignant tumor. The margin of the neoplasm brings out the thyroid origin and the fact that one is dealing not with an encapsulated lesion, as in the preceding case, but with a lesion which is infiltrative and invasive. The tumor is extremely pleomorphic with great divergence from the normal in some cells, with vacuolated nuclei and the presence of spindle cells (fig. 3). In the higher power, one sees again the spindle shape of a number of cells, and often there are multinuclear irregularly lobulated nuclei (fig. 4). I do not believe that this could be a malignant endothelial neoplasm. There was some evidence of calcification of this tumor which might imply that the tumor had been growing for some time. This type of neoplasm was considered for a long time as a sarcoma. However, the tumor cells do not form collagen, and true fibrosarcomas are extremely rare in the thyroid. I would call this neoplasm a giant cell carcinoma of the thyroid.

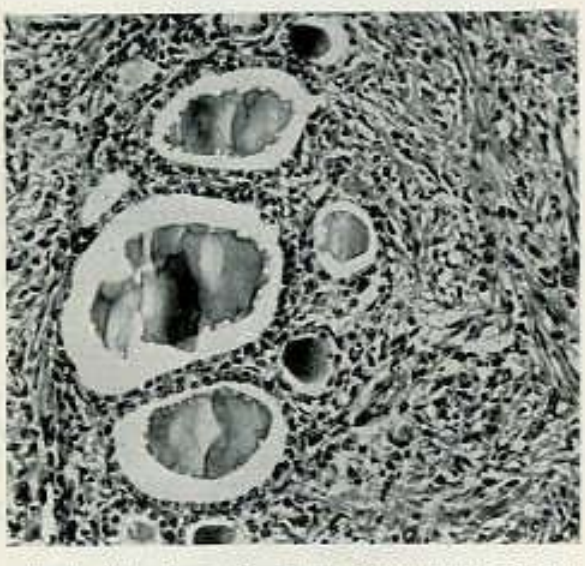

Fig. 3. Photomicrograph. Spindle shaped tumor cells are infiltrating thyroid follicles. (Moderate enlargement.)

Fig. 4. Photomicrograph. Note large cells with lobulated nuclei. (High power enlargement.)

DR. RABSON, Ft. Wayne, Ind.: What emphasis, Dr. Warren, do you place on the presence or absence of large nucleoli in the identification of epithelial tumors?

DR. WARREN: I do not believe that prominent nucleoli will help in determining whether a tumor is of epithelial origin or not. Some of the most prominent nucleoli are in Reed-Sternberg cells. By and large, though, there is a decided tendency for the nucleoli to be unduly noticeable in malignant cells. The Papanicolaou technic tends to emphasize the importance of the enlarged nucleoli as evidence of malignancy. In general, in reviewing these slides, there are no strikingly enlarged nucleoli. The absence of such nucleoli I would not regard as ruling out an epithelial origin.

DR. STOWELL, St. Louis, Mo.: I would like to ask Dr. Warren whether he thinks the size may be re-

lated to the rapidity of growth in a benign or malignant tumor; because three or four nucleoli can be made to appear within twenty-four hours in the same cell by merely markedly altering the conditions of its rapidity of growth and regeneration.

DR. WARREN: That is an interesting observation. One of the points that the older of you will remember was frequently made when Dr. McCarthy was trying to emphasize the nucleoli. He pointed out that the hepatic cell which was called upon to regenerate often showed prominent nucleoli.

DR. WHELOCK, Chicago, Ill.: Would value be placed on connective tissue stains in the differential diagnosis of a sarcoma of the thyroid, from a giant cell carcinoma?

DR. WARREN: I place a great deal of emphasis on the reticulin stains. If one finds that between each tumor cell there is a reticulin net or there are collagen fibers, or if each cell has fibroglia fibrils, then I believe that the evidence is fairly strong that one is dealing with a true fibrosarcoma of the thyroid gland. There have been only two or three of these tumors against eighty or one hundred of the giant cell carcinomas from the Lahey Clinic series.

DR. ACKERMAN: What has been the prognosis of the giant cell carcinoma?

DR. WARREN: The prognosis has been extremely poor. These tumors are completely resistant to irradiation and they do not do well with surgery. Only an occasional case survives and, while radical surgery should be attempted, not a great deal can be expected from it.

3. PAGET'S DISEASE OF THE SKULL WITH OSTEOGENIC SARCOMA

History (presented by Drew F. Agar, M.D., St. Louis City Hospital, St. Louis).—This 60 year old woman was admitted to the hospital on January 2, 1947, complaining of incoherent speech, pain in the head, blindness, inability to walk without support, inability to hear and dizziness. The onset of her illness was in July of 1946 when she began having nervous spells with episodes of pain in the head and the ability to see only half an object. Loss of vision of the right eye occurred at that time. In July of 1946 she was admitted to another hospital where a diagnosis of Paget's disease of bone was made. For two months previous to admission to this hospital she had had dizzy spells, had been unable to walk, could not eat properly because of inability to move the tongue, and loss of hearing began. There was also a history of marked enlargement of the head, especially in the frontal and temporal regions, beginning one year previous to admission. On physical examination there was enlargement of the forehead, with prominence of the frontal and temporal regions, opacity of the lens of the right eye and papilledema of the left eye. The blood Kahn was negative. Roentgenograms of the skull were interpreted as Paget's disease of bone. While in the hospital the patient was stuporous, respiration became labored, and rales developed in the bases of both lungs. The temperature rose to 104 F. on January 12, 1947, and the patient expired on January 13, 1947, with a clinical diagnosis of Paget's disease of bone.

At autopsy there was a mass of soft pinkish gray material extending from the region of the right posterior clinoid process posteriorly to the region of the cerebellopontine angle, at which place it was attached to the brain stem. A nodule was loosely attached to this mass but remained with the brain when the latter was removed. It did not infiltrate the brain and was lifted easily from the meninges. The slides were made from this nodule.

DR. WARREN: The majority opinion is for osteogenic sarcoma either alone or in association with Paget's disease. When one has an osteogenic sarcoma in an individual whose epiphyses have closed, he thinks automatically of two things: first, Paget's disease and, second, poisoning with radium or its related elements (Martland). I think that one has to remember that any local irritant which has been deposited in bone and remains there for a long time may stimulate the development of osteogenic sarcoma. In this particular tumor, Paget's disease provides an etiologic agent. This brings up a neat diagnostic point. Osteogenic sarcoma is one of several tumors in which study of the blood for its enzyme content may be helpful in diagnosis. If one has an elevated alkaline phosphatase, osteogenic sarcoma is one of the neoplasms to consider. However, in Paget's disease, in the active stage, a prominently elevated alkaline phosphatase also can occur. This therefore introduces a little complexity in the differential diagnosis. There are certain statistics which are of interest. In the first place, one should ask how frequently does Paget's disease undergo sarcomatous degeneration. These figures range from as low as 5 per cent to 14 per cent,

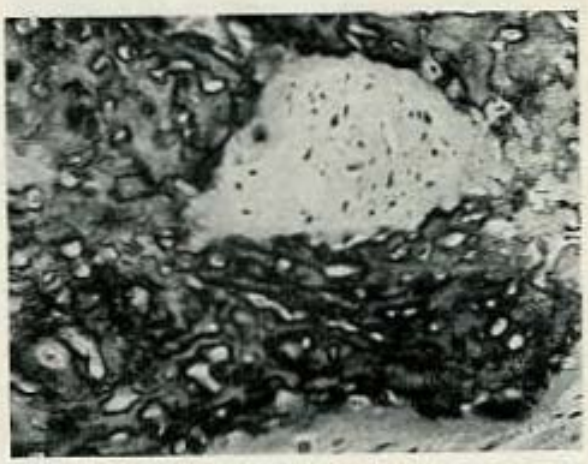

Fig. 5. Photomicrograph. Typical Paget's disease with mosaic pattern. (Moderate enlargement.)

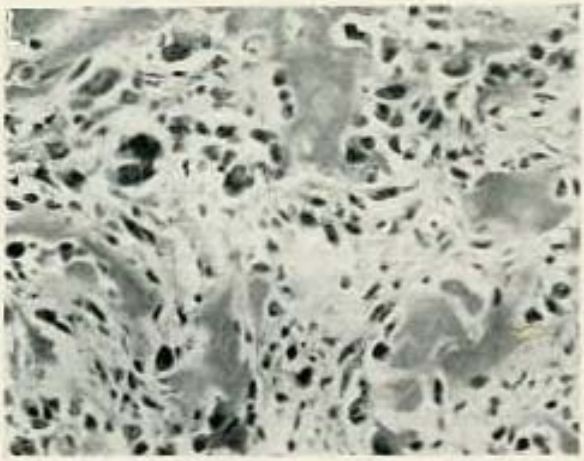

Fig. 6. Photomicrograph. Superimposed osteogenic sarcoma with neoplastic osteoid and sarcomatous stroma. (Moderate enlargement.)

and in one recent series the figure was 28 per cent. There are, of course, obvious reasons for this. In the first place, there is much more rapid formation of bone, greater osteoblastic activity; and in Paget's disease, the tissues may become actively growing after they have been quiescent, and this may be accompanied by an osteogenic sarcoma. The average age of sarcomas in Paget's disease is 66 years. The average age for osteogenic sarcomas as a whole is only 12 years, a very startling difference. Males are affected much more commonly than females, and in one series, there were eighty-four males and twelve females. The bones most frequently involved in the order of frequency are: femur, humerus and skull. The variety of tumor may differ; some of them are osteogenic, others arise from the periosteum and some are fibrosarcomas. The sections show both Paget's disease (fig. 5) and actively growing osteogenic sarcoma with neoplastic osteoid (fig. 6). This case, therefore, represents a classical example of Paget's disease of the skull combined with osteogenic sarcoma.

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4. ADAMANTINOMA OF THE TIBIA

History (presented by Bela Halpert, M.D., The University of Oklahoma Hospitals, Oklahoma City).—The patient, a 24 year old white woman, was admitted to the hospital on November 14, 1945, complaining of swelling of the mid and lower portions of the right leg. In August of 1943 she had fallen and struck her leg against a step. The painful area increased in size and in April 1944 she slipped on a marble floor and fractured her leg. After the cast was removed painful swelling of the leg followed. In October 1945 roentgenograms revealed a bone tumor and amputation was advised. Roentgenograms of the chest were negative. Before amputation, local examination showed a fusiform enlargement of the midportion of the right leg which extended to within 3 cm. of the ankle joint. The mass was firm and the overlying skin was tense, shiny and nonadherent. Roentgenograms showed an osteolytic mass which destroyed about 12 cm. of the distal shaft of the tibia. There was expansion of the bone cortex and only a thin shell remained. There was no bone proliferation. A midthigh amputation was done on November 17, 1945.

On section of the tibia, grayish white neoplastic tissue filled the marrow cavity and replaced the compact layer, extending through it into the soft tissues.

DR. WARREN: This case is one in which a variety of diagnoses have to be considered. Ewing's tumor is one of these. It used to be said that if one wanted to be sure a tumor was a Ewing's tumor, send the slides to Dr. Ewing and have him say it was something else. I do not know of any neoplasm over which there has been more controversy. It is a tumor concerning which little is known as to histogenesis even at the present time. The weight of evidence appears to favor origin from the primitive reticular cells of the bone marrow, but there is no agreement on this. In consideration of the diagnosis of Ewing's tumor, I have sometimes put as much weight on the history and roentgenologic findings as I have on the histology. I feel that in any tumor of bone, if the pathologist tries to make a diagnosis on the slides alone, he is taking considerable risk; and the radiologist in a similar fashion, is taking the same risk if he tries to make the diagnosis on the roentgen rays alone. In bone tumors, above any other group, careful consideration of the history, roentgen ray evidence and the pathology have to be evaluated carefully together. The gross specimen reveals a huge tumor which is expanding the bone with little adjacent bone being laid down. It has a somewhat soap-bubble appearance, is rather well circumscribed, somewhat homogenous in texture and it does not have the jelly-like character one sees in the usual Ewing's tumor. The microscopic appearance demonstrates a clear cut stroma, and individual cells have a tendency to spider-web appearance. There are also lining cells which have a suggestion of an epithelial structure (fig. 7). There is a sharp demarcation between stroma and tumor. Now, I have never seen a roentgenogram of a Ewing's tumor with a soap-bubble appearance, which is the first finding against the diagnosis of Ewing's tumor. Second, while one finds some stroma in a Ewing's tumor, it is relatively meager in amount. And finally, this neoplasm is quite well preserved throughout, and a Ewing's tumor almost always has patches of necrosis and hemorrhage scattered through it. The necrosis and hemorrhage is

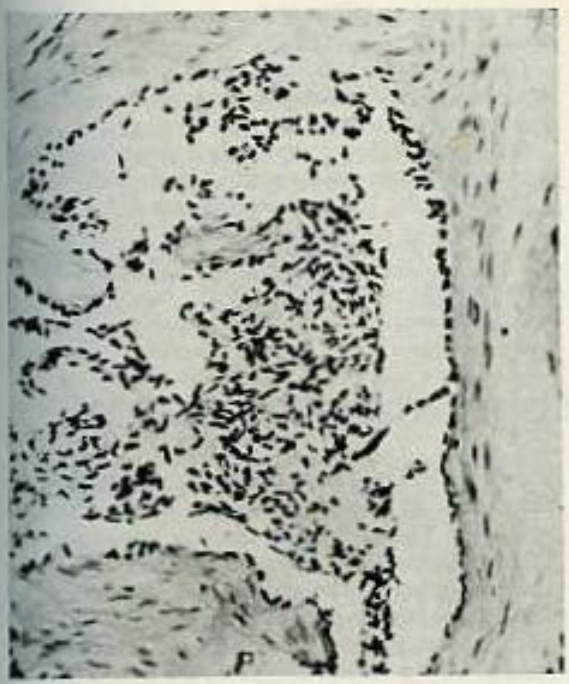

Fig. 7. Photomicrograph. Epithelial-like strands of tumor supported by a delicate connective tissue framework. (Moderate enlargement.)

one of the most characteristic features of this tumor. Time after time, when I have been doing a frozen section on a Ewing's tumor, I have had to ask the surgeon to go back and re-biopsy in order to obtain a specimen in which the cells were well visualized. In this history, there is no mention of pain. The patient complained only of swelling. Pain is usually an outstanding symptom of a Ewing's tumor, and frequently the pain will be apparent long before the swelling appears. Again, one has a long history with an extensive tumor and no evidence of metastases. In a Ewing's tumor, by the time it has reached a fair size, or lasted several months, it has metastasized. All these factors are against the diagnosis of Ewing's tumor, and I would make a diagnosis of adamantinoma of the tibia. Why is this tumor occurring in this region? There is no good explanation of this.

