#179 ©

ARTHUR PURDY STOUT SOCIETY

SEMINAR

1967

Comprised of Fifteen Cases

New York, N. Y.
June 10, 1967

Columbia-Presbyterian
Medical Center

~~Elson~~ - & Gattes - Benign
Intimated he thought it was benign

Case No. 1 LOW GRADE ANGIOSARCOMA SOFT TISSUE OF LEG
Submitted by Dr. Elson B. Helwig

The patient is a 19 year old man who complained of a slowly enlarging mass in the popliteal fossa of the leg. It enlarged for three months and was occasionally painful, The gross specimen consisted of an elliptical portion of skin 3.5 x 1.5 cm., beneath which was a fibrofatty mass measuring 3 x 2 x 1.5 cm. On sectioning a variegated appearance ranging from white fibrous to darker hemorrhagic areas was noted. widely excised

Owen Case

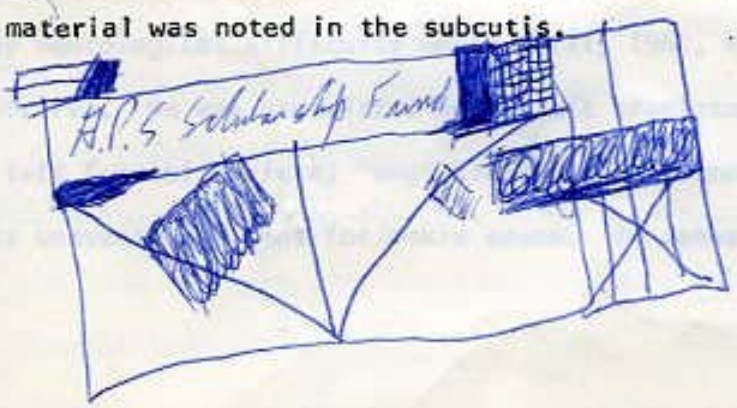
Papillary lesion → malignant. loss of basement membrane | Angiosarcoma

Case No. 2 SUBEPIDERMAL NODULAR FIBROSIS OF LEG -
Submitted by Dr. Saul Kay

Patient is a 52 year old colored woman admitted on September 19, 1966 for excision and graft of a chronic ulcer located on the medial aspect of the right ankle. She had first noticed the lesion in 1945 when it presented as a black, flat, depigmented spot 2-3 cm. in diameter. This gradually grew larger and broke down in 1960 and oozed clear fluid. The lesion was excised on September 23, 1966. She was last seen in March, 1967 at which time there was complete healing. A biopsy previously done on June 7,1966 was reported as granulation tissue.

The excised specimen consisted of an ovoid piece of skin 2.7 x 2.1 x 1 cm. On the epidermal surface was a central, longitudinal, 1.2 cm. slit with infolded borders. A 0.5 cm. cavity filled with mucoid material was noted in the subcutis.

Calcium



Case No. 3
Submitted by Dr. Robert S. Totten

This is an encapsulated tumor shelled out of the pharynx of a 38 year old man.

Case No. 4
Submitted by Drs. Merle Delmer and Alvin O. Severance

The patient had a history of capillary hemangioma diagnosis on a lesion removed eight years previously from the left nasal fossa. Now in January 1967 an apparent recurrent submucosal tumor mass, 2.5 x 1.8 x 1.5 cm., located approximately 1 cm. above the ala of the nose was enucleated. We are told that following biopsy eight years previously, radiation therapy was used. Following this radiation therapy, there is a history of intermittent episodes of bleeding and slow increase in size of the recurrent lesion.

Case No. 5
Submitted by Drs. Kaity Yannopoulos and Raffaele Lattes

This is a 64 year old man who was admitted for the first time to Columbia-Presbyterian Medical Center because of confusion, disorientation, and incontinence. Workup at that time showed a right sided weakness and an arteriogram showed a right frontal parietal tumor. A craniotomy was performed with the removal of an "angioblastic meningioma". There was complete recovery and disappearance of neurological signs. The patient was free of any neurological difficulty until April, 1962, at which time he had two seizures. He was readmitted and a left craniotomy was done with removal of a left frontal parietal "angioblastic meningioma". This time, again, recovery was uneventful except for ankle edema. In January, 1963, the patient was

Case No. 5 - continued

admitted again for right upper quadrant pain with no associated gastro-intestinal symptoms. From the time of admission the patient was continually febrile. All cultures were negative. On physical examination the most important findings were tenderness in the right upper quadrant, right costo-vertebral angle and right flank. A probable rounded mass was attached to the liver and judged to be 8 cm. in the midaxillary line. Neurologically there were increased deep tendon reflexes.

LABORATORY DATA: (At time of admission to Presbyterian Hospital on 1/15/63) ESR 77, Hgb.10.1, Hct. 31, WBC 17,500, P. 88. Urine: sp.gr. 1.020, ph. 5.5, protein (≠), 0-4 RBC/hpf, 2-6 wbc/hpf. Stool guaic (-). BUN 15, alk. phos. 55, repeat 60, serum bilirubin 0.4, VDRL negative, Protein 10, CF and TT (-), SGOT 25, SGPT 20, retic. count 2.3, plts. 171,000, sputum nl. flora. Acid phos. normal, P.E.P. albumin 20, gamma globulin 0.9. BSP 26% at 30 minutes. Ca 8.6, P. 3.9, PPD, 2nd strength (≠). Chest and rib xray showed two extrapleural densities on the right associated with destruction in the right 5th and right 10th ribs. The skeletal survey was otherwise negative except for changes due to previous craniotomy. A gall bladder series was not visualized. Upper GI series showed a small hiatus hernia and a questionable filling defect within the stomach. Barium enema showed a questionable impression of the bowel wall in the region of the pouch of Douglas due to a mass or peritoneal fluid.

A liver biopsy was performed. The patient kept on going steadily downhill with elevated temperature. His NBN rose to 135 mm. percent., and his bilirubin to 8.6. He died on March 4, 1963. An autopsy was performed which showed metastatic involvement in liver, ribs, parietal pleura, vertebrae, mesenteric lymph nodes, right kidney, spleen, occipital bone, right adrenal. The immediate cause of death was a severe bilateral bronchopneumonia with abscess formation.

Case No. 6 LEIOMYOMA OF UTERUS, HOBBS' TYPE vs. DIFFUSE HEMANGIOPERICYTOMA
Submitted by Drs. Merle Delmer and Alvin O. Severance

This 19 year old female had severe cramps and pain in the left pelvic region, less severe around the menses. The uterus was about two times normal size and multinodular with what looked like leiomyomata.

[illegible] of cells outside vessels]

Case No. 7 LEIOMYOSARCOMA OF FEMORAL VEIN
Submitted by Dr. John T. Ellis

This 57 year old white male was under medical care for chronic pulmonary emphysema. He called the attention of the physician to a mass in the left groin which had been present for several months. The tumor was sharply circumscribed, encircled the femoral vein just below Poupart's ligament and could easily be separated from the femoral artery. The specimen consisted of a sphere of firm white tissue covered by a pseudocapsule which measured approximately 6 cm. across and replaced the wall of the femoral vein which was ligated above and below the tumor.

Following the pathological diagnosis, additional xrays were taken and metastatic lesions were identified whereas they had been absent in xrays taken several months previously. The patient died approximately four months following surgery, but was not autopsied.

Case No. 8 ANGIOSARCOMA OF SKIN OF SCALP
Submitted by Drs. Merle Delmer and Alvin O. Severance

This is a lesion on the scalp of a 46 year old male, present for one year. Initially it looked cystic and was incised with the result that blood flowed out of it. It was treated with local cautery but seemed not to be getting any better and was excised in late October 1966 after being followed since July, 1966.

Case No. 9 ANGIOSARCOMA OF LIVER, ARSENIC-INDUCED
Submitted by Dr. John W. Pickren

This patient was referred to R.P.M.I. at age 49 with the following history: He had psoriasis from the age of 12 and took Fowler's solution for 17 years between 1940 and 1957. Dosage varied but generally was around 30 drops a day. After he discontinued taking Fowler's solution in 1957, he was treated with topical cortisone ointment. He was admitted to this hospital in May 1964. At that time, he had a nummular psoriasis. He complained of fatigue and abdominal discomfort. He was jaundiced, and his liver was palpable 4-5 cm. below the right costal margin. The liver was tender and nodular.

On the fourth hospital day, the patient became maniac; shouting and cursing and it took five individuals to steady him. He was given nembutal and chlorpromazine. His condition steadily deteriorated; he developed acute respiratory distress and died on June 4, 1964, about one month after his admission to this hospital.

An autopsy was performed. The main findings were in the liver. The liver weighed 4,000 grams. Its surface was irregular, nodular, and yellow. The liver was very hard and the cut surface showed extensive hemorrhagic nodules. No normal hepatic architecture was found. The largest nodule measured 10 cm. in diameter and the smallest one measured 0.5 cm. in diameter.

Case No. 10 SARCOMA OF PENIS ? MM610
Submitted by Dr. Robert S. Totten

A tumor of the corpus cavernosum in a young male.

No further information at this time.

Case No. 11 Post-mastectomy lymphangiosarcoma
Submitted by Dr. Charles J. Farinacci

A 77 year old woman had been asymptomatic for seven years after radical mastectomy for adenocarcinoma of her right breast (grade II) with no metastases to the axillary lymph nodes. Then massive raised reddish areas appeared scattered over the entire arm and anterior chest wall. A biopsy was done on the lesion of her right arm. On cut section, the specimen contained a well-circumscribed, hemorrhagic, somewhat translucent firm area measuring 1.5 cm. in diameter surrounded by fat and continuous with the overlying skin.

Case No. 12 Post-mastectomy lymphangiosarcoma
Submitted by Dr. John Pickren

This patient, a 55 year old woman, had a right radical mastectomy in 1957 for a carcinoma of the breast. This operation was performed at the Millard Fillmore Hospital in Buffalo and the diagnosis was, "carcinoma of right mammary gland with metastasis to right axillary lymph nodes".

Following surgery, she was given ionizing radiation to the right axilla. The amount of radiation is not available. In July, 1966, whe developed a nodular painful hemorrhagic area on the volar surface of the right forearm. The lesion persisted, and she was referred to this hospital in September, 1966, for treatment.

Physician examination disclosed an obese individual weighing 260 lbs. Her right arm was massively swollen. At the biceps of the right arm, her measurements were 57 cm. while the left arm measured 37 cm. in diameter. In the mid-portion of the forearm, the right side measured 45 cm. and the left side 30 cm. in diameter. Along the radial aspect of the forearm, just above the wrist, there was an indurated area which was hemorrhagic and nodular. Radiographs of the lungs were not remarkable. Following biopsy, a disarticulation of the right arm was performed. The patient has been followed in our clinic. She was last seen on January 19, 1967 at which time she had no evidence of recurrent tumor.

Case No. 13 MYXOMA of HEART
Submitted by Dr. Artemis Nash

A 60 year old white Russian-born male began having progressive exertional dyspnea for 1½ years, and orthopnea and ankle swelling for six months prior to admission to the hospital. Except for inguinal herniorrhaphy and symptoms of chronic peptic disease he had a healthy past history.

On admission he was found to be in moderate congestive heart failure with a Grade III/VI presystolic crescendo apical murmur and xray evidence of cardiomegaly, with left atrial and right ventricular enlargement. It was felt that he had mitral stenosis due to old rheumatic disease, and a cardiac catheterization and cineangiography confirmed this demonstrating, in addition, pulmonary hypertension with no evidence of mitral insufficiency or aortic valve disease.

After symptomatic improvement on cardiotonic and diuretic regime, an exploratory cardiotomy (by-pass) for an intended mitral commissurotomy was performed. Upon entering the left atrium, a large tumor was found filling the entire chamber and attached near the annulus of the mitral valve between the annulus and the left atrial appendage. The tumor was easily removed by blunt dissection in a subendocardial plane.

The gross specimen was an 8 x 5 x 4 cm. lobulated soft mass with a smooth yellow to red surface and a soft, semi-liquid, bright yellow to dark red cut section.

Case No. 14 ANGIOMATOSIS, DIFFUSE, OF EXTREMITY
Submitted by Dr. Raffaele Lattes

This nine year old girl was born with "congenital hemangiomata and arterio-venous fistulae" of the right forearm and enlargement of the heart secondary to the arteriovenous shunt. At different times, prior to the present

Case No. 14 - continued

admission, she was treated with radium therapy, several attempts of ligation of AV fistulae, based on arteriographic study, with little if any result. The entire right arm was diffusely enlarged. There were visible and palpable pulsations of arm and shoulder and a definite thrill and an audible bruit. Over the skin of the extremity there were many "strawberry hemangiomata". Temporary occlusion of the blood supply to the right arm resulted in a changed heart rate from 110 to 70. Arteriograms showed a very large tortuous vessel visible on the inferior aspect of the arm and the axilla as well as innumerable smaller tortuous vessels throughout the soft tissues. In 1952 it was finally decided that since the several previous surgical and radiotherapeutic procedures had not brought about any improvement, and besides this the skin over some of the hemangiomatas often ulcerated, resulting in bleeding episodes, amputation was justified. It was not mentioned above that the humerus and radius were elongated in comparison with the left side and that the right ulna was enlarged and thickened and had a moderate amount of bending of the shaft. On July 1, 1952 an amputation was performed through the lower end of the humerus. Since then the patient has been followed intermittently in our clinics with no further complaints ascribable to vascular malformations. The last recorded visit was in 1961.

The examination of the amputated arm showed a diameter of 9.9 cm. at the site of amputation. The wrist was deviated toward the ulnar side. Besides the multiple scars of the previous procedures, the skin was raised into nodules in several places and showed areas of brown pigmentation. Upon dissection some difficultywas found in identifying the normal blood vessels due to previous scarring. The radial artery was not definitely identified. The ulnar artery was small but in normal position. Numerous tortuous large and small vascular channels were found in the soft tissues of the whole forearm.

LYMPHANGIOMATOSIS OF MEDIASTINUM & RETROPERITONEUM

Case No. 15
Submitted by Dr. Raffaele Lattes

Specimen taken from a 6½ weeks old infant with congenital heart disease. The infant was born after 7 months gestation weighing 5 lb. 4 oz. There was rapid weight loss to 4 lbs. 4 oz. Sometime after birth the infant developed a left pleural effusion with mediastinal shift which recurred after repeated taps, but gradually decreased in 4-5 days on tube drainage. The effusion was chylous, and was refed to the baby. Nevertheless, the infant developed hypoproteinemia and was treated with g-globulin when 40 days old. It died after cardiac catheterization when 48 days old.

Autopsy findings: Body weight: 2425 gm.
Body length (crown heel): 19½ inches.

Significant gross findings limited to the chest.

The great veins and arteries are normal except for a persistent left superior vena cava and absent left innominate vein. Drainage of the persistent LSVC into the coronary sinus.

Heart: Enlarged right atrium, marked hypertrophy of both ventricles. Large anterior patency in foramen ovale with communication between atria. Deformity of all valves by many smooth firm nodular excrescences.