There is also the possibility of another diagnosis for there are cells which are elongate, carrot-like in shape, and could suggest a metastatic neuroblastoma. There were no masses in the abdomen and, again, a firm white fairly solid mass is not characteristic of a large neuroblastoma. Degeneration and hemorrhage are common in neuroblastoma. The cells of the spider-web type are not seen in any type of neuroblastoma.

In regard to the adamantinoma, this is a tumor of twenty years' duration which would of course rule out Ewing's tumor and metastatic neuroblastoma. It grew slowly, finally penetrating the cortex to involve the soft tissues. It was first apparent at the age of 17, and finally removed at 37. There are about thirty-odd of this type of tumor recorded. There are several points of origin from which these tumors might arise. One possibility is from epithelial cells which are buried near bone which might further differentiate to enamel organs. Another possibility cited as a point of origin is that a basal-cell-like proliferation occurs following trauma. However, no satisfactory explanation is as yet at hand. Similar tumors of the cranio-pharyngeal type and one case arising probably from a teratoma of the ovary have been reported.

DR. NEAL, Columbia, Mo.: Would a reticulin stain be helpful?

DR. WARREN: I think a reticulin stain would be useful, but I am not sure that the distribution of reticulin would in any way appreciably alter my diagnosis. I am not convinced that any endothelial tumor can differentiate in two distinct ways: one, toward this epithelial sort of structure and, the other, to the spider-web like cell. If there was only a little better differentiation, and a little enamel being formed by some of these cells, it would be ideal. But practically all of the adamantinomas of the tibia stay in the poorly differentiated group and the formation of enamel does not occur.

DR. SEVERANCE, San Antonio, Texas: Dr. Warren, in looking at this tumor, I tried to find the tall columnar cells with the nucleus away from the basement membrane which you so frequently see along the edge of the various cell nests in the adamantinomas of the oral cavity. I did not find any, and I would like to ask if this negative finding is characteristic of adamantinoma of the tibia?

DR. WARREN: I have seen so few of these tumors in the tibia that I cannot say what is really characteristic and what is not. But in the ones which I have seen, the high columnar cells have not been present.

DR. ACKERMAN: Have you seen any metastases from adamantinoma of the tibia?

DR. WARREN: In the few which I have seen, there have been no metastases. In the literature, in spite of the long duration of these tumors, the majority of cases have not metastasized. Some of the ones that have been reported with metastases impress me as probably belonging to the group of metastatic neuroblastomas or to Ewing's tumor.

DR. ECKERT, St. Louis: If you compare this lesion with one of the usual type occurring in the mandible and consider it a malignant tumor, there is no tendency at all toward the epidermoid growth which one usually observes when the ameloblastoma becomes malignant. One naturally wonders whether this is a malignant tumor.

DR. WARREN: A number of the adamantinomas do undergo epidermoid metaplasia when they occur in the jaw, and also when they occur as part of a cranial pharyngioma. And, as Dr. Eckert has pointed out, when these tumors metastasize as they do sometimes from the jaw, they do not metastasize as an adamantinoma, but as an epidermoid carcinoma. There are a considerable number of cranial

pharyngeal neoplasms or adamantinomas of the jaw which have a long history without epidermal metaplasia taking place. I remember an instance in a medical student who had a tumor for nine years with two or three recurrences while in medical school and has had a recurrence or two since graduation. During that entire period of time, no epidermal metaplasia had taken place.

DR. STOWELL, St. Louis: Although it may be the exception which proves Dr. Warren's rule about the metastases of these tumors, Schweitzer did report one case in 1943 which metastasized as adamantinoma.

DR. WARREN: I am very glad to know that, for there is a special interest in the metastases of highly differentiated tumors.

DR. ECKERT: How frequently is there true enamel formation in ameloblastoma of the tibia?

DR. WARREN: It is unknown as far as I am aware.

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5. SYNOVIAL SARCOMA OF THE SOFT TISSUE OF THE LEG

History (presented by L. S. N. Walsh, M.D., St. Luke's Hospital, St. Louis).—The patient, a white woman aged 31, entered the hospital April 9, 1947, with a chief complaint of a painful, slightly swollen mass on the lateral side of the sole of the left foot. This had been present for three years. On examination, a firm, tender 5 by 3 cm. fixed mass was present beneath the intact skin overlying the distal portion of the fifth metatarsal. The skin overlying this mass was intact and roentgenograms of the foot showed no evidence of bone destruction. The tumor was surgically excised on April 22, 1947; it was grayish pink in color, a portion of it was lying between the fourth and fifth metatarsals and minute cystic areas were present within it.

DR. WARREN: The great majority seem to feel that this is a tumor of the synovial group. A section of the tumor reveals a number of interesting cells, some of which are vacuolated lightly with occasional mitoses, and then there are sharply-defined spaces with a mucinous material within them. Certain areas simulate the appearance of an epithelial structure (fig. 8). Some of the cells obviously have secreted a material which is mucoid in character. Many of these tumors occur in the regions of the knee and ankle. These tumors began to be recognized in 1930 when there were two cases in the literature. The life history of these tumors has been quite variable, some lasting for only a few months and others for a number of years. The longest one that I have had personal experience with has gone some seven years. These tumors, although they appear in the region of joints, do not involve the joint cavities and they do not appear in cases of arthritis with proliferative synovitis where one might think there would be more reason for their occurrence within the joint. In the patients at the Robert Brigham Hospital, Boston, which is primarily for arthritis patients, there has been a wide range of lesions of various types within synovial membranes, many of them associated with active and prolonged proliferations. There has not been a single synovioma in the group. When one sees this type of tumor it usually comes out of a clear sky. The patient may present a history of trauma, but it is difficult to determine whether or not the trauma simply is calling attention to a lesion already in existence. It might be well at this moment to review what criteria should be considered in relating a tumor to trauma. Such a relationship is extraordinarily rare. First, the part has to be proven to be intact prior to the time of trauma and, secondly, the trauma has to be adequate. Some years ago I participated in a court case in Boston in which the relation between trauma and tumor appeared clear. There was an unquestioned sarcoma; there was an unquestioned trauma to the ankle and the ankle was known to be normal prior to the trauma. The only difficulty was (which came out in the course of the trial) the sarcoma was on the right ankle and the trauma had occurred to the left ankle! The tumor must also be of a type which reasonably can be assumed to arise there, i.e., it should not be a metastatic neoplasm and, finally, the tumor must occur within a reasonable period of time following the trauma. So often one hears stories of a tumor arising only a day or two after trauma. One also has to consider time relationships from the aspect of the type and growth-rate of a specific neoplasm. I would be skeptical of even a

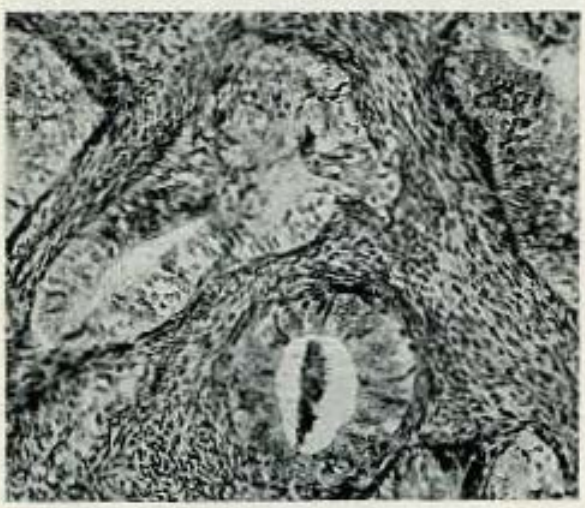

Fig. 8. Photomicrograph. Synovial sarcoma with sarcomatous stroma and glandular components.

rapidly growing sarcoma being able to turn up in less than three weeks after trauma. It also has to come in a reasonable length of time afterward, and I feel that if it is more than three years afterward, coincidence begins to come into the picture. It is rare that a single trauma is a cause of tumor. Most of the cases that have been established by legal precedent are the ones in which the evidence is much more satisfying to the legal mind than to the pathologists.

DR. ACKERMAN: It is well known that this is an extremely malignant tumor in its evolution and frequently occurs in young individuals, particularly in the region of the knee and ankle joints. Naturally the question of therapy often arises and I would like to ask several questions: (1) would there be any contraindication to incisional biopsy; (2) if it proved to be a synovial sarcoma, should one proceed immediately with amputation and, if so, where, and (3) because of the fact that Haagensen and Stout have reported such high frequency of lymph node metastases, what consideration should there be of radical groin dissection?

DR. WARREN: I know of no instance in which incisional biopsy followed fairly promptly by treatment (within a week's time) has done any harm. Pathologists in Massachusetts have been concerned with that problem for there is a State Tumor Diagnostic Service for which material is removed from the patient and then there may be a lapse of several days intervening before the tissue can be examined and a report made to the surgeon. In checking back a number of those cases, I could not find that the percentage salvage varied in any way from a controlled series. I think it is much more important to know what one is dealing with than to undertake radical therapy without benefit of biopsy, and I am strongly in favor of incisional biopsies. I don't like aspiration biopsies. Aspiration biopsies are better than no biopsy at all, but I think that one should remember that the place where the most enthusiasm has been built up for them (The Memorial Hospital) operated until recently essentially as a huge outpatient clinic with few beds. The time when they were strongest for this method was a time when it was not a question of "is this the best way of getting a biopsy" but the question of "shall we get a biopsy or shall we not?" Secondly, the aspiration biopsy can rarely make the diagnosis alone; it has to be considered along with the clinical data. Finally, I do not think there is any evidence that to a few tumor cells, an 18-guage needle looks any different than the edge of a scalpel and I think there is just as much chance of spreading a tumor by aspiration biopsy as by incisional biopsy. There are certain inaccessible lesions where an appreciable operative procedure is called for that would not warrant the incisional approach and where aspiration should be used, but by and large, incisional biopsy is far the wiser choice.

The therapy of these tumors should be radical for their prognosis is gloomy. I believe that radical surgery should be done and that this should include the radical removal of regional lymph nodes. Involvement of lymph nodes can occur in other types of sarcomas such as osteogenic sarcomas; about 8 per cent of my osteogenic sarcomas, for instance, have had lymph node metastases.

DR. ACKERMAN: I have to defend my position on aspiration biopsy. In the first place, I agree with Dr. Warren that in many sarcomas incisional biopsies are necessary for a clear-cut diagnosis. It should be clarified that one is not smearing the material obtained by aspiration, staining it and then trying to identify single cells. At this hospital, we are making paraffin sections which do not differ in any way from the usual section of a biopsy except in size, for architectural pattern is maintained. We find its greatest use in the evaluation of regional lymph nodes in which the primary diagnosis already has been established. In this group of cases one is usually trying to differentiate between inflammation and tumor. I am against the use of aspiration biopsy in breast lesions as a diagnostic measure.

DR. WARREN: I think that Dr. Ackerman and I are in essential agreement. One reason that I am prone to depend on the incisional biopsy, even in lymph node metastases, is that in the Boston area the surgeons outweigh, perhaps unduly, the radiologists and few metastatic lesions of lymph nodes are treated by irradiation. Dr. Ackerman may remember the somewhat caustic comment of one of the Pondville staff members that the chief notoriety of Pondville would be that it was the last place in the world to abandon surgery for metastatic lesions of lymph nodes. In the instances that you outline, I agree that if one has irradiation therapy in mind rather than removal by radical surgery, the obtaining of a core or plug of material—which I would again differentiate, as Dr. Ackerman does, from the traditional type of aspiration biopsy—is a useful procedure.

DR. DEL REGATO, Columbia, Mo.: As a radiotherapist I am in favor of aspiration biopsy in many instances. For example, in a case of epidermoid carcinoma of the tonsil with a large cervical adenopathy in which the treatment of choice, of course, is radiotherapy, I would not favor incisional biopsy since this might interfere with the proper conduct of radiotherapy. If one treats the patient with an adenopathy and the patient gets well, nobody will believe afterward that the patient had a metastatic adenopathy.

DR. GREEN, St. Louis: You stated, Dr. Warren, that no harm would result if an interval of a week's time elapsed between the biopsy and the therapy. I wondered if your series included many pediatric tumors. It has been pointed out time and again by the Childrens Hospital in Boston that twenty-four hours is sufficient time to do diagnostic procedures before therapy, and I wondered if pediatric tumors could be an exception to that general rule.

DR. WARREN: I have not had enough experience

with pediatric tumors to answer that. I will ask my colleague, Dr. Farber, when I return to Boston. I would not expect, however, that they would act very much at variance from the tumors in adults, and I think it is much more important to get an accurate diagnosis than to go ahead with fairly drastic surgery on speculation. Now, I do not wish to imply that a week is necessarily the standard time to wait. Many of you, I know, are getting your diagnoses out in twenty-four or forty-eight hours; however, we do have the problem in Massachusetts, as undoubtedly many of you yourselves have, of some areas where there are no pathology laboratories readily available and where the only way for a surgeon to get a pathology report is to remove a sample, send it to some laboratory at a little distance and wait for the report. That was why I mentioned the possibility of a week's holdup in the report.