The descending thoracic aorta was flanked on each side by a softly nodular purple mass resembling confluent lymph nodes, and measuring 4.0 x 0.6 x 0.3 cm. on the left and 4.0 x 0.7 x 0.3 cm. on the right side. Centrally placed behind the aorta within the crura of the diaphragm was a thin-walled ovoid shaped sac measuring 1.0 x 0.3 x 0.4 cm. and placed in a horizontal position. This chamber communicated by a probe passable channel with the mass on the left side. Communication of the sac with the mass on the right side as well as thoracic duct entry into the venous circulation could not be demonstrated. However, numerous minute vascular branches were noted to open into the persistent left superior vena cava at and slightly below the entry of the left subclavian vein.

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ARTHUR PURDY STOUT SOCIETY SEMINAR

New York City - June 10, 1967

Your Diagnosis:

1. Benign lesion with proliferation of vessels, fibrous tissue and so on I do not have a good name forthis. ~~Is there history of fracture?~~

2. Benign lesion. What used to be called sclerosing hemangioma; I refuse to call this "hemangiopericytoma".

3. Benign tumor, unclassified. Not a primary vascular tumor.

4. Angiosarcoma. Questionably related to previous irradiation or "Sarcoma, unclassified". This has a mixed pattern.

5. Do not know. Questionably "metastatic meningioma". ~~Does not look like~~ renal cell carcinoma.

6. Cellular leiomyoma. I cannot guaranty that it is not malignant. I am worried. Tell me about the lungs.

7. Leiomyosarcoma of the femoral vein.

8. I doubt if this is malignant. Very worrisome of course. I would like to have a fat stain.

9. Sarcoma - arsenic induced?

10. Angiosarcoma - typical example!

11. Lymphangiosarcoma

12. Lymphangiosarcoma

13. Myxoma - Must dig out the base. Otherwise it recurs.

14. Angiomatosis with A-V fistulae.

15. Lymphangiomatous proliferation. Probably not a true tumor.

Please mail this to Dr. Stout as soon as possible.

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MORNING SESSION

(The Seminar convened at 8:30 o'clock, Dr. Arthur Purdy Stout, Honorary Chairman; Dr. Alvin Severance, Chairman, presiding.)

CHAIRMAN SEVERANCE: It is getting a little bit further on in time and I think we better begin the morning session of the Annual Meeting of the Arthur Purdy Stout Society.

This morning I am supposed to be the voice of Dr. Stout. I don't know how well I can fulfill that duty.

We thought we would start the meeting by having the projection operator show some pictures of some of the "wheels" of the Society that Dr. Stout refers to and some of their social activities at some of our meetings in the past.

So, if the projectionist will show some of those photographs of people, we would like to see those now.

(Film.)

Introduction by Dr. Stout:

You see that a year ago I was able to get about and now I'm a hospital cripple. I never thought this would happen to me, but when you get to be eighty-two, the exigencies of fate don't always treat you very well.

I must say that I have received very kind treatment except once during the year when they tried to force me to accept a television set. (Laughter) There was a huge difference of opinion about that. Somebody-- I don't know who it was-- evidently was directed to find out whether Frinda and I would accept a television apparatus in our house, in our apartment. I thought we had established very definitely that we would not, and they told me that it would be a fine

education as to the good old times to see how they have vanished, and it's good to look at sports, and so on.

I said "I absolutely refuse to have your money wasted on buying me a television set," and they got mad at me. I said, "The only thing that I care about is the Arthur Purdy Stout Scholarship Fund." I said to take that money that would be used to buy this accursed television set and turn it back into cash and apply it to the Scholarship Fund of the Arthur Purdy Stout Society." I knew Frinda would not permit a television set in the house and I knew that I would feel the same way.

So, much to their unhappiness, they could not educate me. After all, at eighty-two I thought was time for me to stop being educated. What would I do with education at my advanced age! (Laughter) I would just be unhappy that the money had not been spent on a project that is very close to my heart, and that is the APS Society Scholarship Fund.

So they finally gave me up as a bad risk and they did turn the money into the Scholarship Fund, and then Frinda and I were happy.

I am incorrigible. I don't read the newspapers any more because they are terrible and the news they bring is just as terrible. I don't want to look at the United Nations squabbling amongst themselves and so ineffective.

Is the first case ready, Dr. Severance? We, I think, better move on now to the first case. I might explain that because of being so old and so cooped up in the hospital, that I have had no chance to go over these cases. I have read the histories and I presume I have seen a number of them before, since Rafe and I, particularly Rafe, picked them out.

I think you would agree that they are not very easy. My contribution to the discussion will be not so much to try and get what the case should be called but something that is very near to my heart-- how do you tell a malignant tumor so that the surgeon can proceed on the best form of treatment. I am just going to recount something-- I never did this before and I don't know whether you have heard it or not, but now I feel that it is more important to try to determine the malignancy of a case rather than to try to get a name.

I know that some of the more modern members of the APS Society probably would not agree, but I believe that I have had the good fortune to save more extremities from being unnecessarily amputated, and saved a child and the parents from great unhappiness. So if you expect to hear from me in my comments on cases, what name I would give, I shall probably say I might guess at the name but I would like to try to help recognize the benign from the malignant.

All right.

CHAIRMAN SEVERANCE: As Dr. Stout was commenting about the fact that the television set was useless in his life to further his education at age eighty-two, you must remember that he continues to further his education in other ways, such as reading the medical literature. I'm sure he has not stopped that; just that he didn't think that television would contribute to that purpose in life.

I might also remind the members and friends present that there is opportunity for them at Christmas time, birthdays, and so forth, to remember the Arthur Purdy Stout Society Scholarship Fund. Some of us have in the past. I just want to remind the rest of us to continue to do so in the future.

I don't know whether Elson Helwig has shown up, but he wasn't here a few minutes ago. He hasn't presented himself. So I will call on Saul Kay. But while he's getting up here, I'll tell you a little story that I told once before.

The fact that Elson isn't here reminds me that a mother and a little boy were in a hotel and he had to go places. So she said, "There's a room that says 'Men.' You go in there and I'll wait for you. He went in and he came back a few minutes later, but his pants were wet. And she said, Son what happened?" He says, "Well, there were only two places. They were occupied by old men. One couldn't start, one couldn'tstop, and I couldn't wait." (Laughter).

We can't wait for Elson. So, Saul, will you start with the second case. I understand that Dr. Lattes is going to limit you to fifteen minutes. Does that include the discussion or does that include just Saul's presentation?

DR. LATTES: No. Just for Saul.

Case No. 2
Submitted by Dr. Saul Kay:

DR. KAY: I really don't need all that time. As a matter of fact, I can't see why we need even fifteen minutes, that is, for any of the cases, because Dr. Stout says we are just going to decide whether they are benign or malignant.

Protocol:

Patient is a 52 year old colored woman admitted on September 19, 1966 for excision and graft of a chronic ulcer located on the medial aspect of the right ankle. She had first noticed the lesion in 1945, when it presented as a black, flat, depigmented spot 2 to 3 cm. in diameter. This gradually grew larger and broke down in 1960 and oozed clear fluid. The lesion was excised on September 23, 1966. She was last seen in March, 1967, at which time there was complete healing. A biopsy, previously done on June 7, 1966, was reported as granulation tissue.

The excised specimen consisted of an ovoid piece of skin 2.7 x 2.1 x 1 cm. On the epidermal surface was a central, longitudinal, 1.2 cm. slit with infolded borders. A 9.5 cm. cavity filled with mucoid material was noted in the subcutis.

The first excision was actually done in June of 1966 when the diagnosis of granulation tissue was made. This was made in our laboratory and it didn't seem worth sending to you because it was an inadequate biopsy. But then a total excision was carried out in September, and I have the last follow-up at March, 1967, which admittedly isn't too long but at that time there was a complete healing of the lesion.

Grossly all there was was an elliptical piece of skin 2-½ cm. maximum dimensions, and on cutting through it this appeared to be a small cavity filled with mucoid material. I don't know how accurate that description is by the resident; whether it was mucoid material or just old blood or coagulum. At any rate, we will take a look at the microscopic here on the first slide.

Slides:

MICROSCOPIC DESCRIPTION: (S-66-8503) Section shows skin and subcutis with partial ulceration of the epidermis. The dermis and subcutis are replaced by a vascular lesion which in general is solid with indistinct borders but tends to be lobulated superficially. Most of the lesion is composed of solid whorls of spindly cells with elongated nuclei. I interpret these as endothelial cells since they sometimes line clearly-defined vascular spaces. The latter are more prominent superficially where they can be identified as capillaries. Sometimes these spaces are dilated and may represent venules. In the depth, prominent thick-walled arteries are noted and these may represent "feeding" vessels to the proliferating lesion. Calcific clumps are noted within portions of the lesion again emphasizing the vascular nature of this condition. Superficially abundant inflammatory reaction is present so that the lesion bears a resemblance to ordinary granulation tissue.

DISCUSSION: It is difficult for me to classify this "tumor" in this middle-aged colored woman. It resembles the juvenile hemangioendothelioma but such a lesion in an adult is some cause for concern. I hesitate to call it Kaposi's sarcoma since the vascular proliferation extends right up to the epidermis, and the spaces are real and not just "slits". If the history is accurate, the patient has

been troubled with the condition for 21 years. Is it related to a pyogenic or traumatic condition? This is the diagnosis I would like to make, thought I must admit I have not seen this cellularity with all the pyogenic granulomas I am familiar. In trying to be a prognosticator as Dr. Stout, I would say this lesion will not metastasize.

DIAGNOSIS: Capillary hemangioma (pyogenic type) of ankle region.

This case really only puzzled me by virtue of the history. I think I was told it was an acute process. I probably would have dismissed it merely as an ulcerated type of pyogenic granuloma if it were not for the history and the fact that apparently it had come and gone or never really went away. Of course, it made me worry about whether it was something more ominous than just a capillary angioma of the pyogenic type, but I finally decided it was benign.

The follow-up was not long enough, but I don't believe that this will be any more than a local problem, and from the point of view of the name, I would just personally pick on pyogenic granuloma rather than capillary angioma of the pyogenic type.

CHAIRMAN SEVERANCE: From the votes that have come in from the members of the Society to Dr. Lattes, there is a variety of diagnostic opinions and I want you to comment on them if you see fit.

Sclerosing hemangioma; fibrous xanthoma, vascular type; capillary hemangioma; hemangiopericytoma; foreign body with granulation angioma (complex type with venous, capillary and hemangiopericytoma features); capillary hemangioma, granuloma type (need thinner section, also special stains would help); angioleiomyoma, multiple small capillaries with thick endothelial cells,vascular leiomyoma (venous hemangioma?); fibrous histiocytoma, ? vascular leiomyoma; sclerosing hemangioma or fibroxanthoma in the wall of an epithelial inclusion cyst,

pseudoepitheliomatoma proliferation; capillary hemangioma (pyogenic type); "sclerosing hemangioma".

Would you like to comment on some of these fancy names?

DR. KAY: I'm sorry we don't have the actual numbers just to see what the majority talked about, but we are really not too far apart in any number of them.

The "sclerosing hemangioma" is the old name for what I call dermatofibroma. In most of the "sclerosing hemangiomas" the vascular nature of the lesion is quite obscure and I don't believe that this is what these really are, i.e. that hemangiomas become sclerotic and you are left with this sort of a scar. Some of them seem to show more vascularity than others, but I believe they are different lesions. Why this one is called a "sclerosing hemangioma" I am not really certain.

The "vascular leiomyoma" intrigues me because I would have thought that this would be relatively easy to determine. I did have trichrome stains and silver stains but really, a smooth muscle tumor had really never occurred to me. In addition, of course, the histiocytes had contained a lot of lipid. Now, it is not uncommon to see a collection of histiocytes containing lipid material. This is due to a breakdown of blood. So there may have been some histiocytes. I did not really think this was part of the lesion.

Discussion:

CHAIRMAN SEVERANCE: Anyone in the audience want to talk? Does anyone want to discuss their diagnosis with Saul?

DR. HILL: I would like to ask Saul what he made of the calcification?

DR. KAY: We can see calcification in any type of lesion that has angiomatous features. The x-ray people tell us this is what they look for. They look for the stippling effect, and I think that here it's probably just a question of calcification in a vascular lesion. I admit you don't see this in young hemangiomas too commonly, but every time there is a vascular newly-formed lesion in the soft tissue, the x-ray man almost invariably looks for calcification.

So I think this is part and parcel of a vascular proliferation, whether it be hamartomatous or acquired. Isn't that what you interpreted it as?

DR. HILL: I didn't really know what to make of it.

DR. KAY: Is Vince Collins here? Am I right about the x-ray approach to this soft tissue vascular malformation?

DR. COLLINS: We have of recent years I think given more attention to the extremely fine calcifications that may be seen if radiographs be taken with particular care to demonstrate this; and I refer particularly to mammography and the extremely fine diagnostic calcification we see there. I suspect that it is present more often and we just haven't looked for it or it has been in sites not quite as accessible as that particular organ.

In the slides that you showed here I don't think that we would have recognized any calcification. It would be very difficult to see it in this site. It does seem to me, though, that it is an area for some thoughtful investigation. Merely to say that we see it doesn't explain how it gets there, and between the x-ray man and what you would call the pathologist, the microscope man, if we gave this some combined thoughtful explanation instead of a description, it might be helpful.

I am not able to say how it gets there yet.

CHAIRMAN SEVERANCE: It seems to me that most of us were voting on a benign tumor. I don't remember anybody saying malignant.

Saul, what was that final name you were going to give it?

DR. KAY: As was indicated by some of the others--and I used a term that I learned in Dr. Stout's lab---capillary hemangioma, and then bracketed, pyogenic granuloma type.

I asked Dr. Stout why he used this term for the acquired lesions, as seen on the gum, for example, and he says, "Well, they are capillary hemangiomas. They look like any other type of capillary hemangioma, so I see no reason to separate them." But one could append "pyogenic type" to indicate that these are acquired lesions and not the hamartomatous type of hemangiomas that occur congenitally.

CHAIRMAN SEVERANCE: Saul, there are no inflammatory components in the slide. Did you mean the inflammatory change had long disappeared?

DR. KAY: As a matter of fact, the lesion was already ulcerated. There was a heavy growth of polys on the surface and really, as I recall, this is all one sees.

When you get down into the heart of the lesion it looks like a capillary hemangioma but it seems to occur in compartments of lobules. This is the way this appeared to me, for example, in the gum, when I've seen lesions like this or any place in the mucous membrane, where they are fairly common.

CHAIRMAN SEVERANCE: Of course, any lesion can ulcerate from trauma or otherwise.

DR. KAY: Yes, that is correct.

CHAIRMAN SEVERANCE: Dr. Stout, do you want to make a comment about this case?

CHAIRMAN STOUT: I wish I had another chance to look at it. I don't remember whether I wrote you about it. I thought it was an excellent case for discussion. These are largely an excellent group of vascular tumors.

A MEMBER: Sir, I would just like to offer a possible explanation for the calcification. We have seen this in areas of thrombosis of blood-vessel tumors and I would suspect that with the thrombosis there is a localized area of decreased oxygen tension, and so forth, and there is a good possibility for calcification. You have all seen it in thrombosed veins. I think this is comparable.

CHAIRMAN SEVERANCE: Any other comments? (No response).

CHAIRMAN STOUT: I would like to hear what Lauren has to say.

DR. ACKERMAN: I thought it was a benign lesion.

CHAIRMAN SEVERANCE: That covers it pretty well. We all thought that.

DR. ACKERMAN: I don't have any name.

CHAIRMAN SEVERANCE: Case No. 3, Bob Totten's case.

Case No. 3

Submitted by Dr. Robert S. Totten:

This 38 year old man had a history of a "nasal voice" for approximately four to five months and one month ago noticed himself a mass in his pharynx. He was referred to an ENT surgeon who referred him to a plastic surgeon. Physician examination revealed a smooth, non-tender soft mass protruding into the left side of the pharynx posteriorly, extending from the nasopharynx to the base of the tongue. A carotid angiogram revealed a highly vascular well circumscribed tumor extending from the epiglottis to the base of the skull. The mandible and tongue were split and the external carotid artery ligated. The lesion was then relatively easily excised and proved to be well circumscribed by a thin layer of fibrous tissue. The patient made an uneventful recovery and is living and well with no evidence of recurrence as of May, 1967.

It is made up of numerous capillary sprouts in a background of myxoid tissue with focal areas of rather marked cellularity. Mitoses were rarelyencountered averaging 1 per every 10-15 HPF. In addition to the small vessels, there were larger thin walled sinusoidal vessels devoid of smooth muscle--as well as a few large veins--some of the large vessels had some intricate anastomosing channels.

I would like to propose to you that this lesion is a juvenile angiofibroma. There are at least three reasons why one should question this diagnosis (1) The patient is 38 years old (2) The lesion is well circumscribed (3) The histologic pattern is atypical. I will attempt to counter each of these objections and hope to convince you. First as regards age--although the overwhelming majority of cases occur in adolescent males, there have been well documented cases having their first presentation as late as age 27 and several that have

persisted for many years in patients as old as 50. The mean age appears to be about 16 years but there are exceptions.

Regarding the gross and microscopic appearance, I consulted both the literature and our material. We have 10 such cases in the files, all but this one in young males with ages ranging from 10 to 20 at the time of removal. I found in reviewing our material that there is indeed a great deal of variation in the histologic pattern of these lesions---much more than I was aware of before studying them. Some of this variation in appearance appears to be related to time and some to the inherent nature of the lesion. Here is a lesion first removed from the nasopharynx of a 15 year old boy. This pattern of small capillary sprouts in a moderately cellular myxoid stroma is, I believe, quite similar to the present seminar case. This tumor persisted and was removed three more times, the last when the boy was age 21 by wide excision. Here you see the tumor now having what I consider to be the usual appearance of these lesions--a dense collagenous matrix filled with large thin walled vessels devoid of smooth muscle -- a veritable vascular sponge. He is incidentally free of disease now, 6 years later. Six of our ten cases had this appearance. The others showed much more variation in histologic pattern and in three there were mixtures of the patterns. Here is one of them in which the bulk of the lesion appeared with the usual pattern while adjacent areas showed a pattern of small capillary sprouts in a moderately cellular myxoid stroma. Also seen in this lesion was some degree of "pseudoencapsulation" which was present in the seminar case. Several cases in the literature have been described as "well circumscribed" although the great majority are poorly delineated or actually infiltrative. Sternberg's excellent article in 1954 shows a number of illustrations

of cellular areas in these lesions and emphasizes the marked variation in histologic pattern. My case rests.

CHAIRMAN SEVERANCE: Will you wait a minute, Bob, while I read some of the dissenting opinions?

DR. TOTTEN: Surely.

CHAIRMAN SEVERANCE: Juvenile angiofibroma, juvenile type--rather, cellular type; rhabdomyosarcoma; neurilemoma; mesenchymoma (?) with lymphangioma pattern; liposarcoma (unusually rich in small blood vessels); angioleiomyosarcoma ? embryonal rhabdomyosarcoma; angiofibroma (sarcoma) or (rhabdomyosarcoma?); embryonal rhabdomyosarcoma; mesenchymoma or myxoangiomyoblastoma (looking like sarcoma botryoides); hemangiopericytoma; mesenchymoma; embryonal rhabdomyosarcoma (vascular type).

You have a variety of different ideas here and it seems to me, Bob, this is a most unusual type of tumor and I was stuck by it, too, and didn't think that your diagnosis was correct.

But let's have the discussion first.

Discussion:

CHAIRMAN SEVERANCE: There was a little resemblance to a salivary gland tumor, but I thought it was more of a vascular lesion. I was impressed by some of the little cells and wondered if they were embryonal rhabdomyoblasts with a lot of capillaries mixed up. We all have to admit that there is a vascular lesion there.

Do you want to comment on some of these fancy diagnoses?

DR. TOTTEN: The 5-year survival rate, without any additional treatment, would seem to me to lead one to believe that this is a benign lesion. I don't know how you can argue with survival.

I would think this would rule out embryonal rhabdosarcoma at any rate. As to mesenchymoma, I just wasn't impressed at there being other elements in this lesion. Liposarcoma we considered at the time very strongly here, but I think again the survival rate would indicate that this probably is not a liposarcoma although I don't know that we could completely exclude the sort of differentiated myxoid type of sarcoma and perhaps ten years from now, when it recurs, we will have to change our mind.

CHAIRMAN SEVERANCE: Anyone in the audience that wants to rise to the issue?

DR. KAY: Bob, in the study of the angiofibromas both in your place and elsewhere, I am sure they were probably all in the nasal cavity and in the nasopharynx; isn't that correct? This particular one would be really in the hypopharynx. Isn't that an unusual place?

DR. TOTTEN: This goes clear up to the base of the skull, as you saw there. I don't think that would rule it out. It is in the nasopharynx.

DR. KAY: If it goes all the way up, yes. I got the impression that it shelled out of the pharynx. Of course, that doesn't tell you, but from the X-ray it certainly went down as low as the hypopharynx.

DR. TOTTEN: Right. We have had two of our cases presenting as masses in the cheek. So they can get pretty far distant from the nasopharynx.

DR. ACKERMAN: I don't know what this is but I thought it was a benign tumor. I don't like his diagnosis: it's the wrong age, wrong place, wrong pattern to me. Otherwise it's okay! (Laughter)

But I am mainly saying something because we have had a lot of interesting things found in our material when it was studied by

electronmicroscopy, particularly with well differentiated tumors, and in several instances this has been very helpful from the diagnostic sense.

I am not sure this would have been of any value whatsoever in this case, though in some instances it's been more helpful than the microscope.

DR. TOTTEN: In what way, Lauren?

DR. ACKERMAN: In making definitive diagnoses which you could not make looking through the microscope. For instance, things which seemed debatable through the microscope become obvious with electronmicroscopy.

DR. TOTTEN: I've been looking through the electronmicroscope for a long time.

DR. ACKERMAN: For instance, we had a case where a resident came down and I was talking on the telephone, and he shoved a slide under my microscope and he said, "What's this?" and I said, "Well, that's a so-called lymphoepithelioma." He said, "Oh, take another look. It's a 12-year old child." He obviously felt I was slipping, and he said, "That isn't what the other fellow is saying." I said, "Well, I'm sorry, I just think it might be that."

One of the strongest proponents had thought that it was perhaps in the lymphoma group. So electronmicroscopy was done in this case, and I can just talk the language. Everybody else does electron-microscopy except me, but I know some of the words. So I got the electronmicrograph and I took it to the fellow who had disagreed with me--I wouldn't tell the story if I weren't right (Laughter). I said, "What is that stuff there?" He said, "Why, that's keratin." I said, "Oh, that's interesting. What are those things over there?" He said,

"Those are desmosomes." I said, "What does that make it?"

"Well," he says, "it's a keratinizing tumor." I said, "Well, that's the case of the so-called lymphoepithelioma," and he threw it in the waste basket. But it's been helpful in certain tumors like plasma cell tumors, or metastases in lymph nodes, where you saw no pigment but melanoma was present.

I really don't know where this is going to end because I was skeptical that it would ever have any practical value. We are using it as an investigative tool, but I think at times it can be helpful from a diagnostic sense because there are well differentiated tumors which we are not sure what the cell is, and carefully studying that group it might be quite helpful. One of the fellows is doing a great deal of this, and it has been quite helpful. So I would not say that it would have been of any help in this case, but it would have been of interest.

DR. TOTTEN: It was done in this case, as a matter of fact, and I can't get the cell biologist to identify these cells any more than I can in the light microscope. They say that they are either primitive fibroblasts or primitive angioblasts. But I think the examples you gave are good ones.

CHAIRMAN SEVERANCE: Lauren, what did you call it?

DR. ACKERMAN: I said benign tumor, unclassified.

CHAIRMAN SEVERANCE: I think you are right. Any other comment from the audience? Dr. Collins.

DR. COLLINS: I think this is one of perhaps several instances that are to come where we are overlooking a useful adjunct to the recognition. Angioradiography of the specimen itself I think would be a valuable procedure here because the central question is whether we are dealing with a lesion that is primarily vascular or whether the vessels

that we see are induced or secondary to the growth of the tumor concerned.

We have not had opportunity enough to recognize with certainty the pattern of the two types, but they certainly are distinctive patterns, as recognized under angioradiography. Here is an area that I think has long been overlooked. This patient is sent to the radiology department before the surgical procedure, but this procedure is useful to the pathologist after the operation as it is before.

I would certainly like to have seen what the pattern as clearly defined in the angioradiograph of the specimen might be. It's only suggested pre-operatively, because it is seen through all the other tissues and at a great disadvantage. Nevertheless, there is a rather distinctive and impressive tumor here. If we had this information, I think it would be easier to separate the two from the primary and secondary.

DR. TOTTEN: I talked to our roentgenologist who did all the vascular studies, and he was not aware of what the typical picture of these juvenile angiofibromas was; in fact, he never heard the word and I didn't, in a superficial rundown, find anything in the literature on angioradiography. Are you familiar with that?

DR. COLLINS: No. There just are not enough patients and specimens that have been adequately examined in this fashion. But it's all the details we might hope to identify if you share the specimen with the radiology department before the section.

CHAIRMAN SEVERANCE: Dr. Lattes, did you have your hand up?

DR. LATTES: I just wanted to say that personally I agree with Bob Totten's diagnosis. Recently, with Dr. Karl Perzin of our Department we have reviewed almost two dozen, I think, of angiofibromas of the nasopharynx, and I think at least one of them involved primarily

the maxillary sinus rather than the nasopharynx.

I agree with Bob that in many of the angiofibromas, besides the typical areas that he showed on the screen, there are areas that are quite similar if not identical with the predominant pattern in his case here. At least when I selected it for this seminar, I thought I was selecting a case of angiofibroma.

CHAIRMAN SEVERANCE: You are supported, Dr. Bob.

DR. PICKREN: I would like to ask Bob a question. I agree that this is an angiofibroma. In response to Dr. Ackerman's note that this is a wrong age, the early literature said that these tumors regress after the age of puberty.

In my experience and in our cases I have not observed that. In your own series, how many cases regress?

DR. TOTTEN: There haven't been any that were not treated, John, and I don't have accurate follow-up on all of them. To my knowledge, none of them have spontaneously regressed.

CHAIRMAN SEVERANCE: Any other discussion?

DR. FINE: Bob, you mentioned electronmicroscopy and angioblasts and fibroblasts. Did they see desmosomes? Because these are structures that are endothelial in character and if they didn't find them--and you mentioned fibroblasts--then this would support your fibroblastic interpretation.

DR. TOTTEN: There are basement membranes in the vessels, of course.

DR. FINE: I mean in the cells, as I understand, the basement membranes are found very early in the development of vascular formation. In fact, you don't actually have to get blood vessel formation to see the basement membranes. You can see the angioblasts pretty well.

DR. TOTTEN: The basement membrane material was not found in the site of the vessels. So I would suggest that this would support the diagnosis that these were fibroblasts.

MEMBER: I would like to speak in favor of the diagnosis of mesenchymoma. I think that many people thought they saw rhabdomyoblasts. I think or thought I did, too. I also thought I saw smooth muscle cells. You yourself thought that some of the cells resembled fibroblasts. I also thought I saw vacuolated cells in it. I wonder whether you had done any fat stains or electronmicroscopy had shown any fat globules in some of these cells?

I thought it was a mesenchymoma.

DR. TOTTEN: The fat stains, Sudan stains on this tumor were negative. In the EM there were some very fine lipid droplets in an occasional cell.

CHAIRMAN STOUT: Do you think that is important?

DR. TOTTEN: Not in the light of our current ignorance about lipid in cells. I could not make it diagnostic of anything. You see, you see lipid droplets in the electronmicroscope in many cells.

CHAIRMAN SEVERANCE: Anything else, Bob?

DR. TOTTEN: No.

REFERENCES:

Apostol, J.V. and Frazell, E.L., Juvenile Nasopharyngeal Angiofibroma; Cancer 18:869, 1965.

Hubbard, E.M., Nasopharyngeal Angiofibromas; AMA Arch Path 65:192, 1958.

Sternberg, S.S.; Pathology of Juvenile Nasopharyngeal Angiofibromas; Cancer 7:15, 1954.

CHAIRMAN SEVERANCE: I am designated to talk about Case No. 4.

Case No. 4
Submitted by Drs. Merle Delmer and Alvin O. Severance:

According to the history a lesion diagnosed as a capillary hemangioma was removed from this same area of the nose eight years previously. Following that biopsy, radiation therapy was instituted. Since then the lesion has slowly progressed in size and has had episodes of bleeding. The present tissue is from a submucosal tumor mass which measured 2.5 x 1.8 x 1.5 cm. located in the left nasal fossa approximately 1 cm. above the ala of the nose.

The section shows a tumor which in some places reveals a surface covered by normal appearing respiratory epithelium and then this merges gradually with a somewhat transitional type of epithelium and finally into well recognized stratified squamous epithelium. There seems to be a small zone of normal connective tissue containing lymphocytes in moderate numbers between the surface epithelium and the underlying tumor. Here and there in the tumor, there are broad bands of dense, quite eosinophilic staining collagen with supporting fibroblasts. In some parts of the tumor, I see vascular spaces containing red blood cells and showing considerable irregularity as to shape and varying somewhat in size. These vascular spaces are lined by tumor cells which have moderately chromatic, round, oval or elongated nuclei and varying degrees of light eosinophilic staining cytoplasm. The cells that line the spaces do not appear to be normal lining endothelium but these cells merge indistinctly with adjacent tumor cells which tend to become more elongated and more spindle shaped. These latter cells still have the same nuclei although at times they seem to be a bit more vesicular and at times a little more pointed and elongated. In some areas where these latter, more spindle shaped tumor cells predominate, there is a suggestion

of a whirligit or storiform pattern. In some areas there are cells with slightly paler cytoplasm but I am unable to recognize any pale vacuolated foam cells that might contain lipoid material. Even in some of the more cellular areas, there seem to be small spaces filled with blood. These vascular channels seem to anastomose with each other. In one area in my slide, not far from the surface epithelium, there are two blood vessels representing veins containing tumor cells similar to those we have just described and one of these represents what seems to be a tumor thrombus and is definitely attached to the lining of the vessel but the other mass of tumor lies free in the vessel with associated red cells. With some search I have found mitotic figures but they are not too frequent. They are seen more easily in the spindle shaped area of the tumor. There is moderate variation in the size and shape of these more densely packed tumor cells but even the cells that line the vascular spaces do vary in size and shape to some degree.