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6. DESMOID OF THE ABDOMINAL WALL

History (presented by Lauren V. Ackerman, M.D., Ellis Fischel State Cancer Hospital, Columbia, Mo.).—Four years previous to admission, the patient, an 11 year old boy, had had his appendix removed. Two years later he noted a hard nodule near the site of the previous incision. An osteopath examined him, biopsied this nodule, a report of fibrosarcoma was made, and the patient referred to the State Cancer Hospital. Physical examination showed a well developed young male in good general condition. There was a firm mass in the right lower quadrant which was somewhat movable beneath the skin, painless, and with indefinite margins. There was no evidence of any lymphadenopathy and a roentgenogram of the chest was normal. On June 10, 1947, the abdomen was explored and a well-delineated mass was widely excised, removing tissue down to the iliac vessels.

Grossly, the tumor appeared fairly well encapsulated, measured 8.5 by 6 cm. and on cross section was smooth and grayish in color. This tissue appeared to replace muscle in some areas.

DR. WARREN: My diagnosis of this tumor sides with the majority and I believe that it is a desmoid tumor. The keloid question has been brought up and keloids have been a special concern of mine since I have seen many of the atomic bomb survivors in Hiroshima and Nagasaki. There were a tremendous number of exposure and flash burns, and in the scars of extensive flash burns quite a proportion have shown heavy keloid formation as well as all stages of hypertrophic scars. I had thought of a keloid as involving all of the area of a scar. However, the keloids of many of these flash burns involved only scattered portions of the scar and one sees areas of ordinary scar tissue with foci of true keloid here and there in it. The incidence of keloid is no higher in atomic bomb burns than in incendiary bomb burns or in gasoline burns. The gross of this lesion at once rules out keloid, for one sees the mass of solid infiltrating tumor which caused the previously described abdominal mass (fig. 9).

The microscopic appearance reveals a diffuse fibrosis coming in among muscle cells with here and there attempts at regeneration of muscle cells as they are being compressed and deprived of nutrition by the infiltration of the tumor (fig. 10). Where this desmoid ends and where the stroma begins or the interstitial fibrous tissue, I was unable to say. It faded off imperceptibly at the sides. In these neoplasms trauma does seem to be somewhat of a factor. Every case that I have seen gave either a fairly honest history of trauma externally

Fig. 9. Gross specimen. Grayish white firm tumor is infiltrating muscle.

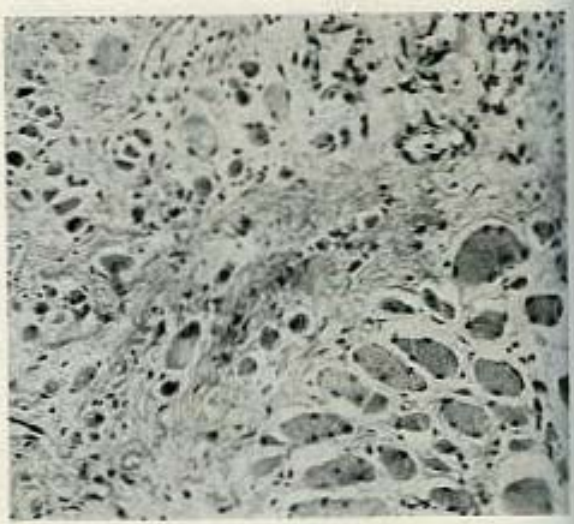

Fig. 10. Photomicrograph. Connective tissue is growing between muscle bundles; some of these muscle cells show degeneration. (Moderate enlargement.)

er of a definite stress involving the abdominal musculature. Two or three have developed following childbirth, others have appeared after heavy lifting with evidence of either a rupture of the rectus sheath or of the rectus itself.

DR. ACKERMAN: How often do these lesions recur, and have you ever seen one that metastasized?

DR. WARREN: I have not seen one that metastasized. They seem to be a fairly localized tumor but their tendency to recur is fairly high.

7. ? HODGKIN'S DISEASE OF AN AXILLARY LYMPH NODE ? FIBROSARCOMA INVOLVING AN AXILLARY LYMPH NODE

History (presented by Warren Winn, M.D., St. Joseph Hospital, Boonville, Mo.)—The patient, a 57 year old white man, was seen by his physician because of swelling under his arm. Physical examination showed a man in good general health. There was a mass of nodes in the right axilla which were matted together and not attached to the overlying skin. There were no lesions in the breasts and no skin lesions of any significance were noted. A roentgenogram of the chest was normal and the rest of the physical examination as well as all laboratory tests were essentially normal. A lymph node was removed which on section cut with increased resistance and showed focal areas of necrosis and partially replaced substance.

DR. WARREN: This is a case in which considerable disagreement and uncertainty is to be expected. The majority of pathologists here are in favor of fibrosarcoma. I believe that this is a malignant tumor, but I am not thoroughly convinced as to just what type of neoplasm it is. There are large tumor cells with giant nuclei and a suggestion of a Reed-Sternberg type of cell (fig. 11). The node is fibrotic and its capsule is reasonably well respected. Here and there among the predominantly spindle cells with abundant collagen are a few large irregular cells. The first time I reviewed this tumor I believed that it was a fibrosarcoma because it was rich in fibrous tissue and I could see what I thought was transition between the large abnormal cells and the atypical spindle cells and because it seemed to be a tumor that was respecting the capsule of the node, in spite of the fact that in the gross description the tumor was noted as extending through the capsule of a mass of nodes that was spoken of as coalescent and adherent. Later, when I looked in detail at individual cells, when I remembered how fibrotic some of the Hodgkin's nodes become, I thought of Hodgkin's disease. There are also areas of focal necrosis described in the gross, which is in favor of Hodgkin's disease. Also there is no evidence of a primary tumor of a fibrosarcomatous nature from which this might have arisen.

I found on looking through my own series of slides a case which had been diagnosed as a fibrosarcoma arising from the stroma of a lymph node. This came from a moderately nearby location, just under the end of the clavicle. In that case there was no involvement of nodes elsewhere and the patient had twelve recurrences in the scar from the time of its inception in 1931 up to 1945. Therefore, I felt that if twelve recurrences appeared locally without going beyond that point, it certainly was not Hodgkin's disease. I wonder if there is any information as to the subsequent course of this tumor; whether the right axilla alone was involved or whether anything developed elsewhere?

DR. DEL REGATO: I have examined this patient subsequently. He received quite a heavy series of radiotherapy to the axilla and the tumor showed some regression, but not as much as is usual for Hodgkin's disease. Since the radiosensitivity is usually characteristic, I believe that those who made the diagnosis of fibrosarcoma might have some satisfaction out of that.

DR. WARREN: Time will make the diagnosis. I have rarely seen a case of Hodgkin's disease as locally extensive as this which remained in a single area. Usually these cases involve other regions. Frequently if there is an atypical type of Hodgkin's in one region, it will be much more characteristic when it appears elsewhere. This case is one I think must be held for the time being as an unusual malignant lymphoid tumor which falls either into the class of atypical Hodgkin's disease or an un-

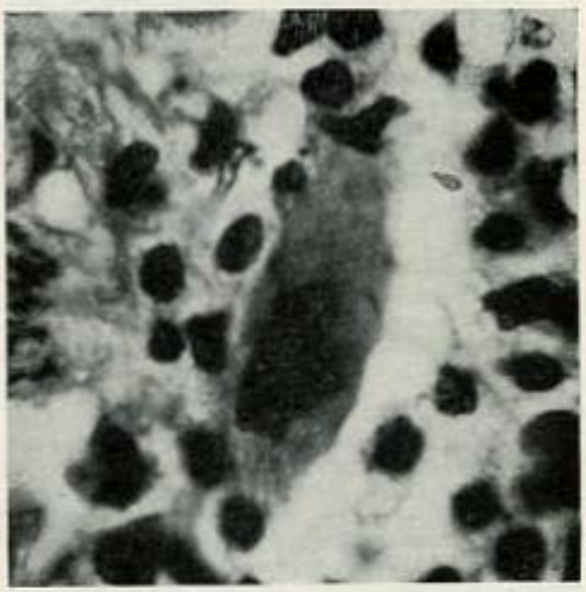

Fig. 11. Photomicrograph. Note large cell simulating Reed-Sternberg type with a multilobated nucleus and prominent nucleoli. (High power enlargement.)

usual form of fibrosarcoma. I am classifying Hodgkin's disease as a malignant tumor; I trust that this group is in agreement with me.

DR. B. F. STOUT, San Antonio, Texas: Would you expect such a fibrotic process as this to take place in only a few months time?

DR. ACKERMAN: I think the time interval was relatively short, but certainly no more than five or six months.

DR. WARREN: I would not think so in a Hodgkin's disease, for in the earlier stages the fibrosis is not too apparent. If one assumes that the history was as short as five or six months, I would be more in favor of an atypical fibrosarcoma.

8. PLASMA CELL LEUKEMIA

History (presented by Shields Warren, M.D., New England Deaconess Hospital, Boston).—Three months previous to admission on October 28, 1940, this 62 year old man noted gradual onset of dull pain in the lower back which was accentuated by movement. There was no history of injury or strain. The patient complained also of anorexia, weight loss of 20 pounds, some nausea (without vomiting), progressive weakness culminating in inability to walk without support, and pain in the ribs on deep breathing and raising of the arms. Physical examination at the time of admission revealed a pale, well developed, well nourished man who appeared chronically ill. With the exception of severe pain on movement, physical examination was noncontributory. Laboratory findings at the time of admission were: Urinalysis, within normal limits; red blood cells 1,440,000; white blood cells 9,400; Hb. 35 per cent; differential: polymorphonuclear leucocytes 48 per cent, lymphocytes 47 per cent, monocytes 4 per cent, and eosinophils 1 per cent. Roentgenograms of bones revealed many small areas of destruction. A blood smear was reported as containing 12 per cent plasma cells. The patient was discharged on November 7, 1940, his condition unchanged.

When readmitted on November 29, 1940, his condition was similar to that on previous hospitalization. Laboratory findings at this time were: red blood cells 1,960,000; white blood cells 203,000; Hb. 38 per cent; differential: polymorphonuclear leucocytes 12 per cent, lymphocytes 15 per cent, large monocytes 5 per cent and immature forms 68 per cent. The nonprotein nitrogen was 93 mg. per cent; serum protein 6.5 per cent, and Hinton test was negative. At that time, 3.75 millicuries of radioactive phosphorus were given on November 30. This resulted in a slight febrile reaction, the temperature rising to 101.8 F. one and one half hours following treatment. The patient was then given a transfusion of 500 cc. of whole blood. He showed some clinical improvement, the white blood cells decreased to 89,000 on December 1, and 139,000 on December 2, with a red blood cells count of 2,390,000 and Hb. of 44 per cent. Roentgenograms of bones at that time showed multiple irregular defects in the ribs, with fractures of the second and ninth on the right; the fourth, ninth and tenth ribs on the left, and defects compatible with multiple myeloma in the shoulder girdle, skull and wing of the right ilium. He was discharged on December 2, 1940, his condition definitely improved.

On December 8, 1940, he was readmitted in poor condition and he died at 3:50 p. m., December 9, 1940.

At autopsy the sternum showed a pinkish gray mass of moderately soft tissue which bulged 1 cm. above the inner aspect, involved almost the entire thickness and extended from the fifth to ninth costal cartilages. In the ribs there were many foci of softening and fracture which on section showed thinned-out cortices and central areas filled with dark red marrow of almost fluid consistency. These varied from 1 cm. to 4 cm. in diameter and the larger showed bony cortex destruction. A mass of tumor tissue was present on the crest of the right ilium which measured 6 cm. in length, penetrated into bone, was pinkish gray in color, moderately soft in consistency and showed a glistening cut surface. The marrow cavities of the lumbar vertebrae were filled with almost fluid, dark red material, the cortex was thinned and trabeculae were virtually absent.

DR. WARREN: In this case the overwhelming majority is in favor of the plasma cell type of lesion. The most common cell type shows a relatively small amount of cytoplasm, a large eccentric nucleus with a rather peripheral arrangement of the chromatin reminiscent of the general structure of the plasma cells (fig. 12). In my slide there were also a number of multinucleated cells which also leads me to favor the plasma cell origin. There is considerable tendency for plasma cells to have multiple nuclei in both inflammatory and neoplastic lesions. Moss and Ackerman have written on plasma cell leukemia; their case was in an elderly male who developed a swelling in the region of the lower jaw as a localizing symptom. It will be noted that in this case there have not been any real localizing symptoms with the exception of gradual onset of pain in the lower portion of the back. In this history there is one point of considerable interest: the serum protein was 6.4, possibly below normal, and

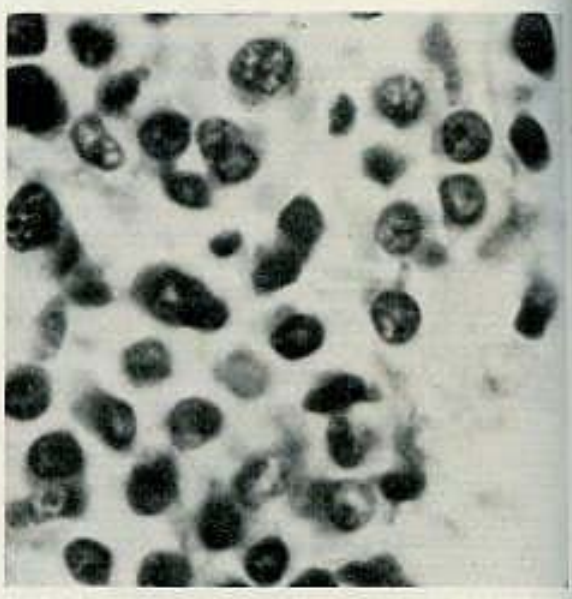

Fig. 12. Photomicrograph: Plasma cells from the bone marrow, some of them multinucleated with well defined nuclei and cartwheel arrangement of chromatin. (Moderate enlargement.)

one would not think much of it if one did not check against the red blood count for, with a prominent anemia, a serum protein of that level is distinctly high. In a large number of cases of plasmocytoma and plasma cell leukemia, the elevation of the protein is a helpful diagnostic point. This patient had a nonprotein nitrogen of 93 and a microscopic section of the kidneys revealed many tubules occluded by casts. It is not infrequent with the elevation of serum proteins, in the presence of Bence-Jones protein or allied bodies, to have renal obstruction as a real problem. I have seen a number of these kidneys which looked more on section like an old chronic pyelonephritis of a type which simulates a section of the thyroid. This case was not from the start a leukemic type. It began with an essentially normal white count (9,000) with a perfectly normal differential. Possibly 47 per cent lymphocytes is a little high. Then in a few months time the white count had increased to 200,000 with the immature cells and plasma cell series being the predominant cell type. A fair number of the localized plasma cell tumors end up in a plasma cell leukemia. One of the points on which enough data has not been accumulated is the significance of local tumors which are rich in plasma cells and occur particularly in the region of the nasopharynx. At first, I thought those were entirely of a chronic inflammatory nature. I have had, however, two or three which I could not distinguish from the rest on initial biopsy, which recurred and progressed to typical myeloma with multiple bone involvement. I believe that it is difficult to say whether this is a tumor of multicentric origin with bone marrow cells as the primary type, or whether it is initially a small soft part focus (perhaps occult) and the bone lesions are metastatic. I would like to ask how many of you have seen either multiple plasma cell myeloma of bone or plasma cell leukemia with normal serum proteins.

Dr. Sam Gray, St. Louis: Whenever one sees a high blood protein one thinks of a multiple myeloma.

Dr. Warren: One point of interest in high blood protein levels: I was very much surprised to find that in spite of the largely rice diet of the Japanese this spring, they were all running practically high normal proteins: 8, 8.2, 8.4.

Dr. Ackerman: I have a feeling, Dr. Warren, that there are a great many variations of the pathologic picture, one shading imperceptibly into the other. For instance, at this hospital we have had the experience of lesions within the oral cavity which appeared to be primary oral cavity neoplasms, but when we took roentgen rays we often found we were dealing with a far-advanced process. On the other hand, we have had definite primary cases within the oral cavity. In this group it is important to appraise the regional nodes for they may become involved. It is possible in certain cases, particularly the well localized ones, that irradiation may be curative for this is a radiosensitive lesion. In plasma cell leukemia it was our experience, after reviewing the literature, that this type of case moved rather rapidly in its evolution.

Dr. Warren: When this man came to our hospital in late November he was in poor clinical condition and it was decided to see what radioactive phosphorous would do. We were not able to give him an adequate dosage, but as far as it could be told the response was not satisfactory. It has been my experience that whenever one has a rapidly progressing fulminating type of leukemia, whether it is a plasma cell or myelogenous, the cells in spite of the fact that they ought to be highly sensitive to irradiation, are exactly the reverse. I think all have seen cases of acute leukemia which theoretically should have done well with irradiation, but which actually have done poorly indeed. I wonder if Dr. del Regato would care to make any comment?

Dr. del Regato: Yes, sir. That is exactly our experience, Dr. Warren. It is usually said that radiotherapy is contraindicated in the treatment of acute leukemias. I would rather say that radiotherapy is not of much value in the treatment of acute leukemia. It probably does not do any harm. There have been several cases of acute leukemia that were kept alive with total body irradiation with relief of symptoms (diminution of leukocytosis and hemorrhagic tendencies) for periods as long as ninety days of daily irradiation. However, after that period of time or less, there is recurrence of leukocytosis and hemorrhagic tendencies. This new thrust of circulating young cells does not seem to be affected by irradiation.

Dr. Gustav Dammin, St. Louis: I wonder what the albumin and globulin ratio was when the blood proteins were done in November 1940? And the second question: at the time of admission when the white count was normal, it was stated that a blood smear was reported to contain 12 per cent plasma cells. Was it your impression that the tumors were present before leukemia, or vice versa?

Dr. Warren: I thought that probably since the roentgenograms of bones were already revealing many small areas of rarefaction, that in all probability, this 12 per cent plasma cells was the first indication of anything wrong, and that the lesion in the bone had been present for some time without any abnormality appearing in the blood. As a rule, these cases will run their entire course without plasma cells appearing in the blood even though a large proportion of the bone marrow may be occupied by them. I do not recall the exact ratio of the albumin and globulin in this case, but there was an appreciable increase in the globulin fraction.

Dr. Schenken, Omaha, Nebraska: Dr. Warren, would you care to comment on the relationship of amyloidosis to the problem?

Dr. Warren: In the cases that I have seen there has been at times an amyloid-like substance both in the tumor and in the kidneys, but I felt that

there was perhaps a concentration or a precipitation of the abnormal protein rather than a true amyloid formation. When one sees this, there is not the characteristic amyloid distribution as one sees it in the liver.

DR. NEAL: In the section I have, there is in the edge of the muscle a trichina-like body.

DR. WARREN: I was not sure that it was going to show in all of the sections. That is keen observation. The frequency of trichinosis in the United States is surprisingly high. Has any one in mind what the percentage in St. Louis and Missouri must be?

DR. GRAY: I think the percentage in St. Louis must be at least 35 per cent.

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9. LEIOMYOMA OF THE STOMACH

History (presented by Arthur Purdy Stout, M.D., Columbia University College of Physicians and Surgeons, New York City).—This 60 year old housewife was admitted to the hospital on March 10, 1947, complaining of discomfort of the throat and upper sternum of three months' duration. There had been no nausea, vomiting, anorexia, change in bowel habits, melena or abdominal pain. A roentgenologist had interpreted a barium study as a "neoplastic structure at the terminal portion of the esophagus," and a biopsy taken at esophagoscopy was reported as carcinoma. Physical examination revealed a moderately obese woman who did not appear acutely or chronically ill. No abdominal masses were felt. Fluoroscopic barium studies of the esophagus were reported as intermittent spasm of the lower esophagus with no abnormality of the cardia or fundus of the stomach. The patient was discharged on March 13, 1947.

Three months later she returned and roentgenograms at that time showed a probable lesion in the cardia. Laparotomy by the thoraco-abdominal approach showed a roughly spherical tumor mass about 5 cm. in diameter projecting from the anterior surface of the gastric fundus about 10 cm. below the cardia. The surface of the tumor was covered with fibrin and the adjacent gastric wall appeared inflamed. No enlarged lymph nodes were present and the liver appeared to be normal. The tumor was resected.

The gastric tumor was firm and projected 1.5 cm. into the gastric lumen where the mucosa appeared smooth and pink except for a 0.3 by 0.9 cm. punched-out ulcer in the center of the mass, giving the gastric aspect of the tumor the appearance of the cervix uteri. A narrow cuff of muscularis was attached around the specimen and did not appear abnormal. The main mass of the tumor projected 3 cm. out on the serosal surface which was pink and shaggy in appearance. On cut surface the tumor was pinkish white and trabeculated. Several areas of hemorrhage and degeneration were seen and a whitish 1.2 by 0.6 cm. nodule with apparent peripheral calcification was seen at one margin.

DR. WARREN: In this case there is a great variation of opinion. The variations of terms one sees on the neural side: neurinoma, neurilemoma or neurofibroma reflect not so much the variation seen in this particular lesion, but reflect the confused state of nomenclature of this group of neoplasms. Those who have been fortunate enough to hear Dr. Arthur Purdy Stout know how clearly and with what sharpness it is possible to establish the nature of these lesions associated with the peripheral nerves. I do not mean to imply that I am in favor of a neural origin in this particular tumor. The characteristic features of the tumor are the bundles of elongate cells, some of which have edematous swollen cytoplasm and others which have perfectly ordinary appearing cytoplasm. There are clear-cut masses of heavy collagen-rich supporting stroma. There is a suggestion of palisading of nuclei and the tumor itself is not demarcated too sharply. There is a hint of encapsulation but there are areas in which the tumor irregularly extends between strands of smooth muscle. The elongate cells have a close relationship to one another and in a number of instances the cells are applied closely to each other without apparent intervening stromal bands (fig. 13). This type of picture would favor a leiomyoma. The palisading, the swollen character of some of the cells, the ribbony, somewhat wavy appearance of some of the nuclei remind one of neural elements. I have a personal interest in these tumors since at a time when it was popular to describe most tumors of this type occurring in the stomach as fibromas, fibrosarcomas, neurofibromas or neurogenic fibrosarcomas, I favored a diagnosis of smooth muscle

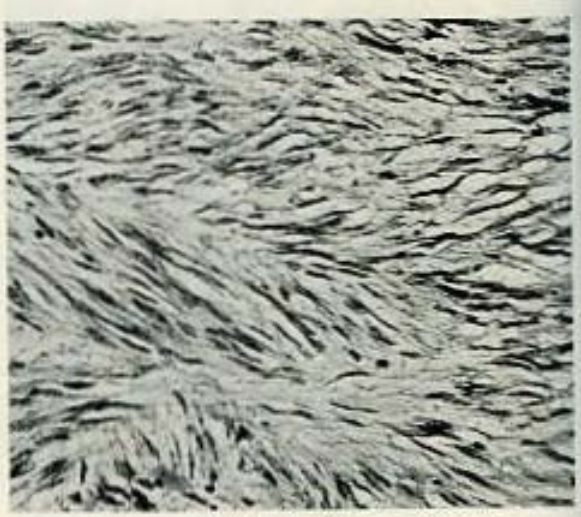

Fig. 13. Photomicrograph. Spindle shaped cells with little stroma and no mitoses. (Moderate enlargement.)

tumors. Dr. Meissner of my laboratory and others have pointed out that these tumors frequently occur in an apparently normal stomach. The Mayo Clinic figures run around 20 per cent of all stomachs (Rienlets). In the routine autopsies at Pondville Hospital and the Deaconess Hospital, the figures were about the same and there were often 7, 8 or 9 in a single stomach. These are logical points of origin for the larger tumors. In the larger neoplasms there is frequently a characteristic roentgenologic picture, and I wonder if Dr. del Regato could outline for us what he finds in this particular tumor.

DR. DEL REGATO: It has been my experience that these cases sometimes do not show a filling defect in the stomach since they might be in the wall without encroachment on the mucosa.

DR. WARREN: My radiological friends have stressed this point to me, for at times the expansion of these tumors is not into the lumen of the stomach but toward the peritoneal cavity so that one might have a pretty good contour of the stomach by roentgen ray and miss the fact that there is a tumor within the wall of the stomach. These tumors are relatively low-grade in type and have a fairly good prognosis. The first one which attracted my attention was a tumor which the late Dr. Dan Jones, of Boston, removed; it weighed some 3 kg. and was accompanied by a huge ulcer of the stomach. In spite of these findings the patient recovered and lived without recurrence for some sixteen years. In this particular section I did not find any mitotic figures. I think that this could be regarded as a larger form of the small leiomyomas that one not infrequently sees. If it were not for the special stains, and only the slides in the Seminar group were available, it would be difficult to say whether this is a smooth muscle tumor or one of the nerve-sheath tumors of the neurilemoma group. In regard to the neurilemomas, have any of you seen one of these tumors arising from sympathetic nerves?

DR. GRAY: I have seen a case in which both peripheral and sympathetic nerves were involved.

DR. WARREN: Which one of the sympathetic nerves, Dr. Gray?

DR. GRAY: The phrenic, vagus and nerves along the abdominal aorta.

DR. WARREN: I am not quite clear whether the vagus is anatomically in the class of sympathetic nerves or not.

SPEAKER: The vagus is a part of the parasympathetic system which is, I believe, practically identical histologically to the sympathetic.

DR. ACKERMAN: Dr. Warren, would you comment on the importance of mitotic figures in calling these tumors benign or malignant?

DR. WARREN: I do not think that mitotic figures make a tumor a carcinoma or sarcoma. On the other hand, I think there are few of the benign tumors which have mitoses in them. I follow the principle that if I can find mitoses fairly readily, let us say they run more than 5 per 1,000 cells (assuming it is not a reparative tissue), that probably it is on the malignant side. If in addition to that, there are abnormal mitoses, I feel a good deal more certain. However, abnormal mitoses in themselves do not make a diagnosis of carcinoma. Dr. Pinkerton will remember a colleague who had a tooth extracted and, as there was considerable granulation tissue in the tooth socket, it was biopsied and this colleaque was appalled to find a tripolar mitosis. It took quite a little assurance from Dr. Pinkerton, myself and others that this could occur in normal granulation tissue. I would say that if I found one or two mitoses in this section, I would not change my diagnosis. I think that if I found a fair sprinkling of them, I would shift to a diagnosis of leiomyosarcoma. The reason I stress the fact that the capsule was not perfect in this tumor is because in a perfectly benign leiomyoma of the gastrointestinal tract there is not complete or perfect encapsulation. This, naturally, may simulate invasion, but this is not evidence of it being actually a sarcomatous process.

DR. GRAY: What proportion of smooth muscle tumors are malignant? There has been a recent series which showed a high percentage.

DR. WARREN: I think that hinges on how carefully benign tumors are searched for. Usually it is only the malignant tumors which reach a large and obvious size and if one takes all the incidental ones which are small, the percentage would be extraordinarily low. I think in the ones that become large enough to be palpated through the abdominal wall, the great majority of them are sarcomata.