In the reticulin stain, there is reticulin present around the walls of blood vessels and among some of the tumor cells but I get the impression that the reticulin is more outside of the vascular space in which there are red cells and outside of the lining tumor cells. There is obviously more reticulin in the areas of collagen and in the areas where there are more of the spindle shaped cells.

In the trichrome preparation, the collagen stains a brilliant blue and elongated spindle shaped cells as well as the cells lining the vascular spaces stain a somewhat brownish red but less red than the blood cells and less red than the smooth muscle cells of some of the blood vessels. The appearance of the nuclei of the spindle shaped tumor cells and the way they stain in trichrome does not support, in my opinion, a smooth muscle type of tumor. Again looking at the H & E, the

nuclei as a rule do not contain nucleoli. Some tumor cells seem to have multiple nuclei.

DISCUSSION- The differential diagnosis in this tumor should include, I believe, a diagnosis of hemangio-endothelioma, hemangiopericytoma, dermatofibroma, fibrosarcoma and Kaposi's disease. For reasons mentioned above, the staining in the trichrome and the appearance of the nuclei leads me away from a smooth muscle tumor and I would eliminate a leiomyoma or leiomyosarcoma. The reticulin stain seems to be outside the tumor cells that line vessels and it doesn't impress me with the way it should stain if it were hemangiopericytoma. The appearance of a fibrosarcoma must be considered and the mitoses in the spindle shaped fibroblast-like cells would suggest that possibility but I believe the lesion is too vascular in too many areas for me to go too far in the direction of a fibrosarcoma. A dermatofibroma is brought to mind by the suggestion of the storiform or whirligit appearance and by the spindle shaped cells. I wasn't able to find histiocytes or fat cells but it may be that they are present and I just don't recognize them. I thought it was a little too vascular and that the spaces were too variable in size and shape and lined by tumor cells to think of a histiocytoma or a dermatofibroma. Kaposi's disease is more difficult to eliminate because we both have the vascular component and we have the fibrosarcoma component. Somehow I thought that the tumor cells lining the vascular spaces looked more like malignant endothelial cells than fibroblasts so I favored the malignant hemangio-endothelioma. Whether it is malignant or not is open to question, but the presence of tumor cells forming thrombi in blood vessels does lend some support to this diagnosis. Therefore, because of the appearance of the cells themselves, because of the vascular component which impresses me the most, because I think the cells that line the vascular spaces are

similar and merge with those outside, because of the way the cells stain in reticulin and trichrome stains, and because of the presence of these cells in blood vessels as emboli, I believe this would support the diagnosis of a malignant hemangio-endothelioma. This would be my first choice. A benign hemangio-endothelioma of aggressive nature that has pursued a long course would be the second choice. Perhaps one could conceive that the tumor was benign for awhile and has now assumed aggressive growth properties. Follow-up 5-25-57. No recurrence so far. Chest x-ray negative.

For further discussion of hemangio-endothelioma see Case #8.

FINAL PATHOLOGICAL DIAGNOSIS: Hemangio-endothelioma (probably malignant) of nasal cavity, left.

I'm going over here and read the diagnosis and then I'll be back. I will give you a list of the votes from the members of the Society who sent their votes in:

Hemangio-endothelial sarcoma; hemangiopericytoma;?; mesenchymoma (?)with lymphangioma pattern; malignant histiocytoma, (or ? malignant hemangiopericytoma; special stains might help); fasciitis and then down below that, "angiofibroma"; fibrosarcoma following radiation (transitional carcinoma??); angiofibroma; fibrosarcoma arising in the area of irradiated hemangioma; Kaposi's sarcoma; Kaposi's sarcoma again; hemangio-endothelioma (probably malignant). That's probably mine.

Discussion:

CHAIRMAN SEVERANCE: Now Dr. Ackerman, lead off.

DR. ACKERMAN: I agree with you in the first place.

CHAIRMAN SEVERANCE: You don't have to.

DR. ACKERMAN: Well, I would like to! (Laughter)

MEMBER: He insists! (Laughter)

DR. ACKERMAN: Yes, I insist.

Sevvy, do you have any possibility of getting the original slides or, did you find out how much radiation the patient received? Because in the first slide which you showed there was some suggestion of a radiation effect and I'm wondering if there is any relationship to the previous radiation.

DR. SEVERANCE: The answer to both your questions is no. I'll tell you, this lesion eight years ago was biopsied in an osteopathic hospital in California and after the complete removal it was treated with radiation therapy and the doctor, Dr. Ownes in Wichita Falls, Texas, who sent this to me as a consultation case, was unable, through all contacts over a period of several months, to get the first slide. We asked for it. He tried to get it and he was unsuccessful in getting hold of that first slide. He was unable to find any information from that hospital in California as to the amount of radiation or even to get the slide. It would have been very nice to have had that.

The question also arises, as some of the members who voted here asked, did radiation have anything to do with the development of this particular lesion. It's very possible.

MEMBER: In your experience how often do you see malignant hemangiomas arising in a benign hemangioma?

DR. SEVERANCE: In my experience?

MEMBER: Yes.

DR. SEVERANCE: You should ask somebody else. In my experience I don't know that; I haven't had any experience.

I'll tell you what I have seen. I've seen malignant hemangio-endotheliomas arise in irradiated tissue of skin when it was irradiated until it blossomed out as a full-blown angiosarcoma. I have seen that. I suppose Dr. Ackerman has too.

DR. Jerry Find !

DR. FINE: How old is this patient, Sevvy?

DR. SEVERANCE: I should have put it down. It's a male, 38.

DR. FINE: Nationality?

DR. SEVERANCE: Well, the name sounded Anglo down in our country. It sounded Anglo-American.

DR. FINE: No other lesions, no skin lesions?

DR. SEVERANCE: No other lesions, no. So far the patient is well; no recurrence. There isn't too much time. Any arguments? I expected a lot more debate or argument.

I got a lot of different things over here in the votes, didn't I?

Dr. Stout, we are through with the audience discussion of this Case No. 4 which I tried to settle as a hemangio-endothelioma, possibly malignant. I got a lot of dissent. Did you get a chance to see it with Dr. Lattes? Do you want to make a comment?

CHAIRMAN STOUT: My handicap is that I did not get a chance to study the various parts of this, and one of my requirements is to have a chance to study all parts of the tumor. I beg you to remember that just as I was ready to make a comment, you probably saw my hand go up in the air, and if you ever went to school, you would know that that means something! (laughter) Consequently, I could

not do anything since I'm a hospital patient under the firm law of the hospital. Sorry.

DR. SEVERANCE: Rafe, at the time he accepted it, said he was thinking about a histiocytoma, but I don't know whether he continues to think about that or not.

DR. LATTES: No. I agree with your diagnosis.

DR. SEVERANCE: All right; I feel more comfortable with you and Lauren agreeing.

CHAIRMAN STOUT: What did you say about Lauren?

DR. SEVERANCE: He agreed with me very nicely. I don't know whether he meant it! (laughter)

After telling that story about Elson Helwig, he is here. So here is Elson. We will let him start with Case No. 1.

Dr. Helwig! It's always good to see you here even if it's a little bit late. Welcome, Elson.

DR. HELWIG: Thank you, Sev. The plane service between Washington and New York is not the best on a Saturday morning.

Case No. 1

Submitted by Dr. Elson B. Helwig:

This case that we have to talk about is a 19 year old Navy man who over a period of about three months developed an enlargement in the popliteal area of the knee. This enlarged and also became painful. It was then excised and the existing mass was 3.5 x 1.5 cm.

On sectioning there wasn't anything particularly outstanding except that there was sort of a fibrous matrix and areas of red or hemorrhage.

The sections of skin show within the corium a rather wide expanse of fibrous tissue. Some of the fibrous tissue is mature and rich in collagen and elsewhere it is cellular. Interspersed throughout the fibrous tissue but particularly in the vicinity of the cellular fibrous tissue are vascular spaces generally small and usually lined by plump atypical endothelial cells. The appearance of the endothelial cells ranges from fairly uniform to those which are quite large and occasionally multinucleated along with hyperchromatic nuclei.

Furthermore, in a few places the endothelial cells are arranged in a papillary formation. On the basis of the spaces lined by the large atypical endothelial-like cells and the papillary formation, I interpret this lesion as angiosarcoma.

In many instances in the areas of the irregularly shaped vascular channels the surrounding stroma contains many erythrocytes and much hemosiderin. Also, a scattering of monocytes and histiocytes are noted in these areas. Several similar lesions have been recorded in the Institute's material and most of these have been on the scalp.

In some fields it is often difficult to say whether the process is inflammatory and reactive with fibrosis or whether it is

neoplastic. When I see foci with the irregularly shaped vascular channels and atypical endothelial cells, sometimes arranged in papillary formation, I always interpret the process as angiosarcoma. The process tends to recur and ultimately many involve a large area of the scalp and underlying tissue. Metastasis may occur but the patient often dies with an intercurrent infection. This lesion is differentiated from Kaposi's sarcoma since Kaposi's sarcoma is characterized by a vascular slit pattern in which fairly uniform spindle shaped cells are separated by vascular slits filled with erythrocytes. This pattern is not noted in the present lesion.

Very rarely Kaposi's sarcoma undergoes a transition from the characteristic vascular slit pattern to an extremely pleomorphic type of growth and when this occurs, Kaposi's sarcoma is capable of metastasizing. When Kaposi's sarcoma shows the typical vascular slit pattern it may, of course, be multicentric but we have not seen it metastasize.

DIAGNOSIS: Angiosarcoma.

CHAIRMAN SEVERANCE: If you will wait there a minute, Elson, I will read the diagnoses from the audience.

DR. HELWIG: All right.

CHAIRMAN SEVERANCE: Sclerosing fibromatosis; sweat gland carcinoma; Kaposi's sarcoma; benign mesenchymoma (angiolipofibroma) with atypical endothelial proliferation; hemangio-lymphangiomatosis; lymphangioma; hemangio-endothelioma (? benign); ? hemangio-endothelial sarcoma; angiomatosis; benign mesenchymoma-basically fibromatosis; benign vascular tumor of the skin, probably combined blood vessel and lymphatic origin; angiomatous fibroxanthoma ("sclerosing hemangioma").

Discussion:

CHAIRMAN SEVERANCE: Having seen Elson's slides, there is no question I vote for malignancy on these nice slides of his.

Now the audience. You have Dr. Helwig up here.

DR. KAY: I wonder I don't go away more confused today than when I first came. Angiosarcoma, malignant hemangio-endothelioma, whatever you call it, to me has always been a very serious diagnosis. If you look in the literature, the books, the five-year survival may be nine per cent or less.

Now we are bandying around this term with the implication that maybe this is a sort of a semi-malignant lesion, but it might have disastrous implications if you don't cut it out well.

Elson, having studied a number of these with good excisions, what has been the follow-up of these cases? Is this a sort of a no-man's lesion, or is this like the angiosarcomas of old, where they were very serious?

DR. HELWIG: I think this lesion, as you look at it, is quite misleading. I think this is represented by the diagnoses that were made by the audience. I think it is more serious than the diagnoses indicated by the audience.

This lesion, if it is not excised completely, is going to recur and pretty soon you've got a mess on your hands that the patient is going to die from. So I don't put this in a semi-malignant class. I'm not quite sure what you mean by "semi-malignant" but I put it over on a malignant category and if I had one of these lesions I would want to be sure that initially they had widely excised it as wide as they could. It is not something just to toy with and hope maybe it will go away.

CHAIRMAN SEVERANCE: Any more comments?

DR. SOMMERS: Kaposi's sarcoma has come up in the differential diagnoses in several cases including this one. Something like twenty years ago I thought I knew the criteria: They were Russian or Jewish or Mediterranean people. Supposedly they had heavy legs and these people said they worked all day long standing on cement floors. That was the background.

Then they developed these rather purple nodules on their feet and gradually up their legs, and they were hemispherical.

Then when you got the biopsy, the first thing you saw, or at least I have thought, was hemorrhage, and then afterwards they were sort of vascular. That's the way you came at the diagnosis of Kaposi's sarcoma.

I wonder, are those criteria wrong? Have they changed? In other words, could you give the criteria of the diagnosis of Kaposi's sarcoma, if you please?

CHAIRMAN SEVERANCE: You asked the right man. Elson!

DR. HELWIG: To me the criteria for the diagnosis of Kaposi's sarcoma are quite clear and straight forward. One can sum it up in a vascular slit pattern, and that's exactly what I have to see before I ever make the diagnosis of Kaposi's sarcoma.

There isn't anything in this lesion that resembles that at all. If you are seeing this in a parallel section, with the attempts to form this vascular pattern, there are spindle shaped cells separated by slits filled with red blood cells, and you see the elongated cells. If you see it in cross section, you see a round nucleus, a round cell. I don't believe that one can make the diagnosis of Kaposi's disease or Kaposi's sarcoma without seeing that.

The histologic appearance then other than that is a uniform picture. This is carried out throughout all the lesion. One doesn't see areas of large multinucleated cells and that sort of thing except in a rare instance. Out of a group that Dr. Cox and I studied, there were about 50 cases in which there was this classical vascular slit pattern. Eight of these cases had single lesions. The others had multiple lesions. But in four of these patients, after a period of time, in one instance as long as twenty years, in another instance only after two years, this vascular slit pattern, which is fairly uniform, was completely replaced by a lesion that was really difficult to tell what kind it was, it was so malignant. You could get the impression though that it was a sarcoma.

So we feel that in some instances, after a period of time this lesion that we call Kaposi's sarcoma of the vascular slit pattern may undergo a true transformation to sarcoma and then this lesion is capable of metastasizing. Otherwise, we don't feel that they do metastasize. Each area is an autonomous area.

CHAIRMAN SEVERANCE: Does that answer the question, Charley?

DR. SOMMERS: Yes.

MEMBER: I would like to ask, because there is papillary formation and many of the vessels did not contain red blood cells and the epithelium had a resemblance to mesothelium with vacuolization, how should the concept of a malignant mesothelial cell in that location be considered?

DR. HELWIG: Of course, it's always difficult, if you've got spaces lined by atypical sort of cuboidal cells, to tell whether they are mesothelial or lymphatic or blood vascular type of cells.

We have gone over our lymphangiomas in trying to develop them, get some criteria to distinguish them from the hemangiomas, and one of the things that you really come back to lean on a great deal is whether they have blood in there. We all know that that could vary.

I would not know how, I don't think, in certain instances with a small focus, to tell whether a space was lined by mesothelial cells, synovial cells or by endothelial cells. Perhaps there are others here in the audience that have that down pat, but I don't.

MEMBER: Can you comment on any special relationship between sweat gland and vascular tumors?

DR. HELWIG: Nothing in particular except that we have studied the sweat gland adenoma, which is very painful in 90 per cent of the patients. It has a very characteristic picture, showing a little bit of a picture of vascular formation, but by light microscopy it appears to have a smaller cell and a larger paler cell.

Many of these lesions were in our files as a vascular tumor; a good many of them as a glomus tumor and some were in as synovial sarcomas. The two-cell pattern I think takes this lesion out of any controversy as far as it being a tumor of blood vessel origin and puts it over into the sweat gland group.

DR. FINE: In the group of Kaposi's that become so bizarre, as you mentioned, do you ever see the endothelial cell participate: In other words, if you find an endothelial proliferation do you pretty well rule out Kaposi's?