DR. RABSON: I think in one of the monographs of the Henke-Lubarsch Handbuch it is recalled that the leiomyoma is the most common benign tumor of the entire gastrointestinal tract and, second, the question of the relative frequency of benign versus malignant smooth muscle tumors rests on the fact that too often the pathologist takes the criteria of the so-called leiomyoma of the uterus. In that instance one has apparent encapsulation and in the case of the myomas of the intestinal tract, I doubt if one ever sees encapsulation. In leiomyomas of the uterus, mitoses occasionally are identified at the periphery of the myomas.

DR. WARREN: I do not recall whether in the Henke-Lubarsch monographs they were speaking of large easily palpable tumors or including the small tumors. I believe they included all sizes and if one includes the small tumors which are extremely frequent, there is no question but that the leiomyoma is the commonest tumor of the gastrointestinal tract. If one takes the large neoplasms which get up to the size of one's fist, they are extraordinarily rare in the leiomyoma group.

DR. DECOURSEY: Does not the same article also bring out the point of palisading in both leiomyomas of the intestinal tract and uterus? I think it was called "rhythmic palisading."

DR. WARREN: All have seen a number of sections of leiomyomas of the uterus with as nice palisading

as one can see in any of the neural tumors, and I do not think that one is ever safe in regarding palisading as a characteristic of a neural tumor as opposed to a smooth muscle tumor.

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10. LEIOMYOSARCOMA OF THE ILEUM

History (presented by Shields Warren, M.D., New England Deaconess Hospital, Boston).—The patient, a 31 year old man, was struck in the upper abdomen by a heavy chain and the following morning a large lump appeared in the right lower quadrant. It gradually increased in size and the patient was given heavy irradiation over the area. He showed no improvement and died shortly thereafter. Postmortem examination showed a tumor mass in the wall of the ileum which projected into the lumen. It measured approximately 3 cm., was elastic, nodular and showed small central area of ulceration. This mass penetrated through the peritoneal surface, where it involved the bladder and rectal walls. Six centimeters above in the mesentery there were two marble-sized nodules of similar tissue. There were also nodular masses in the liver. The sections are from one of these liver masses.

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Dr. Warren: In this tumor there is a suggestion of a line of cleavage or possible encapsulation,

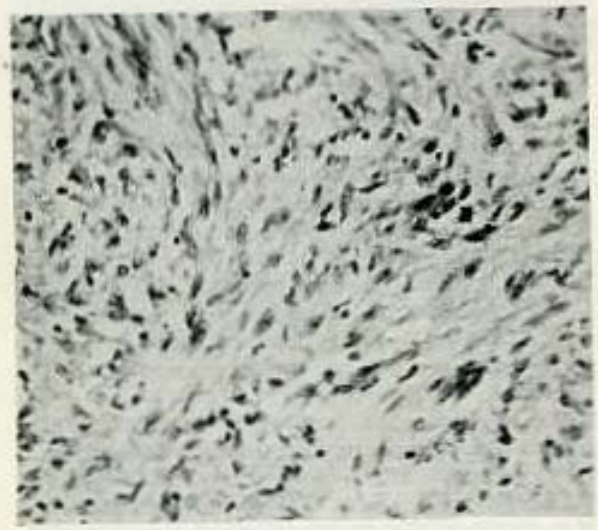

Fig. 14. Photomicrograph. Disorganized pattern of smooth muscle cells with variable size and moderate numbers of mitotic figures. (Moderate enlargement.)

rather similar to the other tumor. One sees a rather loose network of cells, much less orientation of cells and nuclei than existed in the preceding tumor. Under high power variations can be seen in nuclear size and shape with often irregular nuclei, some of horseshoe shape and others of a spindle type (fig. 14). There are a fair number of mitotic figures scattered through it. The majority opinion of sarcoma holds. On detailed study, there were numerous clusters of closely-approximated cells of elongate type without collagen fibers between, and although reticulin stain was not used, I would say that the distribution of reticulum in this case is characteristic of a smooth-muscle tumor. This particular section is from the liver and there are a few clusters of liver cells in one side of the section. In this case there were also pulmonary metastases. In the primary tumor, as a result of ulceration, there was a central excavation. The most striking degree of such excavation which I have encountered was in a large leiomyosarcoma of the ileum which was not recognized for a considerable period of time. It attached itself to other loops of intestine into which there had been ulceration, so that the center of the tumor became a huge cavity filled with fecal material, with a number of stomata opening up into several loops of intestine to which it had become adherent. This is a good example of history of trauma in relation to tumor. It is noted that the patient was struck in the upper abdomen by a heavy chain and the next morning he had a large lump in the right lower quadrant. This mass was unusual in other ways. Ordinarily these leiomyosarcomas tend to remain intraperitoneal for a considerable period of time. This one had come in contact with the peritoneal wall, was invading retroperitoneally and was filling up the retroperitoneal tissues in the region of the pelvis. Ordinarily they are free within the peritoneal cavity and only attached to the intestinal tract itself.

II. INTRADUCTAL PAPILLOMA OF THE BREAST

History (presented by Sam Gray, M.D., Jewish Hospital, St. Louis).—When first seen, this 45 year old nulliparous woman complained of a thin yellow, at times chocolate colored, discharge from the nipple of six weeks' duration. There was no associated pain. On examination, a marble-sized firm mass was present in the region of the nipple. This was surgically excised and on gross examination was seen to consist of the nipple measuring 2 cm. in diameter and a fragment of skin 0.5 cm. in diameter. Just beneath the duct there was a cystic 0.3 cm. mass which, on pressure, extruded soft yellowish tissue through the nipple. On cross section a firm white homogeneous nodule was seen just beneath the skin.

DR. WARREN: This type of tumor can cause as much trouble as any single neoplasm. The microscopic section demonstrates a lumen into which there are papillary ingrowths which have a fair degree of stromal support and stalks (fig. 15). There are no Paget's cells on the epidermal surface. This type of tumor can be difficult on frozen section. The symptom complex is a fairly characteristic one and the type of discharge described in the history is usual. Sometimes there may be actual bright red blood. Would you mind discussing this tumor further, Dr. Gray?

DR. GRAY: As Dr. Warren has indicated, this is the type of tumor with which those who do considerable surgical pathology have a great deal of difficulty. The decision as to whether it is benign or malignant is important for if the decision is on the malignant side the patient must have a radical mastectomy. Of course, one can always play safe and say this is malignant or will be malignant; the breast is removed, and if it is not malignant the patient will never have a cancer; but if it is malignant, one has done her a service. Personally, I call this a nonmalignant tumor for the reason that even though the cells lining the papilliferous arrangement do show some variation, still they are quite uniform. One of the difficulties in this type of tumor occurs when one looks along the outside of the wall of the tumor and sees a few small glands or probable cross sections of glands which give one the impression of invasion. Due to the irregularity of the surface, a section frequently will show glands lying beyond the so-called capsule or beyond the cystic structure from which it arose. I believe this is a harmless lesion of the benign group.

DR. WARREN: I am particularly glad that you stressed, Dr. Gray, that the duty of the pathologist is just as much to conserve tissue, if possible, as to see that it is removed when it is a reasonable source of injury to the patient in whom the lesion occurs. It is easy to say that this tumor is not cancer now but it will be pretty soon and one might just as well call it cancer. That is an unsound attitude to take.

DR. GRAY: I think the injury is not only physical through the loss of the breast, but I think that frequently it is mental, for it is difficult to convince the patient after one has taken the breast off that there is no cancer. Frequently, the pathologists do not have the courage to tell the patient that this is not cancer for fear their reputations might be impinged upon.

DR. WARREN: I wonder, Dr. Stout, if you would care to comment on this tumor?

DR. STOUT: The slide examined showed ducts at the periphery filled with cells which were not supported by fibrous trabeculae and demonstrated considerable anaplasia. This caused me personally to consider this neoplasm as demonstrating early malignant change. Frankly, I don't think that there was any reason to have done any more than was done for this case. It is a matter of academic importance or practical importance to note these slight changes, because one has been taught that the absence of fibrous trabeculae in these ducts with cells that are anaplastic means carcinoma.

DR. WARREN: Would you like to comment, Dr. Ackerman?

DR. ACKERMAN: I think that these lesions are more often called malignant when they should be called benign than the reverse and I think that a high percentage of them are benign. I read Dr. Saphir's article on intraductal papilloma with interest. He makes a division of three separate types. In the first two types (invariably benign) the tumor was either predominantly fibrous or glandular. He felt that on serial section one could demonstrate the tendency of this tissue to invaginate from without into the ducts and that in most instances these lesions were single rather than multiple. In

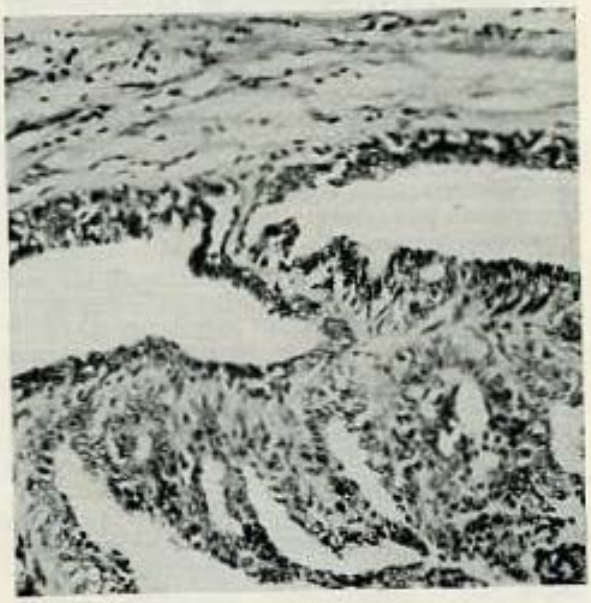

Fig. 15. Photomicrograph. This demonstrates wall of intraductal papilloma with well defined and regular pattern of epithelial cells. (Moderate enlargement.)

the third and smallest group (usually malignant) he drew a parallelism between the transitional tumors within the pelvis which have a tendency to implant along the ureter, while this third group of Saphir's have a tendency to implant along the duct system. For this infrequent third group, Dr. Saphir was prone to recommend radical treatment. Dr. A. P. Stout has made the observation that papillomas located away from the nipple have more chance of being malignant and that if one of them recurs after one removal, there should be no hesitation in doing radical surgery.

DR. WARREN: Would you care to comment, Dr. Moore?

DR. ROBERT A. MOORE, St. Louis: Certain factors should be kept in mind. One would be, of course, the anaplasia of individual cells and the problem of invasion. I don't think that one need necessarily wait in this type of tumor for invasion before saying that it is malignant. The diagnosis of malignancy can be made on the basis of anaplasia, lack of orientation and the distribution of the cells.

DR. WARREN: Another point of interest is the age incidence of these lesions. How many have seen a lesion of this sort appear after the menopause? Apparently no one has. It has been my experience that practically all of them appear in the younger or middle aged groups. One point of special interest is the question of therapy if this type of lesion is associated with any appreciable amount of chronic cystic mastitis. If the lesion occurred in an older woman with considerable chronic cystic mastitis, probably a simple mastectomy would be the safest procedure to follow rather than more conservative therapy. With these intraductal papillary tumors, occurring usually in younger women, there often is no other abnormality in the breast. In this instance the best treatment is simple excision.

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12. CYSTOSARCOMA OF THE BREAST

History (presented by L. S. N. Walsh, M.D., St. Luke's Hospital, St. Louis).—One year previous to admission on March 14, 1947, this 47 year old woman had noticed a consistently mildly painful lump in the left breast which gradually had increased in size. Physical examination revealed a stony hard mass almost filling the left breast. There was no attachment to the chest wall, the overlying skin had a peau d'orange appearance and did not move freely over the mass and there was no palpable axillary lymphadenopathy. The patient refused surgery and disappeared until May 19, 1947, at which time the mass had increased to double its former size, but there were still no axillary nodes felt. It was thought that this was an inflammatory carcinoma and that, as a palliative procedure, a simple mastectomy followed by irradiation should be done.

On gross examination there was an enormous, centrally-located, largely encapsulated mass about 14 cm. in diameter which showed great variation on section, presenting homogeneous gray areas, mucoid patches, cystic cavities and areas of cartilaginous density. In some zones the capsule appeared to be invaded by solid tumor tissue. The cyst fluid coagulated in formalin, had a greenish tinge and was translucent.