DR. HELWIG: What happens in these instances, this vascular slit pattern is just replaced by cells that become extremely pleomorphic.

DR. FINE: They never develop an anastomosing pattern in endothelial cells that are prominent in Kaposi's?

DR. HELWIG: I'm not sure exactly what your question is. It doesn't come through in my mind.

DR. FINE: I mean do you ever see in any of your Kaposi's, spaces with prominent cells that you would say are endothelial cells?

DR. HELWIG: Normal endothelial cells?

DR. FINE: Yes.

DR. HELWIG: There are these spaces. I don't know what these cells are, lining the spaces. As you know, there are many different theories and I don't even think electron-microscopy or enzymatic histochemistry has proved the very nature of this. I don't think the exact nature of that cell has been proved. It does line the space. If you want to say that's an atypical endothelial cell, I am not going to argue with you because I don't know, but it doesn't look like a normal endothelial cell.

Also in some instances of Kaposi's sarcoma around the periphery there is a reaction on the part of the normal tissue so that one may see almost granulation-like tissue at the margins, which is not exactly a part of the Kaposi's sarcoma.

CHAIRMAN SEVERANCE: Any other comments from the audience?

CHAIRMAN STOUT: If one of these tumors recurs after removal in various lengths of time, do you call that an angiosarcoma?

DR. HELWIG: No, I would not call that an angiosarcoma unless it changed its cytologic picture and became quite pleomorphic. If it is just a recurrence of the vascular slit pattern, I don't know whether it is something that was residual or actually a new lesion. If it had the vascular slit pattern, I would not put it over into

calling it an angiosarcoma at this time.

I would certainly agree that once the lesion had recurred, that from that time you better look very carefully at the cell type. I think that would be a clue to making a very extensive study cytologically, and then if those cells are pleomorphic then we are talking about a sarcoma. But if they are a standard, uniform pattern or a slit pattern, I would say a Kaposi's sarcoma in the sense of one that is growing locally and not one that is going to metastasize.

CHAIRMAN SEVERANCE: If any angioma recurred, would you call it angiosarcoma?

DR. HELWIG: We all know of various kinds of tumors that recur. We just don't jump over and say, "Well, this is malignancy." I would have to see the cytological appearance before I would call it a sarcoma.

We know benign lesions where the surgeon has left a little bit behind may start growing again. That doesn't mean to me necessarily that that particular lesion is malignant.

CHAIRMAN SEVERANCE: I think Dr. Stout feels that hemangioendothelial tumors that are benign may recur. He wanted to see exactly what you were going to call malignant.

DR. HELWIG: I would agree that there are these lesions that are benign and recur. We don't see these all the time.

CHAIRMAN SEVERANCE: Any other comments from the audience?

MEMBER: How about radiation in these tumors? Don't some of these tumors do much better with radiation?

DR. HELWIG: I don't have any degree of experience as far as radiation. You would have to break it down into different types of tumor. I think there are people in here that can speak much

more thoroughly on that.

CHAIRMAN SEVERANCE: A fellow named Collins. He has experience in radiation.

DR. COLLINS: With the obvious difficulty of establishing unanimity as to diagnosis, it would be hard to say what lesion we might be speaking of if I say a certain category is radiosensitive. Let's say that of lesions of this general class submitted to radiation, we have some dramatic examples of radiosensitivity; even some dramatic examples of response of chemotherapy.

As this case was being discussed I was recalling a woman whose primary lesion was in the same site, did metastasize to bone and lung. We treated her with Cytoxan with remarkable gross regression of this angiomatous lesion.

Lacking our ability to precisely and with certainty establish the diagnosis, then the predictability of response to radiotherapy is certainly going to be equally uncertain.

CHAIRMAN SEVERANCE: Any other comments?

DR. KAY: What happened to this particular case?

DR. HELWIG: This patient has been followed for six months. There is no recurrence.

DR. LATTES: I have one question. Maybe I missed some statement you made as I walked out a moment. Do you know whether those prominent cells lining the spaces contained any detectable substance? For instance, did the PAS stain show any reaction? I'm asking this because in studying the case I was reminded of a morphologically similar case we have seen this year and we didn't think we were dealing with a malignant lesion, and so far I haven't heard any history of recurrence. But almost all of those prominent cells lining the vascular spaces, which we thought was an unusual capillary hemangioma,

contained PAS positive material. I don't know if you have had a similar experience.

DR. HELWIG: I have not studied this detail of the PAS.

DR. KAY: How about alkaline phosphatase? I presume they had a lot of that?

DR. HELWIG: I have not done enzymatic studies on this.

CHAIRMAN SEVERANCE: Any other comments?

(No response.)

At this time then, before we have a little break, Dr. Lattes I think would like to have any written comments from the exhibitors or discussers of these cases that you may have so that it would facilitate his compiling the minutes of this particular meeting. If you have them, I think Rafe would like to have that. Is that correct?

DR. LATTES: Yes.

CHAIRMAN SEVERANCE: Now we have a coffee break of fifteen minutes and then come back.

(Fifteen minutes recess.)

CHAIRMAN SEVERANCE: I think we better get started with the rest of the program this morning. Case No. 5 is coming up next. Dr. Lattes!

Case No. 5
Submitted by Drs. Kaity Yannopoulos and Raffaele Lattes:

This is a 64 year old man who was admitted for the first time to Columbia-Presbyterian Medical Center because of confusion, disorientation, and incontinence.

Workup at that time showed a right-sided weakness and an arteriogram showed a right frontal parietal tumor. A craniotomy was performed with the removal of an "angioblastic meningioma". There was complete recovery and disappearance of neurological signs.

The patient was free of any neurological difficulty until April, 1962, at which time he had two seizures. He was readmitted and a left craniotomy was done with removal of a left frontal parietal "angioblastic meningioma". This time again recovery was uneventful except for ankle edema.

In January, 1963, the patient was admitted again for right upper quadrant pain with no associated gastrointestinal symptoms. From the time of admission the patient was continually febrile. All cultures were negative.

On physical examination the most important findings were tenderness in the right upper quadrant, right costovertebral angle and right flank. A probably rounded mass was attached to the liver and judged to be 8 cm. in the midaxillary line. Neurologically there were increased deep tendon reflexes.

Laboratory data (at the time of admission to Presbyterian Hospital on January 15, 1963): ESR 77, Hgb. 10.1, Hct. 31, WBC 17,500, P. 88. Urine: sp. gr. 1.020, ph 5.5, protein (+), 0-4 RBC/hpf, 2-6 wbc/hpf. Stool guaic (-). BUN 15, alk. phos. 55, repeat 60, serum bilirubin 0.4, VDRL negative, Protein 10, CF and TT (-), SGOT 25, SGPT 20, retic. count 2.3, plts. 171,000, sputum nl. flora. Acid

phos. normal, P.E.P. albumin 20, gamma globulin 0.9. BSP 26% at 30 minutes. Ca 8.6, P. 3.9, PPD, 2nd strength (+).

Chest and rib x-ray showed two extrapleural densities on the right associated with destruction in the right 5th and right 10th ribs. The skeletal survey was otherwise negative except for changes due to previous craniotomy. A gall bladder series was not visualized. Upper GI series showed a small hiatus hernia and a questionable filling defect within the stomach. Barium enema showed a questionable impression of the bowel wall in the region of the pouch of Douglas due to a mass or peritoneal fluid.

A liver biopsy was performed. The patient kept on going steadily downhill with elevated temperature. His NPN rose to 135 mm. percent, and his bilirubin to 8.6. He died on March 4, 1963. An autopsy was performed which showed metastatic involvement in liver, ribs, parietal pleura, vertebrae, mesenteric lymph nodes, right kidney, spleen, occipital bone, right adrenal. The immediate cause of death was a severe bilateral bronchopneumonia with abscess formation.

This case actually was selected by Dr. Yannopoulos, I believe in complicity with Dr. Stout. It was a case that was studied terminally in Delafield Hospital but originally in our Neurological Institute. Dr. Yannopoulos felt that I could speak Greek better than her; so she asked me topresent it.

To begin with there are two errors in the clinical abstract submitted to you. It was omitted to mention that the date of first admission was January 1960. At that time a right frontal parasagittal tumor was removed which consisted of two larger masses of tissue measuring respectively 4 x 4 x 2 cm and 5 x 3 x 2.5 cm. The second error was that the second operation was performed not in 1962 but in September 1960 and that at that time a left frontal parasagittal

tumor was removed which measured 6 x 6 x 5.5 cm. In reading the surgeon's descriptions it appears that both times the tumors were attached to the falx, once on the right and once on the left of the falx. From here on the history given to you is reliable.

You have heard that the original diagnosis by the neuropathologist was that of an angioblastic meningioma. The slides distributed to you represent the autopsy findings of one of the masses in the liver. They are essentially similar to the original tumors in the dura and therefore I am going to discuss them together. Essentially we are dealing here with a fairly cellular tumor containing varying amounts of intercellular ground substance which appears to be collagenous and in which the tumor cells are predominantly spindle shaped or at least elongated and tend to be arranged into loose whorls which frequently appear to be centered around vascular spaces. There is considerable mitotic activity and frequently the nuclei of the tumor cells are hyperchromatic and irregular in shape, in other words anaplastic. The reticulin stains confirmed the vascularity of the tumor and show varying amounts of reticulin between the individual tumor cells. At autopsy some of the metastases were much more undifferentiated, consisting only of highly cellular collections of slightly elongated cells in which the ground substance was almost absent and in which the vascular pattern could not be discerned any more. This was particularly true in the bone marrow metastases which appeared to be a pure culture of tumor cells without stroma.

How should we classify this tumor? The term "angioblastic meningioma" is a very vague term and even Kernohan in the fascicle on tumors of central nervous system suggests that the term "meningioma" should be reserved to the meningothelial tumors and that the other

tumors occurring in the meninges should be classified with terms consistent with those used when they occur in other parts of the body. Specifically he makes the suggestion when he briefly mentions angioblastic meningioma. The histological pattern of this tumor, the high vascularity, the spindle-shaped cells arranged around the sinusoidal blood vessels, and the malignant behavior leading to distant metastases seem to justify the classification of this tumor among the hemangiopericytomas. In fact, this is the diagnosis that had been suggested by Dr. Stout when he reviewed the autopsy findings as well as the original neurosurgical findings. More recently reviewing this case I started having some mental reservations especially after having seen the non-hemangiopericytomatous pattern of some of the metastases. For a fleeting moment I considered classifying this tumor in the currently more popular category of fibrous histiocytoma or fibrous xanthoma. However, I believe that the weight of evidence is that this is really a vascular tumor of the hemangiopericytomatous variety. Primary hemangio-pericytomas of the meninges have been described before and some references will be appended herewith. In our files we have records of 12 hemangiopericytomas primary in the meninges.

DIAGNOSIS: Malignant hemangiopericytoma of cranial meninges with multiple hematogenous metastases.

CHAIRMAN SEVERANCE: Dr. Lattes, if you will stay there, I will read you the diagnoses from the members of the Society: Malignant hemangiopericytoma; renal carcinoma; malignant hemangiopericytoma; malignant hemangiopericytoma again; metastatic angioblastic meningeal sarcoma; angioblastic meningiosarcoma; malignant hemangiopericytoma again; meningioma, angioblastic type; angiosarcoma;

malignant hemangiopericytoma again, and malignant hemangioendothelioma.

You have a lot of support, Dr. Lattes.

DR. LATTES: I'm afraid I selected a case that was too simple.

I omitted to say something about the term "angioblastic meningioma." I don't see enough neuropathology material to pretend being an expert. So I went to the experts. Kernohan seems to suggest that the term "meningioma" should really be reserved to the typical meningiothelial tumors and that when tumors that occur in the meninges would receive different names had they occurred elsewhere in the body, they better be classified with the same term that they would have been given elsewhere. In other words, if you have a tumor that morphologically and biologically behaves as a fibrosarcoma, it is better to call it a fibrosarcoma of the meninges rather than a sarcomatous meningioma or meningeal sarcoma. The same thing, I believe, applies to the angioblastic meningioma which probably would be better classified with the term we would give if we had seen it elsewhere in the soft tissues.

The term "angiosarcoma" should be better defined. I believe we all feel a malignant hemangiopericytoma is a variant of angiosarcoma, in which the pericyte and not the endothelial cell proliferates.

I did not think this was a metastasis from the kidney and the autopsy did not suggest that there was a primary tumor in the kidney. There was metastasis in the hilus. But that is a good point.

In fact, we have in our material a case that came up only four or five years ago in which the patient came in with a tumor in the soft tissues of her leg which we all, including Dr. Stout, felt was a hemangiopericytoma until we found that there was a primary clear

cell carcinoma with areas of extreme spindle cell metaplasia and high vascularity, which fooled us all,because we certainly were dealing with a pseudosarcomatous metastasis from a carcinoma of the kidney.

Discussion:

CHAIRMAN SEVERANCE: Any discussion from the audience?

MEMBER: Dr. Lattes, I wonder whether you would like to comment about metastases of any intracranial tumor outside, say to the liver. It is so uncommon. I wonder whether you would like to incriminate the factor of craniotomy and establish some vascular anastomosis that may bring this up?

DR. LATTES: This is an excellent question. That is, what is the probability of an intracranial tumor to give distant metastasis unless it has somehow been tampered with by surgery, right?

MEMBER: Yes, sir.

DR. LATTES: I believe that if you limit that question to the true central nervous tissue tumors, astrocytomas, other gliomas, and ependymomas, etc., it is probably true that they will not metastasize spontaneously unless something has been done to break the barier between the central nervous system and the remainder of the body.

I am not sure that the same concept applies to a mesenchymal tumor of the meninges. I'm not sure. I was thinking that perhaps the case presented here many years ago had metastasized prior to cranial surgery, but I would have to check on it. There probably are people more experienced on this point.

MEMBER: I believe that was a case that I submitted, Rafe, and he had three craniotomies before the tumor metastasized.

DR. LATTES: That's the case that was presented here years ago?

MEMBER: Yes.

CHAIRMAN SEVERANCE: Any other discussion or comment?

(No response.)

Thank you, Rafe.

References:

Begg, C.F., and Garret, R. Hemangiopericytoma, occurring in the meninges. Cancer 7:602, 1954

Fisher, E.R., Davis, J.S., and Lemmen, L.J. Meningeal hemangiopericytoma - Archives of Neurology and Psychiatry 79:40, 1958

Kernohan, J.W. Sarcomas of the Brain, Chas. Thomas, Publisher, St. Louis, 1963

Ramsey, H. J. Fine Structure of Hemangiopericytoma and Hemangio-endothelioma - Cancer 19:2005-2018, 1966

Stout, A.P. and Murray, M.R. Hemangiopericytoma: A Vascular tumor featuring Zimmerman's Pericytes. Ann. Surg. 116:26, 1942

Stout, A.P. Tumors Featuring Pericytes: Glomus Tumor and Hemangiopericytoma. Laboratory Investigation 5:217-223, 1956

Zulch, K.J. Brain Tumors. Their Biology and Pathology, translated by A.B. Rothballer, and Jerzy Olszewski. Springer Publ. Co. Inc. N.Y., 1957

CHAIRMAN SEVERANCE: Case No. 6. Dr. Merle Delmer will be the discusser.