DR. WARREN: The microscopic section demonstrates areas in which there are elements of epithelial nature as well as strange mesenchymal zones. In other slides there are elongate cells with, at times, rather distorted nuclei and the fiber-poor intercellular substance (fig. 16). In this neoplasm there is a rather characteristic history in which the patient had a mildly painful lump which gradually increased in size, presumably over a considerable period of time. Although the mass was stony hard and practically filled the breast, there was no attachment to overlying skin. This again is a characteristic point in regard to tumors of this nature as to whether they are benign or malignant. I have seen lesions of the fibro-adenoma group weigh up to 1 kg. or more without evidence of fixation. There was no involvement of the skin in this case, no peau d'orange, and there were no palpable axillary lymph nodes. The patient was lost to follow-up for a while and for several months she apparently was unwilling to have anything done. During that time the mass increased to double its former size, which gives a good index of its growth rate. The gross appearance is characteristic and a protein-rich edematous fluid is characteristic. At times there was sufficient protein in it to cause coagulation, and its greenish translucent character was quite striking. The appearance of calcification within the tumor was interesting, but this particular tumor did

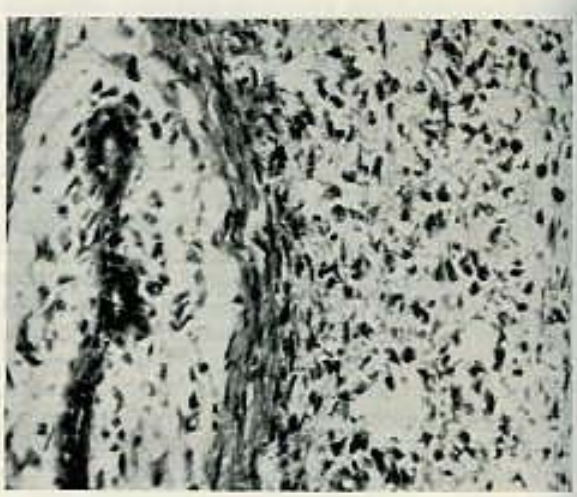

Fig. 16. Photomicrograph. Loosely arranged masses of cells growing in a myxomatous-like stroma. (Moderate enlargement.)

not form bone. Some of them I have seen form appreciable amounts of osteoid within a wide variety of mesenchymal structures of all types. In spite of the huge size, there was no axillary metastases. I have had axillary lymph node involvement in about 5 per cent. There was a wide variety of diagnoses, and if one takes different areas in this tissue, it is easy to justify each diagnosis. I think the fundamental point to have in mind is: here is a fibro-adenoma; in all probability, the stroma has become markedly neoplastic and is differentiating in a variety of ways and, in some areas, it has differentiated hardly at all. I found some areas in this tumor in which there were cells that remind me of striated muscle cells and I found longitudinal striations in a few of them. I could not find any cross striations. Did anybody pick up any cross striations? Apparently none. There are other areas in which there is definite myxomatous structure. There are all types of differentiation of fibroblastic cells to fibrocytes. There are some cells with vacuoles in them which make me wonder about the possibility of a liposarcoma. In this particular tumor, the cell type is not too important. The clinical behaviour of these tumors seems to hinge more on relative encapsulation and the focal origin of a central point rather than on the characteristics of the involved cells. If one had a picture of this sort in a retroperitoneal tumor, the prognosis would be poor. The tissue could have been widely invaded yet, in this tumor, there is encapsulation in spite of the large size and I think the prognosis will be good. Since there are some portions that suggest liposarcoma, I looked up an article of Dr. Ackerman's and there, in reporting a multiple primary liposarcoma, he stressed the relationship of special mesenchymal cells of varying degrees of differentiation as well as the cells presenting fat. Would you like to elaborate a little further, Dr. Ackerman, with regard to these liposarcomas that are closely related to mesenchymal types?

Dr. Ackerman: I would like to say more about the specific type of tumor because of an experience in this hospital. This type of neoplasm usually occurs a little earlier in life than carcinoma and only infrequently metastasizes to nodes. However, if these lesions are incompletely or not widely excised, there is a great predilection to local recurrence. There is a case in the literature of the persistent surgeon and the submissive patient with twelve recurrences. The patient finally died of the thirteenth recurrence which was in the mediastinum (Hoffman). In the case at this hospital the lesion had recurred the second time and, while there were no palpable nodes, I felt because of the relative undifferentiation that a radical mastectomy should be done in preference to a simple mastectomy. A definite lymph node metastasis was found. Therefore, in consideration of therapy of this type of lesion, I believe that particular attention should be paid to wide removal—perhaps including pectoral muscles—and, if there is any question of the tumor being truly malignant, the patient should have a radical mastectomy. I believe that Dr. Neal has reported liposarcoma of the breast.

Dr. Neal: It was fortunately our luck that I reported what I believed to be the first case of liposarcoma in the male breast. But in a review of the literature at a later date, I found that there had been one reported from the Cook County Hospital some fifteen years before.

Dr. Warren: I tried to find in the literature as long as a duration of fibro-adenoma before it became malignant as possible and, in the French literature, there was a case reported by LeRoux. This case occurred in a 45 year old woman and the tumor had been present for thirty-four years before it began to grow suddenly. Because of the possibility of rhabdomyosarcoma, I looked up figures of Dr. A. P. Stout. He stresses the frequency with which they may occur combined with liposarcoma and the primitive type of fibrosarcoma. The average age of Stout's series of rhabdomyosarcomas was 42 years, and the average duration of the disease was about 0.5 years. In many of these there had been long periods in which the tumor had persisted from nine to twenty-odd years. The surprising thing from the standpoint of rhabdomyosarcomas is the poor prognosis; he presented 121 cases and only four were symptom free five years after operation. One finds striated muscle cells in many unexpected places, not only in teratoid tumors but in undifferentiated sarcomas of the nasopharynx. Striated muscle certainly does not belong in the substance of the breast, and thus it is assumed that there has been complete loss of differentiation to the primitive mesenchymal cells and then a partial redifferentiation along the lines of the striated muscle cells. This tumor can be designated as a cystosarcoma phyllodes of the breast.

Dr. Ranson: Fibro-adenoma was described almost 100 years ago and it apparently includes two categories. One group should be called fibro-adenoma phyllodes, in which the skin is not adherent, there is no peau d'orange, no enlarged lymph nodes and the skin is ulcerated only through pressure. Often the patient seeks relief not because of the mass which may last from six to twelve years but also because there is hemorrhage within it. The second group resembles the fibro-adenomas that are usually quite small. One rarely sees a fibro-adenoma greater than a few centimeters. I saw one last week that was 8 cm., which was the largest I have seen. Would you say that there is a difference in these two types, one being neoplastic and the other non-neoplastic?

Dr. Warren: That is a hard question to answer. The great majority of tumors, like the one recorded here, arise from small lesions which have persisted over a considerable period of time. A number that I have seen have recurred also after removal of a perfectly obvious fibro-adenoma from which I had

not expected a recurrence. In general I think this lesion does not arise out of a clear sky but does come from preexisting fibro-adenoma. One can see in sectioning some of the more cellular, slightly larger fibro-adenomas transitional stages that are rather suggestive and which under appropriate circumstances might go on to form this sort of lesion.

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13. ADENO-ACANTHOMA OF THE CECUM

History (presented by Lauren V. Ackerman, M.D., Ellis Fischel State Cancer Hospital, Columbia, Mo.).—The patient, a 64 year old woman, was admitted to the hospital because of pain in the right lower abdomen of from eight to ten months' duration which was associated with some bloating and intermittent tarry stools. A barium enema revealed a large mass deep in the right lower quadrant which caused mesial displacement of the terminal ileum and cecum. The mucosal patterns of the cecum appeared to be intact. At the time of exploration a mass was found in the region of the cecum, and the cecum, ascending colon, 18 cm. of terminal ileum and the appendix were removed.

On gross examination there was a large firm yellowish gray circumferential mass in the cecum which obliterated the wall of the cecum and showed deep central ulceration. The appendix appeared to be normal.

DR. WARREN: The microscopic appearance reveals the general structure of the tumor with undermining of the normal mucosa of the bowel occurring in two forms: definite cell clusters which reveal clear-cut keratinization with apparently definite intercellular bridges (fig. 17), and glandular areas as well as keratinized areas (fig. 18). I do not believe that this tumor is a carcinoid. In the carcinoids the cells are smaller than in this tumor. I have not seen an instance of a carcinoid in which keratinization occurred. There are some characteristic glands also and in the usual carcinoid lesion there are no lumina. There may be a suggestion of lumina, but clear cut lumina with orientation of cells about them are not compatible with a carcinoid. The gross is much more characteristic of an extensive adenocarcinoma than of carcinoid. When carcinoids occur, it has been my experience that they rarely encircle the gut. It is also true that the carcinoid is slow to ulcerate even when large, and this is an ulcerating tumor. There are a fair number of carcinoids, particularly those which occur in regions other than the appendix, which metastasize, so involvement of lymph nodes is not helpful. When

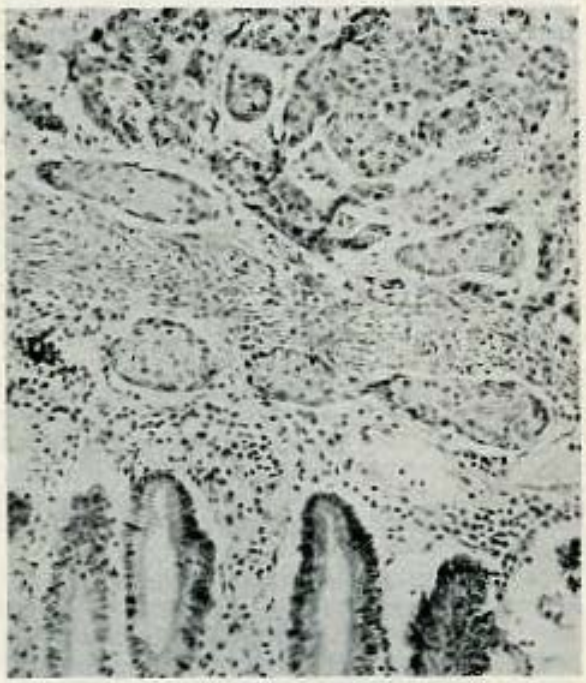

Fig. 17. Photomicrograph. Poorly differentiated squamous cells growing in lymphatics in the submucosa. (Moderate enlargement.)

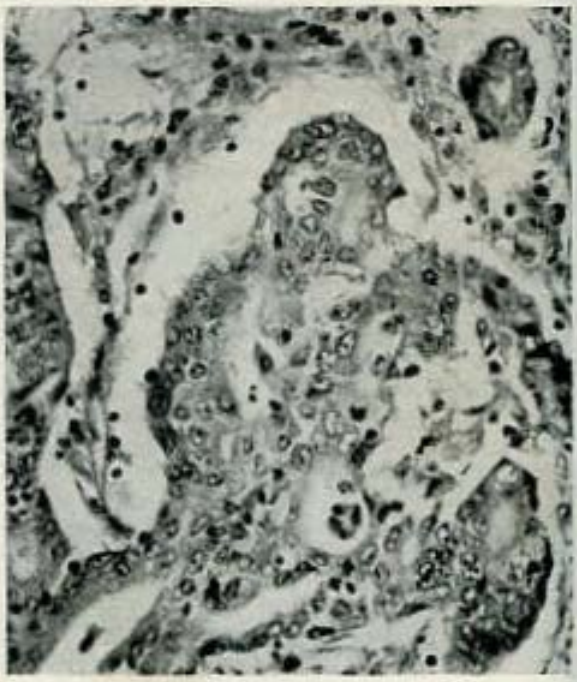

Fig. 18. Photomicrograph. Poorly differentiated carcinoma with glandular and squamous components. (Moderate enlargement.)

I have found a tumor of the gastrointestinal tract other than in the stomach that has keratinized cells and glandular areas, it usually has been a tumor of the cecum. In this type, I see several times as many cecal as sigmoid or rectal tumors. In rectal tumors I found only two that showed an adeno-acanthoma. More than one third of the cecal tumors that I went over showed the appearance of an adeno-acanthoma. My first experience with this neoplasm occurred in a woman who had multiple malignancies; she had an adeno-acanthoma of the uterus, and I tried very hard to make her second neoplasm of the cecum a metastasis of an adeno-acanthoma of the uterus. As I studied it further, I found more and more tumors of this sort occurring characteristically in the cecum and I came to the conclusion that actually one is dealing with two independent tumors. The stomach has a fair scattering of adeno-acanthomas and they frequently occur where two types of epithelium join; they are a little more frequent toward the cardiac end than they are in the body of the stomach. I have found it important from the prognostic standpoint to determine microscopically the presence or absence of blood vessel invasion. In the rectal tumors, it has been possible with the help of Dr. Lahey and Dr. Cattell to work out the prognostic significance quite carefully; it is only an extraordinarily rare case (under 1 per cent) in which there has been hepatic metastasis without blood vessel invasion. The involvement of lymph nodes has been of little prognostic help in these lesions except if all the nodes are involved, one has a poor prognosis. On the other hand, the cases which have had blood vessel invasion have been uniformly much worse than the cases that did not have blood vessel invasion. I think that it is well to extend the check-up for blood vessel invasion from the thyroid where we have been doing it to the large bowel tumors as well, because its occurrence is fairly frequent there. Incidentally, this has not any immediate bearing, but it might be of interest: I went over a considerable number of carcinomas of the breast, and in only 3 per cent of the breast carcinomas (all pretty advanced lesions) was there blood vessel invasion; overwhelmingly there is a lymphatic spread in that type of tumor. There is a considerable number of pathologists who voted carcinoid here.

DR. ACKERMAN: Dr. Gray asked about silver stains on it. Silver stains were noncontributory. There is, however, some further information on this case: this patient had definite evidence of blood vessel invasion. (In all large bowel cases Verhoeff van Gieson stains are done routinely to demonstrate the presence or absence of blood vessel invasion). This patient also had evidence of nerve sheath invasion and special stains for mucin also were done; these showed that tumor cells were forming mucin, which is against a diagnosis of carcinoid. Also, in a short period after operation this patient has already developed a large recurrence.

DR. WARREN: Has anybody any ideas as to why intestinal carcinoids frequently do metastasize and appendiceal carcinoids rarely metastasize? I have never been satisfied as to the difference in these two groups.

DR. ACKERMAN: Do you think, Dr. Warren, that the size of the lumen of the appendix would have any bearing on the early diagnosis, as compared to the size of the ileum?

DR. WARREN: I think that might be a real point. Before the carcinoids in the appendix get large and have a chance to metastasize, there is pain and they are taken out early because of this symptom.

DR. STOUT: One sees more active peristalsis in the small intestine than in the appendix.

DR. WARREN: I think that is a good point, Dr. Stout. Certainly appendiceal peristalsis is a pretty sluggish and feeble thing. I remember one accident early in the days of the Palmer Memorial Hospital when a patient had some radium needles implanted in the nasopharynx and one of these needles became unthreaded and the patient swallowed it, much to the consternation of all concerned. The course of the needle downward was watched by fluoroscopy and, fortunately, it came to rest in the appendix where it remained for four hours. The surgeon went in and retreived the radium by way of an appendectomy.