Case No. 6
Submitted by Drs. Merle Delmer and Alvin O. Severance:

DR. DELMER: The history of this case is short and that's all the history there was. A 19 year old female who had experienced severe cramps and pain in the left pelvic region which was less severe around the time of her menses. This is a switch from the usual picture. The uterus when it was removed was about twice normal size and it was described as full of lumps and bumps.

This particular gross photograph suffers from having been formalin fixed, carried by automobile from San Antonio to New York in the back seat of a car in the middle of the winter. It froze, it thawed out and here it is.

We studied it up here in conjunction with Dr. Stout, the uterus having been removed in San Antonio, and I just happened to be lucky enough to appear on the scene down on vacation to get half of it. This is the outer surface looking at it laterally. It has been cut, and you can see the multi-nodular character. I think it weighed probably 250 grams.

This is a closer view that shows the individual lobulations. The resident and everyone concerned looked at these and thought they were leiomyomata and, indeed, many of them are.

This is the cut surface so that you see the endometrial cavity here and the clearly defined nodules from place to place within this specimen.

Microscopic: The sections distributed demonstrate only a small area of the lesion, but they are representative. Scattered through the wall of much of the uterus there is a diffuse, non-encapsulated proliferation of small closely spaced vessels with a confluent

mass of oval cells surrounding each. These structures do not form tumor masses of any size. They lie as multiple small aggregates between bundles of smooth muscle of myometrium as well as within small leiomyomas. The endothelial lining of these capillaries is distinct, one cell layer thick. The oval cells that proliferate around the vessels often obscure the lumen. Nuclei are uniform, vesicular, show distinct membrane, fine chromatin pattern, and lack mitoses. The cytoplasm is ill-defined and with the trichrome stain is pale red, non-descript.

The wilder reticulum stain accentuates the vascular nature of this lesion. Vessels not obvious in H & E stain become conspicuous. It shows the individual oval cells outside of the endothelial layer each wrapped in its own reticulum fiber.

DISCUSSION: This combination of features leads me to a diagnosis of diffuse hemangiopericytoma of uterus. Glomus tumor needs to be considered, but I do not recognize the characteristic organoid appearance that one usually associates with that lesion. Dr. Stout[1] discussed the distinction betwen glomus tumor and hemangiopericytoma. He pointed out that the cells of the latter have no loose stroma interrupting their continuity between vessels. Glomus tumors have been described in many locations where glomuses were thought not to exist. Dr. Stout along with Margaret Murray[2] helped to explain that phenomenon when they cultured the cells of a glomus tumor and showed them to be the same as the pericytes of Zimmerman. These have wide distribution in the deeper structures of the body, so glomus tumors may arise some place like the uterus. Such a happening was reported by Borghard-Erdle and Hirsch[3] in the form of a 4 mm. tumor of the uterus.

Another possibility to consider is stromal endometriosis.

I can not feature such a clearly vascular makeup in endometrial stroma. Nor are the cells as compact and dense-staining as the stromal cells should be. Frank Foote[4], et al have recently written of "Plexiform Tumorlets" of myometrium. These authors felt they had evidence of transition between endometrial stroma and a peculiar plexiform lesion in the myometrium. They believe this is evidence for endometrial stromal origin of the lesion. Most published examples that fit this plexiform pattern have been isolated accidental findings of very small lesions[5]. I would dismiss stromal endometriosis as unlikely in our case.

Hemangiopericytomas are uncommon tumors any place, and must be extremely rare in the uterus. Greene and Gerbic[6] described[5] which have what looks to me like a similar makeup to our case. These 5 tumors were interpreted grossly as leiomyomas in each instance, and each was less than 2 cm in diameter. The original diagnoses in these tumors before they were recognized as hemangiopericytomas included cellular leiomyoma, leiomyosarcoma, angiosarcoma, and simply sarcoma. These authors had a follow-up of 2 years at most with no recurrences.

In Dr. Stout's[1] report of 25 cases of hemangiopericytomas of various other sites, he mentioned having seen one unreported case in the uterus. I also found a reference by Lamy[7] to a diffuse pericytoma of uterus with metastases to both ovaries. I have not seen this paper, but the word "diffuse" in the title is reminiscent of our case. One might wonder whether this feature should suggest the possibility of malignancy.

The follow-up in this young girl in our case ends 3 years following surgery when she moved to California. At that time she was experiencing no further difficulty.

DIAGNOSIS: Diffuse hemangiopericytoma of uterus.

Discussion:

Dr. Stout in CANCER in 1949 discussed the distinction between a glomus tumor and pericytoma, and he pointed out this failure of interruption of the cells involved by a loose stroma and he said this favors the diagnosis of pericytoma. Someone might want to say, "Well, what's a glomus tumor doing in the uterus?" and Dr. Stout has explained this along with Dr. Margaret Murray, because they cultured a glomus tumor and were able to grow out cells which were similar to Zimmerman's pericytes, and although we recognize glomus structures in just a few places, they had no trouble accepting the fact that a glomus tumor can be deeply located.

There was a report of a 4 mm glomus tumor which was probably more or less accidentally discovered, in the Archives of Pathology in 1948, but the author did see one and reported it in the uterus.

Another thing that should be considered, although I don't believe it's a very strong possibility, is stromal endometriosis. I can't conceive of this being stromal endometriosis with this distinctly vascular element, and to me the cells are not as compact and dense as you might expect in stromal cells.

I guess it's fair to say that hemangiopericytomas are uncommon in about any location and particularly they must be rare in the uterus, because the literature is not filled with them. Greene and Gerby in 1954 in Obstetrics and Gynecology reported five cases and their illustrations are to me identical with what we see here. Again these were small individual lesions, in each instance less than 2 cm. in diameter and they had a variety of interesting diagnoses before they were recognized as pericytomas, if that's what they are.

Finally, in the French literature there was a reference by Lamy in the Federation of Gynecology and Obstetric French Bulletin in 1965 and the title was all I was able to come by in this particular article. It is called "Diffuse Pericytoma with Metastases to Both Ovaries." This is the closest I could come to finding anything that was comparable to our lesion as far as the nature of it is concerned. The indication by the title would suggest that this was a malignant disease that had spread to the ovaries from the uterus. In our case, we have no way of proving or disproving this because we don't have the ovaries and the little girl has them with her. She moved to California. She was last seen three years following surgery, so that at the last follow-up she was living and well. She had married; she had no problems except for sterility.

So you have a list of the diagnoses that were submitted, Dr. Severance?

CHAIRMAN SEVERANCE: I will read them right now: Angiomatous lesion, type ?; hemangiopericytoma (benign) in leiomyoma; hemangiopericytoma; benign hemangiopericytoma, microscopic into uterine leiomyomata; stromal endometriosis; hemangiopericytoma; hemangiopericytoma again; vascular leiomyoma; endolymphatic stromal myosis; leiomyoma-pregnancy? hemangiopericytoma pattern in a leiomyoma of uterus; vascular leiomyoma (1 mitosis seen; poorly differentiated in a few places; rapidly growing, but doubt malignant growth).

DR. DELMER: They must have gotten better slides than I thought they did.

CHAIRMAN SEVERANCE: Dr. Totten said he didn't notice in his slide these little foci, but I checked these slides myself from beginning to end and there is a little bit of tumor in each slide, but I have to tell you it isn't much.

DR. DELMER: I think maybe some of them came back that you don't know about.

CHAIRMAN SEVERANCE: Any other comments from the audience?

DR. KAY: I remember sometime ago asking Dr. Stout how he would differentiate stromal endometriosis from a hemangiopericytoma because, after all, the pattern is the same field for field; the pattern duplicates itself so nicely.

I think one of the things that Dr. Stout said-- I don't know whether this would hold in every case--is that in stromal endometriosis there would be at least some connection with the endometrium so that you could see its downgrowth as it was permeating through the uterus and, of course, even outside the uterus. Otherwise I really don't know on a pure histological basis that you have anything to stand on from the point of view of saying that this is hemangiopericytoma or, as somebody else said, endolymphatic stromatosis.

DR. DELMER: I'm not going to argue with you. I'll give the answer that Dr. Severance gave the other day, which I think he heard someplace else. He said, "I think it's a Cadillac because it's got hubcaps like a cadillac."

CHAIRMAN SEVERANCE: We had a seminar down in San Antonio one time and somebody was heckling Dr. Foote from the audience. He said, "Now, Dr. Foote, you haven't really come out and said what this is; what kind of a tumor this is." He didn't really know; so he says, "Well, you know, it's just like you see a Cadillac coming down the street. It's a Cadillac because it looks like a Cadillac," and that was the end of his comment. He wouldn't go any further.

Any other comments from the audience?

DR. PICKREN: I have a comment about Dr. Foote's remark. I trained at Columbia, at Presbyterian under Dr. Stout and I'm very glad I did because in Dr. Stout's department we learned to describe things. We made histological descriptions on all our tumors. If Dr. Foote would take the Cadillac and describe it, he would come up with good reasons why he thinks it's a Cadillac.

I think that with the histological records we made we come up with reasons, and if you ever read Dr. Stout's letters you follow right along with his ideas and how he comes to the reason why he makes the diagnosis. So I think that this is a very good lesson and that Presbyterian Hospital does a much better training job! (laughter and applause)

DR. LATTES: John, what is your diagnosis?

CHAIRMAN SEVERANCE: We all know that! (laughter)

Any other comments from the audience? You fellows better go home and give a good description, because when you get home you may come up with different answers.

DR. TOTTEN: There's a lot of reticulin in these lesions, not really what was shown here. I think this might be one small point in the differential diagnosis of those two lesions.

REFERENCES:

Stout, A.P.: Hemangiopericytoma, A Study of 25 Cases. Cancer, 2:1027-1054; 1949

Murray, Margaret R. & Stout, A.P.: The Glomus Tumor. Am. Jour. of Path. XVIII: 183-203; 1942

Borghard-Erdle, A. & Hirsch, E.F.: Glomus Tumor of the Uterus. A.M.A. Arch. of Path. 65:244-246: 1958

Larbig, G., Clemmer, J., Koss, L., & Foote, F., Jr.: Plexiform Tumorlets of Endometrial Stromal Origin. Am. Jour. Clin. Path. 44:32-35; 1965

Budinger, John & Greene, Ronald: A Distinctive Myometrial Tumor of Untetermined Origin. Cancer- 17:1155-1158; 1964

Greene, Ronald & Gerbie, Albert: Hemangiopericytoma of the Uterus. Obstetrics & Gynecology 3:150-159; 1954

Lamy, M., et al. Diffuse Pericytoma of Uterus with Metastases at the Level of Both Ovaries. Bull. Fed. Gynec.-Obstet. Franc. 17:228-232; 1965

CHAIRMAN SEVERANCE: I see John Ellis was afraid I would not be able to put that microphone on around his neck, so he's up there all set and ready to go on Case No. 7.

John!

Case No. 7
Submitted by Dr. John T. Ellis:

This 57 year old white male was under medical care for chronic pulmonary emphysema. He called the attention of the physician to a mass in the left groin which had been present for several months. The tumor was sharply circumscribed, encircled the femoral vein just below Poupart's ligament and could easily be separated from the femoral artery. The specimen consisted of a sphere of firm white tissue covered by a pseudocapsule which measured approximately 6 cm. across and replaced the wall of the femoral vein which was ligated above and below the tumor.

Following the pathological diagnosis, additional x-rays were taken and metastatic lesions were identified whereas they had been absent in x-rays taken several months previously. The patient died approximately four months following surgery, but was not autopsied.

In Sum, this is a case of a 57 year old man who had a tumor of the femoral vein. This was removed by an unsuspecting surgeon who thought that the patient had a hernia. The patient died four months later from a metastatic tumor.

Slides:

Many of the preparations did not show the relationship to the vein. This is the vein wall, media, and adventitia, and here is the tumor at this junction with this large artifact.

This is the vein wall that directly led into the tumor.

The tumor was made up of bundles, whorls of spindle shaped cells such as one sees here. In many areas there was a good deal of pleomorphism, and I'll show you a number of sections that illustrate the variations of the tumor.

This is a cross section of the tumor cells and I think one can see that in this view they are round, in bundles, and again one sees the whorled appearance.

These are spindle shaped cells in this area. In longitudinal section you see that they have rather blunt ends but particularly pleomorphic in this area. I don't see any mitotic figures.

This is a cross section---

CHAIRMAN STOUT: May I interrupt you. How long did you look for the mitoses?

DR. ELLIS: I'll demonstrate those in just a moment.

CHAIRMAN STOUT: But that doesn't answer my question. (laughter) How long did you look?

DR. ELLIS: I didn't have my stopwatch!

This shows the relationship near the adventitia of the tumor to one of the small arteries in this area. It shows the similarity between the types of tissue.

Another view showing one of the areas that is not particularly pleomorphic and looks somewhat like a benign tumor.

Another showing a different view where there is a great deal of pleomorphism and nuclear variation.

Again a very pleomorphic area. Many areas, Dr. Stout, did contain mitotic figures such as one sees here; here are three mitoses that are quite evident, but this was variable. Some areas contained very many; some few.

Another variant showing the nuclear variation and a mitotic figure in this point at least.

In some areas, such as one sees here, where there was fibrosis and there was a good deal of nuclear abnormality.

Finally one sees these bizarre nuclei that Dr. Stout has described so well.

Discussion:

First of all, there have been twenty-seven of these tumors described. I see a number of illustrious compatriots here: Dr. Stout, Dr. Fine, Dr. Ackerman is here somewhere.

The age variation in these leiomyosarcomas is quite great. Some occurred quite early in life, and they go up into the 80s. There is a predominance of females in this group, or so it is reported in the literature.

The most likely site seems to be the larger vessels, particularly the inferior vena cava.

Many of these cases that have been reported have been autopsy findings, but many have been resected, and of the cases that have been treated, a number have metastasized or have recurred.

In the particular case we have, there was no autopsy although there were metastases to the lungs, we believe. The growth of these tumors is primarily intraluminal and the evidence would indicate that they are present for long periods of time before they are noted clinically. If they are superficial vessels, they usually don't cause any symptoms. In the deeper vessels you frequently get edema, and if they are in the inferior vena cava they may cause the Budd-Chiari syndrome.

May we have the dissenters?

CHAIRMAN SEVERANCE: All right, here we go: Leiomyosarcoma; fibrosarcoma (leiomyosarcoma ?); leiomyosarcoma; leiomyosarcoma arising in the wall of the femoral vein; leiomyosarcoma of femoral vein; angioleiomyosarcoma; leiomyosarcoma again; leiomyosarcoma of femoral

vein; leiomyosarcoma again; again leiomyosarcoma; leiomyosarcoma of wall of femoral vein with multiple pulmonary metastases, and vascular leiomyosarcoma.

You have a pretty good unanimity of opinion.

DR. ELLIS: It was really a very easy case, although I must say that in the slides that I got back in my set I couldn't recognize the lesion! (laughter)

CHAIRMAN SEVERANCE: Do we have any comments from the audience? Since the votes were pretty unanimous, does anybody want to make any comments who did not write in their votes?

MEMBER: Do they ever occur in the arteries?

DR. ELLIS: I presume they do. I don't know of any examples, though. Since there are other distinguished authors who have written on this subject, perhaps they may want to comment on that question.