DR. SCHENKEN: Dr. Warren, if you have small vessels completely full of tumor, how do you tell that it is true blood vessel invasion rather than artifact?

DR. WARREN: That is where the Verhoeff stain or any of the elastic tissue stains come in handy. The small lymphatics (lymphatics other than the thoracic duct) have practically no elastic tissue in them and the thoracic duct has relatively little. One of the main reasons that I like to use, as Dr. Ackerman does, a combined connective tissue and elastic tissue stain for checking on blood vessel invasion is that it makes the blood vessels stand out nicely by virtue of their elastic elements, and helps to differentiate them from the lymphatics. I think sometimes one is on pretty shaky ground in trying to determine whether tumors are simply lying in spaces in the tissue, particularly where there is a lot of smooth muscle as in the case of the large intestine, unless one does either a Verhoeff or one of the other elastic tissue stains.

DR. H. T. BLUMENTHAL, St. Louis: Dr. Warren, do you feel that besides the morphologic similarity there is a deeper relation between the carcinoid tumors and the bronchial adenomas?

DR. WARREN: I don't know. I have tried time and time again to carry out satisfactory silver staining on bronchial adenomas and I have not been able to demonstrate a positive silver stain at any time. There is a striking similarity from the point of view of the moderate power histologic picture. I have not been able to prove that similarity in spite of pretty hard attempts at it. Masson, who is really the expert in this field, has been interested in them

and, up until the last I heard which was some two years ago, he had not succeeded in demonstrating clearly any argentaffine granules in the bronchial adenomas. Do any of you have any later information?

DR. MOORE: I might say, Dr. Warren, that Dr. Foot, of New York, had one example of bronchial adenoma back in the thirties in which silver stain showed typical silver positive granules. Whether or not he has made another observation of the same sort, I do not know.

DR. WARREN: I am interested to hear about it and will endeavor to find out whether there are more. As one looks at them under H & E stain, certainly they should be closely allied to one another.

DR. PINKERTON: I would like to ask how many separate sections you do in the course of studying whether blood vessel invasion is present or not. I don't know whether these should be serial sections or sections taken at different areas of the bowel.

DR. WARREN: That is a hard question to answer. I have been using a routine of four sections through four different parts of the tumor and then a random section in the block. It is probable that one misses an appreciable number of the instances of blood vessel invasion in that way and that if more serial sections were taken additional evidences of blood vessel invasion might be found. My guess is that the frequency of metastases even from an invaded blood vessel is not high. It has to be pretty obviously involved so that it will be picked up readily on routine section before successful hepatic metastases are started. I have tried to check on that in reverse by taking the cases in which it was known there was hepatic metastases and checking to see what the initial diagnosis had been, and it checked closely with the routine four sections on them. One of the things that every pathologist has to keep in mind is how heavy he can load the technical side of his laboratory and what is what one might term of "practical" value rather than theoretical value. I think undoubtedly perhaps twice as many instances of blood vessel invasion might be found but I don't think that the clinical significance would be much increased.

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14 LYMPHOMA OF THE RECTUM

History (presented by The Army Institute of Pathology, Washington, D. C.).—The patient was an 18 year old white male T/Sgt. The only history available is quoted: "Protruded from anus. At about 1 inch from anus and pedunculated. Posterior wall of rectum."

DR. WARREN: In this case, the malignant lymphoid tumors are well in the lead. This is a characteristic type of lesion: a polypoid growth with normal mucosa spread smoothly out over a region of heavy lymphoid infiltration and, in this area of heavy lymphoid infiltration, there are not only the normal cells, but there are some enlarged cells of reticular type as well (fig. 19). This appearance, then is of a tumor in which there are many well differentiated cells. Now, there are two problems: first, is it an inflammatory lesion or is it a tumor? Second, if it is a tumor, what specific type of lymphoid tumor is it? From the hyperplasia viewpoint, in lymphoid hyperplasia as seen elsewhere in the intestine, whether it appears acutely as in typhoid fever or whether it occurs chronically as in regional ileitis, one does not see this type of isolated polypoid growth occurring. The fact that this growth is fairly circumscribed and is well-demarcated from the rest of the intestinal wall leads me to believe that it is a true tumor. The type cell within it is a fairly mature lymphocyte with some scattered reticular cells. Now, those who like to call a tumor a reticulum cell sarcoma because it has reticulum cells in it would call this a reticulum cell sarcoma. I like to see the predominant cells the reticulum cell before calling it a reticulum cell sarcoma. The presence of some reticulum cells does not necessarily make it a reticulum cell sarcoma, because even a normal lymph node has a fair proportion of reticulum cells present and in any one

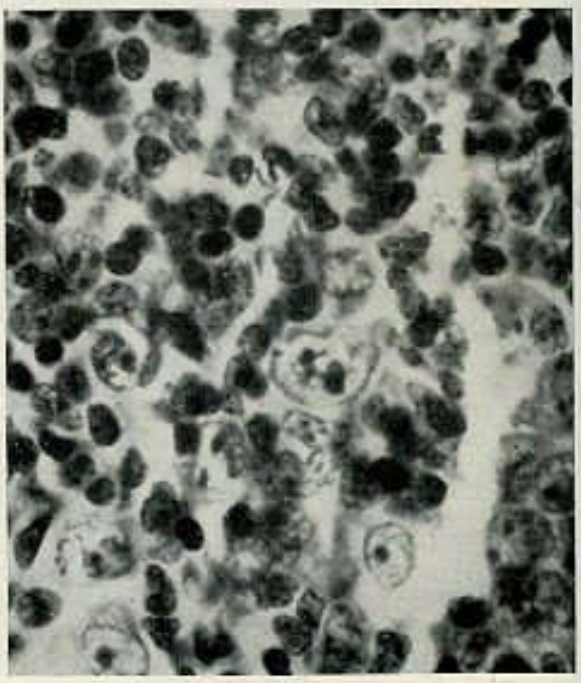

Fig. 19. Photomicrograph. Well differentiated cells of the lymphoid series and large reticulum cells. (High power enlargement.)

of the lymphoid tumors, so far as I know, there are some reticulum cells. So this tumor I would call lymphosarcoma, or if one wants to be fancy about the subdivision of these tumors, which probably is not justified, I would put it in the better differentiated of the lymphoid sarcomas and call it a malignant lymphoma or a lymphocytoma. Now, there has been little interest until recently in these tumors. They are pretty rare and have not been too well recognized. A study was made of 3,132 malignant tumors of the gastrointestinal tract at the Deaconess Hospital and Pondville. Twenty-eight of them, or .9 per cent, were solitary lymphoid tumors; of those, fourteen were in the stomach, eight in the large bowel and six in the small bowel. Of the eight occurring in the large bowel, three were of this polypoid rectal type (Warren and Lulenski). It is a small proportion of the tumors of the bowel in general and a relatively small proportion of the lymphoid tumors as well. I do not see any follow-up on this case. In some of my cases I have had as long as eight years follow-up and there has been no recurrence with a local removal of the growth, all of the stalk being removed. That makes one wonder, of course, as to whether one really is warranted in calling these malignant tumors, but, in view of the nonencapsulated mass of cells, with evidence of growth, with evidence of some loss of differentiation and no normal pattern, I think one is warranted in calling it tumor. Nonneoplastic lymphoid tissue has a tendency, whether it is inflammatory or not, as long as some of the lymphocytes build up to any degree, to make secondary follicles, and in this case I do not recall that there was secondary follicle formation. Can you check me on that, Dr. Ackerman?

DR. ACKERMAN: I found none.

DR. WARREN: I think it is just a more or less structureless mass, and that would be strong evidence to my mind against this being an inflammatory type of lesion. Any aggregation of lymphoid cells as large as this of inflammatory type would certainly have in its structure secondary follicles appearing among them. Col. DeCoursey has been quite close to the registry of lymphomas at the Army Institute. I wonder if he would like to add any comments on this?

COL. DECOURSEY: No, except I think I saw follicles in this.

DR. WARREN: Good. We will have to reexamine it. There's a suggestion of one, with a possible outline. I would hesitate to call that a really good follicle. Certainly I would say that follicles in the form that one usually sees them in inflammatory lymphoid tissue are not apparent here. Here and there are larger cells of reticular type that I think led some to put this in the category of the reticulum cell sarcoma. There is a suggestion of a follicle, but I would like to see rather more sharply-defined follicles scattered through it before regarding it as sufficiently characteristic to class it as inflammatory.

DR. H. M. WOOD, St. Louis: Do you think, Dr. Warren, that the good prognosis in this tumor is because of something inherent in the tumor itself or because of its location and configuration with early removal?

DR. WARREN: I think probably the location and configuration with early removal are the most important factors in the good prognosis of this particular tumor. The gastrointestinal lymphomas have a prognosis somewhat ahead of lymphomas in general. In 1942 we had a group of twenty-eight tumors of the gastrointestinal tract with three five year cures. This is a much higher proportion than one would find in lymphoid tumors elsewhere. I do not believe any of the series of lymph node tumors would be as high as that.

DR. W. R. PLATT, Louisville: What are the possibilities of a giant follicular lymphoma arising in this location and giving rise to this particular tumor?

DR. WARREN: I would think relatively slight because a giant follicular tumor as it spreads usually takes its characteristics with it. In this there was not a suggestion of the giant follicles or the coalescent secondary follicles that are so specially a feature in this type of tumor. The fact that a considerable number of these patients, rare as the lesion is, remain well for long periods of time, would not be important because some of the giant follicle tumors will go for relatively long periods of time but, sooner or later, the tumor usually becomes rapid in its evolution. A not infrequent history (some of Symmers' cases) went along for ten or twelve years and then took on a spurt of growth with loss of differentiation and the development of polymorphous cell sarcoma.

DR. DEL REGATO: Dr. Warren, you mentioned in the discussion the question of reticulum cell sarcoma, and that brought to my mind that many years ago Dr. Oberling, who originally described the reticulum cell sarcomas, told me that he did not think that more than 5 per cent of all lymphosarcomas were of that type. Now Dr. Arthur Purdy Stout who was here last year gave as his opinion that 50 per cent are of that type and, I believe, Dr. Fred Stewart says there are 90 per cent of that type. What is your own opinion on the percentage?

DR. WARREN: My own per cent would be closer to that of Oberling than the others. I do not like to call a tumor a reticulum cell sarcoma unless the predominant cell type is the reticulum cell. The mere presence of a few reticulum cells does not entitle a lymphosarcoma to be called a reticulum cell sarcoma. There are marked extremes: Dr. Henry Jackson, of Boston, is much more enthusiastic about calling lymph node lesions reticulum cell sarcoma than I am and Dr. Ackerman will remember, probably, frequently Dr. Jackson's coming into the laboratory, putting the slide under the scope and saying, "Oh, yes. That's reticulum cell sarcoma"; my coming along a little later or at the same time saying, "Oh, no, it is not a reticulum cell sarcoma."

I believe that there is no real purpose served by attempting to differentiate the reticulum cell sarcoma as a type of tumor unless it is sufficiently distinctive, sufficiently clear-cut to be readily recognized and sufficiently varied from the usual type in clinical behaviour and prognosis to make it worthwhile to set it apart from the general run of the lymphosarcoma group. The reticulum cell sarcoma, as I see it, is one which makes one wonder when he looks at it whether or not he is dealing with a metatastic carcinoma. Now those who favor 50 to 90 per cent of the lymphoid tumors as belonging to this category are taking those isolated cells of reticular type that I pointed out in this case under discussion and by virtue of their presence, calling it a reticulum cell sarcoma. It is exactly as though there was a group of vessels at anchor in a harbor and because there are a few trawlers among them, calling them all trawlers, regardless of whether there were battleships, tramp steamers and liners mixed in with them.

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15. HEMANGIOPERICYTOMA OF RETROPERITONEAL SPACE

History (presented by Lauren V. Ackerman, M.D., Ellis Fischel State Cancer Hospital, Columbia, Mo.).—This 68 year old man entered the hospital because of lower right abdominal pain, constipation which was relieved only by enemas, and prominent abdominal distention. On physical examination he appeared chronically ill. The abdomen showed no definite palpable masses. A scout film of the abdomen showed a rounded mass with calcification within it at the level of the twelfth rib posteriorly and lateral to the vertebral column. A barium enema was within normal limits and a gastrointestinal series showed no intrinsic lesion. On exploration a large mass was found in the right retroperitoneal space situated between the kidney and the right adrenal. It apparently was encapsulated and was removed with considerable difficulty.

On gross examination the mass weighed 1,020 gms., appeared encapsulated and, on section, was cellular with areas of hemorrhage, necrosis and focal zones of calcification. The patient's postoperative course was stormy but he left the hospital on the sixteenth postoperative day.

DR. WARREN: I am well pleased that evidently there is a varied opinion here. The gross reveals an encapsulated tumor with an attached normal adrenal. The kidney was not involved. So here is a huge retroperitoneal tumor situated between the kidney and the adrenal which did not involve either. The microscopic appearance is puzzling. There are rather nondescript cells tending to be somewhat elongate with a suggestion of clustering and orientation of these cells relative to one another (fig. 20). If one had only that, I do not think a diagnosis could be made. In the higher power there is a tendency again to the clustering of cells and with distribution of the chromatin rather reminiscent of the cells of the endothelial family. In general,

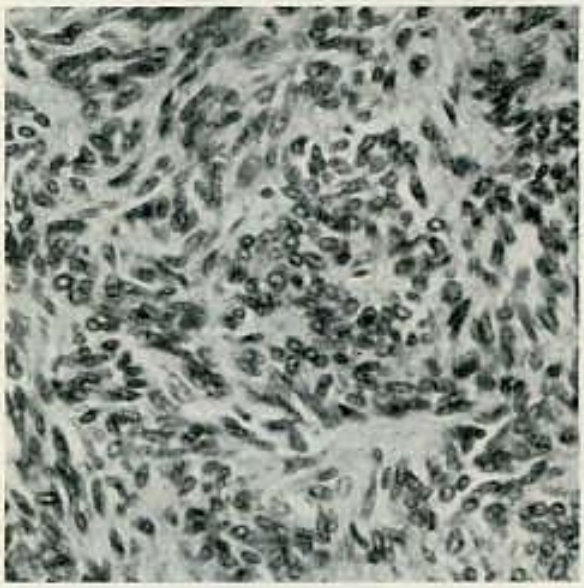

Fig. 20. Photomicrograph. Well differentiated cells suggesting blood vessel origin, grouped around slit-like spaces. (Moderate enlargement.)