I might add that I talked to Dr. Mannion in the A.F.I.P. a few weeks ago. He indicated to me that they probably had about 100 of these tumors in the files and he was working it up there and that they primarily occurred in larger veins. He did not mention any arteries.

DR. ACKERMAN: I talked to Dr. Mannion, too, and I asked him about the artery question and he said that he had a few cases in the abdominal aorta.

CHAIRMAN SEVERANCE: Any other comments, questions?

DR. HELWIG: May I make one comment not particularly with regard to the sarcoma but we do have some angiomyomas that are originating in arteries. So it's conceivable that if an angiomyoma could originate in an artery, a myosarcoma could, too.

CHAIRMAN SEVERANCE: Dr. Stout was just saying he had seen leiomyosarcomas in both arteries and veins. First he was thinking only of veins and then he said that he had seen them in the arteries.

Rafe, can we go on with another case?

DR. LATTES: Yes.

Case No. 8
Submitted by Drs. Merle Delmer and Alvin O. Severance:

As you remember from the history, this was a 46 year old male with a lesion on the scalp of one year duration. Initially it looked cystic, was incised and blood flowed out, and it was treated with local cautery. It did not get better. It was excised late October, 1966.

In the slides you see a section of skin in whose deeper corium and subcutaneous fat as well as the upper and midcorium we see a tumor made up of anastomosing, vascular spaces lined by what I believe are tumor cells. The tumor cells look like neoplastic endothelial cells and they have moderately chromatic elongated, round or oval nuclei and cytoplasm is difficult to make out. In some portions of the tumor these cells seem to be proliferating outside of the lining of the vascular spaces and in these proliferating cells the nuclei tend to be more rounded or more oval and vesicular. Nucleoli are small or absent. Mitoses are seen occasionally among these cells. In other levels through the block which you may not have seen there are areas of hemorrhage and necrosis and some foreign material that stains a dark brown. This may be the result of the use of the silver nitrate for cauterization. Also there is quite a bit of hemosiderin pigment which might be explained by the incision that has been done. The lesion as I see it goes to the base of the specimen and would be considered incompletely removed as I look at the slide, although in some levels there seems to be some normal fat beneath the tumor. In the reticulin stain, as I interpret it, there seems to be considerable blackened reticulin fibers outside the endothelial cells which line the vascular spaces. The red blood cells seem to be in the center of these spaces.

The microscopic picture suggests to me a hemangioendothelioma and I believe the reticulin stain supports this. Because of the mitoses, I believe that one should consider it malignant. I don't believe that this fits the picture of a hemangiopericytoma or the picture of Kaposi's disease.

FINAL PATHOLOGICAL DIAGNOSIS: Malignant hemangioendothelioma of skin.

Follow-up: The lesion recurred following this partial excision and the patient was seen at the M.D. Anderson Hospital where further treatment was carried out, but I am unable to know what they did.

DISCUSSION: Any discussion of hemangioendothelioma must refer you back to the article written by Dr. Stout in 1943 in the Annals of Surgery. We must also refer you to his fascicle on Tumors of the Soft Tissues in which he has a discussion of this tumor at which time in Sept. of 1951, he had accumulated thrity-four cases with varying sites of distribution. Refer to the fascicle for this information. Fink and Overman in 1963 reported on nine patients with malignant tumors of blood vessel, five of which were classified as "hemangioendothelial cell sarcoma" and four of hemangiopericytoma. Of these nine patients studied, seven died from the neoplasm, one was alive with disseminated disease and one had a long term survival with repeated recurrences of the primary lesion in the nasal fossa during a twenty-five year period. Of the six patients with disseminated disease, all showed pulmonary metastases. Other sites of metastases which were apparent before death, were skull, central nervous system and liver. The route of metastasis was predominantly vascular. Patients with primary gluteal lesions had the shortest survival time. Response to radiation therapy was generally

poor with an occasional good palliative result. None of the neoplasms were eradicated by irradiation. Four of the nine patients received one or more courses of nitrogen mustard including one in which pelvic perfusion was done. Two of these four had significant palliation. In the hemangioendothelial cell sarcoma there did seem to be some correlation between the clinical course and the histologic pleomorphism and the increased mitotic activity rate. They recommended surgical resection as the treatment of choice for the primary lesion and mentioned that significant palliation may be obtained with radiation therapy or with nitrogen mustard administered systemically or by perfusion. Attempts to correlate histological appearance of hemangiopericytoma with response to radiation or the clinical course was unsuccessful.

In Cancer 1961, Shirley Kaufman and Dr. Stout reported on malignant hemangioendothelioma in infants and children and they had nine cases in their laboratory files and found eighteen others in the literature which they accepted. They divided their nine cases into two groups, five of whom they thought were in the class considered more malignant because of extensive cellular anaplasia and the other four were classified as less malignant. In Cancer 1962, Hartman and Stewart reported ten cases of primary bone tumors which they classified as hemangioendotheliomas. They considered that this is an unpredictable, potentially malignant neoplasm of bone but more indolent than most tumors considered under the category of angiosarcomas. In Surgery, 1960, Barber et al reported on a case of angiosarcoma of the breast in a 47 year old woman and their patient died of metastasis fifteen months after the onset of the disease. Their second case was a 32 year old woman who had a simple mastectomy. These authors point out that there had been no cures of this disease of the breast and they say

their only hope for cure is early surgical removal. In Gastroenterology, Feb. 1961, Davis reports a case of hemangioendothelioma of the liver in an eighteen year old boy. He notes in this discussion that there were five cases of hemangioendotheliomas of the liver in which thorotrast had been implicated. Surgery and irradiation therapy have generally been unsuccessful in this disease in this organ.

Now I will hop over there in my other capacity and give you the diagnoses from the votes of the audience: Angioma (? malignant); hemangioendothelioma; malignant hemangioendothelioma; hemangioendothelioma (interanastomosis of capillaries suggest malignancy); malignant hemangioendothelioma; malignant hemangioendothelioma again; malignant hemangioendothelioma (angiosarcoma); hemangioendothelial sarcoma; hemangioma; another hemangioma; Kaposi's sarcoma, and capillary hemangioma with areas of malignant hemangioendothelioma.

I think I pointed out to you why I didn't think it was Kaposi's disease and if I didn't, Dr. Helwig in his discussion probably did because I think these cells are malignant cells of endothelial origin and I didn't see the fibrosarcoma pattern that I like to see.

Any dissenters? (No response)

References:

Barber, Kent W. Jr., Harrison, Edgar G., Clagett, O. Theron and Pratt, Joseph, H., Surgery, Vol. 48: 869-878, Nov. 1960, Angiosarcoma of Breast.

Davis, George N., Hemangioendothelioma of Liver with Unusual Roentgenologic Findings, Gastroenterology 40: 253-258, Feb. 1961.

Fink, Howard E. Jr., and Overman, Harold A.: Hemangioendothelial Cell Sarcoma and Hemangiopericytoma, Am. Journal of Roentgenology, 89: 115-165, Jan., 1963

Hartmann, William H. and Stewart, Fred W., Hemangioendothelioma of Bone: Unusual Tumor Characterized by Intimate Course, Cancer 15: 846-854, July-August 1962.

Kaufman, Shirley L. and Stout, A.P., Malignant Hemangioendothelioma in Infants and Children, Cancer 14: 1186-1196, Nov.-Dec. 1961.

Stout, A.P.: Hemangioendothelioma: A Tumor of Blood Vessels Featuring Vascular Endothelial Cells, Ann. Surg. 118: 445, 1943.

Stout, A.P.: Tumors of the Soft Tissues, Atlas of Tumor Pathology, Section 2, Fascicle 5, Washington, D.C. 1953, Armed Forces Institute of Pathology.

CHAIRMAN SEVERANCE: It is 12:00 o'clock, Dr. Lattes, do we stop or do we go on?

DR. LATTES: I would suggest stopping now and be back here and ready to go on at 2:00 o'clock.

CHAIRMAN SEVERANCE: You have heard the ruling.

(adjourned at 12:00 o'clock.)

(AFTERNOON SESSION)

(The Seminar reconvened at 2:00 o'clock.)

CHAIRMAN SEVERANCE: I think we better take our seats and get started even though a few others straggle in. My arithmetic says we have seven more cases to go. So we want to get on the ball.

John, do you want to come up and start with Case No. 9.

Case No. 9
Submitted by Dr. John W. Pickren:

Last year when I presented my case I decided I would never do it again because I did such a poor job in comparison with the other experts who were up here. But Dr. Lattes called me sometime around February and he said that he would like to have some cases submitted from my place. So I dug into my files and I think I submitted eight cases that I felt sure he would not accept, and then he came up with two of them. So here I am talking again when I really should not be up here at all.

This patient was referred to R.P.M.I. at age 49 with the following history: He had psoriasis from the age of 12 and took Fowler's solution for 17 years between 1940 and 1957. Dosage varied but generally was around 30 drops a day. After he discontinued taking Fowler's solution in 1957 he was treated with topical cortisone ointment. He was admitted to this hospital in May, 1964. At that time he had a nummular psoriasis. He complained of fatigue and abdominal discomfort. He was jaundiced and his liver was palpable 4-5 cm. below the right costal margin. The liver was tender and nodular.

On the fourth hospital day the patient became maniacal, shouting and cursing, and it took five individuals to steady him. He was given nembutal and chlorpromazine. His condition steadily deteriorated; he developed acute respiratory distress and died on June 4, 1964, about one month after his admission to this hospital.

An autopsy was performed. The main findings were in the liver. The liver weighed 4,000 grams. Its surface was irregular, nodular, and yellow. The liver was very hard and the cut surface showed extensive hemorrhagic nodules. No normal hepatic architecture

was found. The largest nodule measured 10 cm. in diameter and the smallest one measured 0.5 cm. in diameter.

Summing up, this case that I have submitted here is basically a man who had psoriasis and who had been treated with Fowler's solution for a long period of time. We don't know the exact amount of solution but he took it off and on and the total amount of arsenic that he received from this Fowler's solution must have been quite a bit. At any rate, he eventually developed a lesion in the abdomen and they found an enlarged liver by clinical evaluation. He died from liver failure and at autopsy we found a very large liver.

Slides:

This shows the liver that was removed at autopsy and we can see that it is a big liver weighing 4,000 grams. The liver has multiple nodules. There are different colors here and even in this picture we could recognize that there are some very rather hemorrhagic ones.

This is a cut surface. As we cut through this liver we find that there are broad bands that seem to be some connective tissue. But the most striking feature is the very large hemorrhagic areas. We took multiple sections through these areas, and this is what we present to you.

Microscopic: The striking gross picture is matched by the histological pattern. Multiple anastomosing channels are lined by cells ranging from typical endothelial cells to bizarre forms. These bizarre forms include spindle shaped cells, monstrous forms, and anaplastic cells. In many areas, the cells form a single layer within vessels, but others are layered. Papillary enfoldings and mitotic figures are present. Reticulin fibers outline the channels and show that even in the solid areas that the neoplastic cells form congeries

of vessels. In most areas, liver cells remain and the liver cords are well recognized, but the sinusoids are increased in width and surround groups of liver cells, suggesting that liver cells are afloat in vascular spaces. In a few foci, masses of tumor cells have destroyed the liver cells. Foci of hematopoiesis are extremely numerous.

Discussion: The carcinogenic action of arsenic is well known. The most common arsenically induced tumors are skin cancers. The location of these skin cancers are predominantly on the extremities, and frequently the patient has multiple cancers. Tumors of internal organs also have been described following the ingestion of arsenic compounds, often in association with a skin cancer. Malignant hemangioendothelioma following arsenic ingestion has not been reported in the American literature, but it has been well documented in foreign journals. Roth found 8 hemangiosarcomas in reports on 82 autopsies of vineyard workers. These workers were exposed to arsenic intoxication from sprays, dusts, and ingestion of large quantities of grape wine containing high levels of residual arsenic.

It is interesting to note that the frequency of arsenic induced tumors in these vineyard workers was lowered by stopping the policy of issuing cheap wine to the workers for payment of work. This wine contained as much as 8.9 mg.% of arsenic.

The usual duration of arsenic exposure was 12-17 years with an estimate of 54 gms. of arsenic intake over the calculated period. The latent period for tumor development has been estimated at 13-22 years after the first exposure. The latent period of 24 years in the patient under discussion is not inconsistent with these estimates. The total amount of arsenic that he ingested in the form of Fowler's solution is not known. However, if he averaged 15 drops a day for

half the period of ingestion, the quantity of arsenic intake would approximate that of the vineyard workers.

The absence of arsenic in the organs of this patient is not surprising. After stoppage of a prolonged intake of arsenic, it is completely excreted in 4 years. Following single injection in laboratory animals, the bulk of arsenic is excreted rapidly in 24-48 hours, although it can persist in visceral organs for 7-10 days. In contrast to acute ingestion, chronic arsenic administration results in sustained high liver values, but the exact pathophysiological pattern of liver change induced by arsenic is not known.

Foci of hematopoeisis present in this case has been reported by others in patients with malignant hemangioendothelioma, regardless of whether arsenic had or had not been ingested. It may represent a response to anemia but it is interesting that the bone marrow appears highly cellular. Baker feels that hematopoiesis is a specific feature of the tumor for it is well known that hematopoietic stem cells may arise by differentiation of the sinusoidal endothelium in the adult when occasion demands. This extramedullary production of blood cells does not appear to be a feature of malignant hemangioendothelium when primary in other sites than liver.

Diagnosis: Malignant hemangioendothelioma of liver following arsenic intake.

It is really striking to me that whenever I look at a lesion and I go to the literature and look at the literature to see what has been reported, I always find the names of you people in the literature that reported these cases. Of course, Dr. Stout's classical article on malignant hemangioendothelioma which occurred in the Annals

of Surgery, which was mentioned previously, has a wealth of material, and in that article he mentions two cases of malignant hemangioendothelioma of the liver.

Of course, as far as our tumors are concerned, Haagensen reported four cases of tumors of the skin occurring after prolong administration of arsenical compounds and, of course, Dr. Helwig and his associates more recently have reported on this. So I can't come up with anything new.

At any rate, the carcinogenic action of arsenic is well known and, in fact, most of these tumors that do occur following arsenic ingestion are the tumors of the skin, basal cells and squamous cell carcinomas. But, interestingly enough, these tumors occur more prominently along the lower extremities and the arms than it does in the face. I don't know the reason for this. Perhaps Dr. Helwig will tell me later why it occurs on the extremities.

Tumors of the internal organs have also been described but they are not nearly as common as the skin lesions. Of course, the skin lesions are often times multiple in these cases.

Malignant hemangioendothelioma has also been reported in the foreign literature to occur following the ingestion of arsenic. We have found no case in the American literature of malignant hemangioendothelioma occurring following arsenic ingestion. The ones that are reported in the foreign literature have been cases where these people have worked in the wine industry, and one of the things that they did was to pay these people off for their labors by giving them cheap wine.

The levels of arsenic that would be present in that cheap wine would be as high as 8.9 mg. %. So there is a very high level of arsenic. In calculating the amount of arsenic that was received, these

authors said that some of these patients received on an average as much as 54 gm. of arsenic over the calculated period. The "calculated period" again is a long period such as we have here. 13 to 22 years is the delay between the time that they started the arsenic ingestion to the time that they develop a tumor, and in our case 24 years occurred.