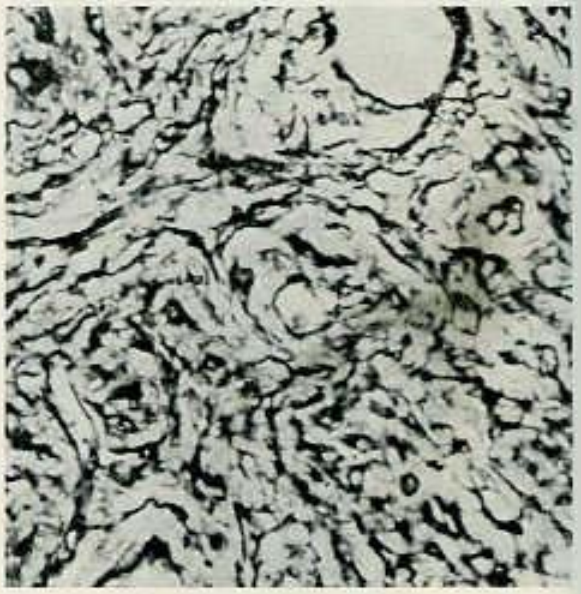

Fig. 21. Photomicrograph. Wilder stain for reticulum. Even patterning of reticulum suggesting blood vessel origin. (Moderate enlargement.)

there are not enough changes to enable one to call it flat-footedly an endothelioma. Now Dr. Ackerman has a reticulin stain and one can see the diffuse, even patterning, of the retimulin which helps to rule out some of the other diagnoses (fig. 11). I think that one can, in light of what is seen here, rule out the sympathicoblastoma, Schwannoma and neurofibroma; the reticular nests would not be compatible for a diagnosis of neurofibroma. Neuroblastoma might puzzle a little because there are some elongate cells the same as some of these clusters, and there are attempts at rather poor rosette formation, but none of them are sufficiently satisfactory for a diagnosis of neuroblastoma. One has to consider malignant melanoma of the spindle type. First, there is no pigmentation; I do not know that that means much because there are plenty of amelanotic melanomas, but the type cells here and the nuclei are not characteristic of the nuclei of the melanoma cells. The nucleus of the melanoma, even in the more spindly type of melanoma, is rarely as consistently elongated as the nuclei are here. There is no fairly prominent, rather clear, sharply-demarcated cytoplasm that goes along with a melanoma nor the abnormal mitoses and the bizarre tumor giant cells which are frequent in the more malignant forms of melanoma. I do not find sufficient clear-cut vessels to be satisfied with a lymphangioma. For the diagnosis of lymphangioma, I like pretty good lymph vessels to be forming and evidence of lumina within the cell clusters. Now, the next problem is whether to consider this as an undifferentiated type of primitive mesenchymal tumor or whether to consider this as a tumor of the hemangiopericytoma group. There are some who would properly say, "Well, we see cell clusters similar to these; we see suggestions of circular or pseudocircular arrangements of nuclei in some of the tumors of the primitive myotome that might go on, as in a Wilm's tumor, to form renal tubules eventually. The location also would be in favor of this." Dr. Ackerman, I wonder if you would care to discuss this further?

Dr. Ackerman: I felt first when I looked at this tumor that it might be of vascular origin for I could see areas which suggested that cells were grouped around vascular spaces and that the individual cells somewhat suggested endothelial origin. Now this tumor also was an encapsulated tumor with calcification in it and, therefore, it was apparently of fairly long duration. I considered the diagnosis of hemangioendothelioma, the malignant tumor of blood vessel origin. In that tumor usually one has, as Stout has pointed out, layering of the cells within the lumen against the framework of the reticulum and with anastomosing areas. The layering of cells was not present. Stout has been interested in a group of lesions of this character which he has designated as hemangiopericytoma: pericyte coming from the pericyte of Zimmerman, a modified smooth muscle cell. He has been able to demonstrate with Masson-trichrome stain that these cells suggest smooth muscle or modified smooth muscle origin. With a reticulin stain and with Masson-trichrome stain, and with the encapsulation of the tumor, I timidly called this a hemangiopericytoma. Now, hemangiopericytomas as a group grow rather slowly, metastasize reluctantly, but these tumors, however, can recur. Dr. Stout also concurred in this diagnosis. I think that this patient probably will have a fairly good prognosis; however, I think that the prognosis must be uncertain for there is a chance for local recurrence.

Dr. Warren: That is a clear exposition of the probable nature of this tumor and of the type cells involved. I think we all owe Dr. Stout a great deal for what he has done to advance knowledge of the tumors of this vascular and endothelial group, as well as the fine progress he has made in clearing up many of the tumors of nerve origin. This tumor I think is of special interest from the growth relationships. Here is a large tumor, 1,020 gms., which was still encapsulated, which elbowed its way between the adrenal and the kidney without involving either, and which for that reason must be assumed to be of low-grade malignancy. And then with the calcification as further evidence of slow growth, I think one can fairly assume that the probability is that the patient in this case will continue to do well and metastases will not appear. One of the things that struck me in going over this tumor was the rarity of mitotic figures and the complete absence of abnormal mitoses.

Dr. Neal: I would like to ask, why hemangio-? Why not lymphangio- or angio-?

Dr. Warren: I think one reason would be that some of the vascular slits contained red cells.

Dr. Gray: Dr. Stout has reported a group of tumors he calls mesenchymomas.

Dr. Warren: As a matter of fact, that is a group in which I was seriously considering placing this tumor; the location is good for these queer neoplasms of mesenchymal origin as remnants of primitive myotome frequently do remain behind in this area, and my memory is that in these relatively primitive mesenchymal tumors one does not find the type of regular patterning of the reticulum as was brought out by the stain in this case. Also, there is usually more in the way of mitotic activity and immature cells.

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16 ? BENIGN GIANT CELL TUMOR OF TENDON SHEATH

History (presented by Lauren V. Ackerman, M.D., Ellis Fischel State Cancer Hospital, Columbia, Mo.).—The patient, a 74 year old man, was admitted to the hospital on July 10, 1947, complaining of a painless lump of the right anterior chest which had been present for four months and had gradually increased in size. Physical examination was noncontributory except for the tumor mass located beneath the uninvolved skin on the right anterior chest wall and questionably attached to the right sternoclavicular area. There was no regional lymphodenopathy and roentgenograms of the chest were normal.

The tumor was rather radically excised; it measured 7.5 cm. in diameter, was relatively firm, yellowish brown in color and showed a few areas of necrosis.

DR. WARREN: The majority of the pathologists here are anxious to call this a malignant neoplasm. The hemisection of this tumor shows it to be fairly homogeneous and yellowish tan in color. The microscopic appearance reveals the presence of giant cells of the foreign body type, of spindle-shaped cells, and of rather nondescript cells of indefinite character with a moderate amount of chromatin in the nucleus (fig. 22).

DR. NEAL: What about those vacuoles?

DR. WARREN: There are scattered vacuoles throughout. Some of the giant cells have striking vacuoles. There was some hemosiderin present. I thought this was a giant cell tumor but one of the benign ones rather than a malignant one. First, the yellowish-tan color with a somewhat lobulated or moderately compact tumor, is pretty indicative of a tumor of the benign giant cell family. Foster had an article about a benign giant cell tumor of the tendon sheath in which he tied it in with the sclerosing hemangioma. I am not ready to go 100 per cent of the way with him, but there are some well-defined points. He has carried further a view that Dr. Wolbach has had for some time and that I am inclined to share to a considerable degree: that there is a marked gradation all the way from the ordinary run of the hemangioma through the sclerosing hemangioma to some of these benign giant cell tumors. In this tumor there are the giant cells of foreign body giant cell type, some of them with inclusions and some without. One assumes that the reason the giant cells formed initially was that there was something there to stimulate their formation and that the ones which have no vacuoles have successfully digested what had been within them. Second, there has been a hemorrhage in the region, as evidenced by the hemosiderin. Third, the fibrosis implies that there probably has been a definite stimulus for fibrous tissue proliferation, which may be due to old blood from hemorrhage. Wolbach has long been interested in this type of tumor and it is well to remember that as far back as 1912 he had a paper on the hemangioendothelioma, giving the histologic appearance of giant cell xanthoma. He has been pretty consistent in continuing his emphasis on this field. Apparently, aside

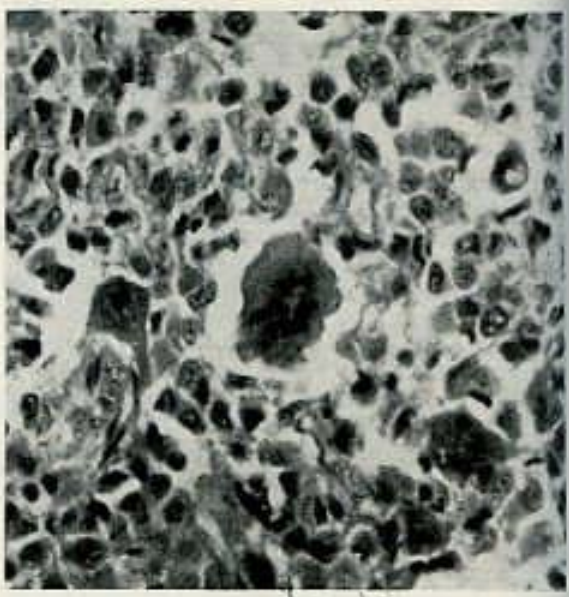

Fig. 22. Photomicrograph. Note numerous giant cells with multinuclei and well differentiated cells surrounding them. (Moderate enlargement.)

from Foster's article, there has not been any very special interest in this field during the last few years. An article by King from England back in the early thirties described the extra-osseous type of the giant cell tumor, not attempting to separate the tendon sheath group from the others. He brings out that there may be the spindle cells with various gradations down to a spheroidal type, that there are the vacuoles, many of which contain material which stains positively for fat, and some may be so marked as to resemble a lipoma; and that the giant cells are present and often spottily present, sometimes closely packed in areas of almost solid giant cells, and other times, relatively few. And then, in addition to the spindle cells, are these spheroidal types of cells I mentioned that tend to occur in clusters and bundles and sometimes become multinucleated. There is much intercellular material laid down, mostly collagen, and frequently there may be foci of mucoid degeneration. I have seen some of these which make one wonder whether he is dealing with an inflammatory reaction in a traumatized area—the ganglion, for example—or whether one is dealing with a degenerated area. This tumor has been thought to have a possible relationship with the synovial tumors. That is not so well supported, however. The commonest lipoid present is a cholesterol-rich lipoid and frequently pure cholesterol crystals are present. All have undoubtedly, on frozen sections, caught doubly refractile crystals. The giant cells with the vacuoles are incidental in this tumor and I am inclined to believe that probably this general group of tumors is a true tumor. I do not go as far as Jaffe and Lichtenstein do to say that the tendon sheath tumors are purely

inflammatory phenomena, but I believe that they are initially neoplastic, probably of endothelial origin and with a terrific superimposed response that is reaction to lipoid-rich material and to areas of old blood either from the vascular channels present or from hemorrhagic foci that have occurred. What did you think, Dr. Ackerman?

DR. ACKERMAN: I will have to say that I did not know what this tumor was; but I think, in retrospect, that Dr. Warren is entirely correct. I think that if one agrees that it is a giant cell tumor, whoever says that it is a malignant giant cell tumor, is going to put himself in a group in which there have been only rare, if any, malignant ones before this.

DR. SCHINKEN: Dr. Warren, I believe that I have had an osseous one that I will see in heaven, I hope, that I doggedly maintained was benign for about three or four recurrences and the patient died of metastases. You, Dr. Warren, saw the sections of this tumor and you suggested repeatedly that it must be malignant.

DR. WARREN: I think that in giant cell tumors that arise from bone, one has to study them carefully for evidence of a malignant tumor. I have yet to see one of the extra-osseous type which is clearly malignant. I did see a woman at the Palmer who had a tumor of the radius which was first curetted, then recuretted, and bone chips put in; she had some irradiation therapy in between these procedures. Finally it was necessary to resect the bone and then tumor recurred, necessitating amputation. She then got an extraosseous recurrence of that tumor in the soft parts of the stump. That was removed and she has been well for eleven years since, and I think will stay well. That was one of the most persistently recurring of the osseous giant cell tumors.

DR. W. H. BAUER: I would be rather inclined to consider the tumor malignant since I saw in my slide an area of necrosis in the center, pleomorphism, an irregular pattern of distribution of giant cells, and even a few tumor giant cells.

DR. WARREN: That is a sound point. In the margin of areas of necrosis, reparative cells will become hyperchromatic without taking on malignant potentialities. I think that the areas you described were evidence of reparative activity on the part of the cells rather than evidence they had taken on malignant characteristics. That is only a matter of personal interpretation and ultimately we will have the answer in this case from the patient. We will then regard this tumor as belonging in the group of benign giant cell tumors and wait and see whether we are right.