The fact is that in our case we examined the tissues for arsenic and we found no arsenic. But we must remember he had stopped taking arsenic seven years before he finally developed this tumor, and it is well known that even after a prolonged arsenic intake that arsenic will not be able to be found in the body after a period of about four years. So we really did not expect to find any arsenic.

In acute experiments where arsenic is given in one single injection, most of the arsenic disappeared between 24 to 48 hours, but some was retained in the internal organs up to a week to ten days. The arsenic, by the way, goes primarily to the liver and the skin and the kidney, and most of the arsenic is excreted through the kidney.

These foci of hematopoeisis are interesting to me because in looking through the literature I find that hematopoeisis has been seen in cases of diseases of the liver but it is not something that is reported to be seen in malignant hemangioendothelioma of other organs. It is primarily only seen in those cases involving the liver. It does not matter, however, whether the patient has received arsenic or not, because any malignant hemangioendothelioma of the liver often times has these large areas of extramedullary hematopoeisis.

One author said that they felt that the reason for this was that it really was part of the tumor rather than being a response to anemia, because these patients may or may not have anemia.

In our case the patient had a mild anemia. The hemoglobin was 10 gm. at the time the patient came into the hospital.

In summary I would say that we are dealing here with a case of malignant hemangioendothelioma, (I use that term, Dr. Helwig, because I was taught by Dr. Stout, who uses that term), occurring in a patient after a long exposure to arsenic.

May we have the diagnoses, please, Dr. Severance?

CHAIRMAN SEVERANCE: Metastasis to liver of malignant hemangioendothelioma; angiosarcoma of liver; malignant hemangioendothelioma again; hamartomatous angiomatosis of liver, diffuse, extensive. Area suggestive of malignancy; angiosarcoma of the liver; angiosarcoma (Kupffer's cell sarcoma); malignant hemangioendothelioma of liver; Kupffer's cell sarcoma; angiosarcoma of liver; "hemangioendothelial sarcoma" of liver; malignant hemangioendothelioma of the liver, and massive multiple cavernous hemangiomas of liver with compression and necrosis of many liver cells.

Discussion:

DR. PICKREN: Most come to the same diagnosis but using different terms. There are a couple of instances where people felt it was a benign lesion. The only lesions that were present were in the liver. Perhaps this is in your favor, but I can't bring myself to call this benign because of the monstrous and bizarre forms that are present in the liver.

CHAIRMAN SEVERANCE: Any comments from the audience?

DR. LATTES: John, what is the difference between malignant hemangioendothelioma of the liver and Kupffer's cell sarcoma of the liver?

DR. PICKREN: There may be a difference between those two lesions that I don't know enough about.

The reason why I say that is because, as I pointed out, the tumors of this type that occur in the liver have these significant areas of extramedullary hematopoiesis while I have not been able to find it occurring in malignant hemangioendotheliomas outside. Has anyone here seen that?

DR. LURIE: Yes.

DR. PICKREN: So it does occur outside the liver, too. In that case I don't see any reason why we could not say that they are the same disease, Dr. Lattes.

CHAIRMAN SEVERANCE: Dr. Lurie says he has seen it outside the liver.

DR. MCKAY: I think that there is some support for the ideas that the extramedullary hematopoiesis is part of the tumor from the observation that very often in an old thrombus, in almost any old blood vessel, if it has been there the right length of time and the right conditions have been established over this period of time, then one will see extramedullary hematopoiesis arising from the endothelial cells in the wall of the blood vessel. It seems to me that this ability of the endothelium to produce hematopoietic cells, red cells, not the granulocyte series but red cell series, is simply a recapitalation of the embryonic development of erythroblasts in the yolk sac of the embryo, because there the cells join together from the mesenchyma. Then they form channels; then within the channels circulating red cells.

I think it is part of the tumor. I think it supports the histogenetic idea about what cell is the primary cell of the tumor.

DR. PICKREN: Dr. McKay, may I ask you a question. In cases where we have bone marrow destroyed, there is no bone marrow present, we know extramedullary hematopoiesis often occurs in the liver in significant amounts and also in the spleen. Perhaps the extramedullary hematopoiesis that we see in the liver is a response to the tumor rather than being really a part of the tumor.

CHAIRMAN SEVERANCE: Dr. Kay, you had your hand up a minute ago.

DR. KAY: I was just wondering; I want to leave this question to the group here. There must be a difference theoretically between a Kupffer's cell sarcoma and the hemangioendothelioma unless the endothelial cell is the Kupffer's cell. I thought there was a difference in cell makeup of the sinusoids. The Kupffer cell, of course, is very phagocytic. I don't think there was any evidence of phagocytosis here with this tumor; is that correct?

DR. PICKREN: I did not see any phagocytosis here. Who is the histologist here who would like to answer what the difference is?

CHAIRMAN SEVERANCE: Their names are not on here.

DR. LATTES: Dr. Azar.

DR. AZAR: Sir, I believe I've seen what was called a Kupffer's cell sarcoma. This is a malignant reticuloendotheliosis of the liver, and there you see evidence of that feature. Dr. Sommers may recall a case of this sort.

There is another thing that comes to my mind that may be pertinent. I wonder, Dr. McKay, whether you don't have here two processes, one merging into the other. That is, you have an angiomatosis where the hepatic cords are perfectly safeguarded and the cells

don't seem to compress or push the cords. This is where you have your hematopoiesis. Then as you go to other fields, then you have a very dense, very cellular sarcoma, and this is pertinent in view of the arsenical dermatoses that evolve into full-fledged squamous cell carcinoma.

I wonder whether you would like to comment on this.

DR. PICKREN: It seems to me there is a transition between the two, as I showed you pictures here; that you can find very definitely normal endothelial or Kupffer's cells and then you find these very definite malignant cells or you find all the cells in between, and when I come to that kind of a viewpoint, I don't know how to answer the question other than that.

CHAIRMAN SEVERANCE: Dr. Lurie wanted to ask a question, or comment.

DR. LURIE: You called it a Kupffer's cell sarcoma. I was the one who gave it as a synonym for angiosarcoma and it is a term that we have been accustomed to use---the Kupffer's cell sarcoma, and I don't think that there is any difference. I think they are tumors that arise from the lining cells of the sinusoids and I think that, like all other tumors, some may mature more towards endothelial cells and others more towards the histiocytic type of cell.

DR. PICKREN: The report I have read about the Kupffer's cell sarcoma, the one that used the term first, says it's a better term than malignant hemangioendothelioma. I really would stick to the endothelioma rather than the Kupffer's cell sarcoma.

CHAIRMAN STOUT: I have something that might interest you. When I was a medical student in P&S, McCallum taught me and he introduced me first to this involvement of liver and spleen. He was under

the impression at that time that the cells that got involved were the ones that were involved usually in the liver first rather t'an the spleen, and then the spleen.

I have all the notes that I took in the course in cytology as taught by McCallum, who was a very remarkable man. And when I wrote the book "Human Cancer"; you may have heard of it. It's a very old one.

DR. PICKREN: We have a copy of it, Dr. Stout.

CHAIRMAN STOUT: All right. It impressed me very much that almost always both were involved. I don't recall that McCallum mentioned (which must have been present) the proliferation of red blood cells in this disease of liver and spleen. That's a recollection. McCallum was a very stimulating talker and I just loved to listen to him. But when it came to being examined by him, I found myself troubled. I could not take in all that he said, but he really was a very remarkable man.

I think also that you will find in Delafield and Prudden some mention of the involvement of the liver and the spleen. I cannot remember whether they studied the formation of the red blood cells, but it would be easy to develop.

DR. PICKREN: Yes, sir. Actually we have Delafield and Prudden's book and we also have McCallum's. So I will look it up when I get home.

I would just like to check here to see what the spleen weighed. I don't recall and I don't have it in my notes. I think the spleen was enlarged and there are areas that are certainly abnormal in the spleen, too. There are some sort of spindle cell proliferations but nothing that I really would want to call malignant in the spleen.

But it is not a completely normal spleen and, of course, as you saw in the pictures, there was extramedullary hematopoiesis. I certainly will take that note home.

DR. DeCOURSEY: The history of arsenic ingestion and the microscopic picture of a possible Kupffer cell sarcoma elicits consideration of a similar hepatic tumor seen in thorotrast injected patients. Some of them also had a history of arsenic intake which has led several authors to believe arsenic may be the specific agent in such tumors. However, Looney and others have inferred that Kupffer cell sarcoma are particularly associated with thorotrast, the mean latent period being about 15 years and the dosage being somewhat around 1,000 to 1,500 rads from the radioactive thorium dioxide contained in thorotrast.

DR. PICKREN: There was one interesting report I saw on the thorotrast which was a case where they had extramedullary hematopoiesis in the liver and not only was thorotrast found in the normal Kupffer's cells but it was also present in the malignant cells. In that case the malignant hemangioendothelioma was also present.

DR. RICHTER: I would like to add to Dr. McKay's comments on the presence of nucleated red cells in the tumor.

The development of nucleated red cells requires a certain type of environment. This is an intravascular environment in a type of vessel that has a slow circulation; a sinusoidal type of circulation, and any situation that provides a slow sinusoidal type of circulation is a potential site for the development of nucleated red cells. That is the case here; that is the case in organizing thrombi and in various other situations. It does not necessarily mean that the nucleated red cells developing in the tumor are neoplastic in the sense that they can metastasize as other tumor cells do.

Incidentally, if Dr. McKay will look up the old P & S autopsy records in probably the early 30s he will find a case of hemangioendothelial sarcoma of the liver that is very similar histologically to this one. As I recall it, at the time there was a controversy between two schools, P & S being on one side and I think Memorial Hospital on the other side, as to whether this was a hemangioendothelial tumor or a variety of hepatoma. I think the controversy has been settled.

There was also a hemangioendothelial sarcoma of the liver that I saw at Post Graduate years ago in which the first symptom was rupture in the peritoneal cavity.

CHAIRMAN SEVERANCE: I think we had better go on. Dr. Haagensen was commenting at our business meeting how at some scientific meetings there is very little discussion, but if we haven't had discussion now, I don't know what it is!

Dr. Totten, if you will come up, I will pin this microphone on you. This is going to be Case No. 10.

Dr. McKay: It wasn't discussion that Cushman recommended; it was debate. In this regard it seems to me that sometimes we are overlooking the forest for the leaves.

We've had lots of malignant hemangioendotheliomas and several today. The really crucial point of the last case was the relationship to the 17 years of arsenic therapy. No one said that this was due to the arsenic therapy; no one objected. So I am not sure whether this was implied or inferred because it wasn't just referred to. But in any case I know John said that the liver tumor developed seven years after cessation of arsenic therapy.

I think this has an implication, at least has an inference for me that here is a seven-year lag between the last of the presumably

carcinogenic agent and the development of tumor. Carcinogenesis may be a good deal more interesting than the actual polysyllabic names that we can apply to the end product.

CHAIRMAN SEVERANCE: Well said.

John, do you want to say something before we go on?

DR. PICKREN: I don't know whether I said it or not, but in the studies that these people did on these wine workers there were 82 cases that they autopsied. Of those patients there was an awfully high rate of hemangioendothelioma. After they stopped giving them wine in payment, the number of tumors that developed in these wine workers disappeared almost completely. So it's a pretty good epidemiological evidence that there was a relationship between the taking of the wine with the arsenic in it and the development of the tumor.

CHAIRMAN SEVERANCE: I think Vince has the idea that you believe that arsenic had something to do with it.

DR. PICKREN: I think Dr. Haagensen should comment on this because he wrote the peper.

DR. HAAGENSEN: We need not worry because they quit spraying grapes with arsenic. So it's okay!

References:

Regelson, W., Kim, U., Ospina, J., and Holland, J.F.: Hemangioendothelial Sarcoma of Liver from Chronic Arsenic Intoxication by Fowler's Solution. Cancer (in print)

Franklin, M., Bean, W.B., Hardin, R.C.: Fowler's Solution as an Etiologic Agent in Cirrhosis. The American J. of Medical Sciences 219:589-596, 1950

Graham, J.H., Mazzanti, G.R., Helwig, E.B.: Chemistry of Bowen's Disease: Relationship to Arsenic. J. Invest. Derm. 37: 317-332, 1961

Neubauer, O.: Arsenical Cancers- Review. Brit. J. Cancer 1: 192-251, 1947.

Sommers, S.C., McManus, R.G.: Multiple Arsenical Cancers of Skin and Internal Organs. Cancer 6: 347-359, 1953.

Vallee, B.L., Ulmer, D.D., and Wacker, W.E.C.: Arsenic Toxicilogy and Biochemistry. A.M.A. Arch. of Indus. Health 21: 132-151, 1960.

Haagensen, C.C.: Am. J. Cancer 15:656-659, 1931

Baker, H. De C., Paget, G.E., and Davson, J.: Hemangioendothelioma (Kupffer-cell) sarcoma of the liver. J. Path. & Bact. 72:173-182,1956.

Stout, A.P., Hemangioendothelioma-A tumor of Blood Vessels Featuring Vascular Endothelial Cells, Am. Surg. 118: 445, 1943

CHAIRMAN SEVERANCE: Let's go on with this next case or Bob Totten won't get started.

Case No. 10
Submitted by Dr. Robert S. Totten:

This was a 17-year old boy who noted a mass at the base of his penis approximately two months before admission with gradual enlargement over this period of time. Physical examination showed a firm but movable mass 2.0 cm. in diameter at the base of the penis on the left side just beneath the pubis. Exploration revealed it to be in the corpus cavernosum just distal to the bulb.

Following local excision of the mass he received radiotherapy from a Cesium unit over a 25-day period, estimated dose to the tumor, 3600 rads. During his hospitalization he developed severe back pain and although roentgenograms were negative, a Strontium-90 scan showed increased uptake in the thoracic spine. He received an additional 2400 rads to this area. He was discharged two years ago and started school, and he is now finishing his sophomore year at Baylor University. He is well and without evidence of disease as of this month, 28 months after this was removed.

We received the specimen as a consult from another hospital and here you see half of the formalin fixed specimen. It was well circumscribed--in fact almost encapsulated-- and grossly hemorrhagic. The remainder represents part of the corpus cavernosum. Microscopically, the tumor had a variety of patterns--in many areas a rather non-specific fibrous pattern predominated--consistent with fibrosarcoma or leiomyosarcoma. In other areas, it was much more cellular with more or less solid sheets of cells--and here you see the sharp margin--the cells were almost syncytial in nature and in these areas mitoses were easily seen. In several areas, however, there were large, vascular spaces frequently with anastomosing channels that Dr. Stout has taught us are seen in malignant vascular tumors. These are lined by the same pleomorphic cells as are seen in the more solid areas. The reticulin preparation was poor but did seem to suggest enclosure

of cell groups by a thin membrane. I believe this is a hemangioendothelial sarcoma with origin most likely in the corpus cavernosum. With the exception of one possible case of reticulum cell sarcoma, we have no other cases in our files of sarcoma involving the penis. In reviewing the literature on this subject, one runs into the usual problem of finding really acceptable cases. Urologists, it seems, do not get along too well with pathologists and have two bad faults: They publish with no photomicrographs (or poor ones) and they write the manuscript while the patient is in the recovery room, so that adequate follow up is not available. I have reviewed all of the cases I could find and can only say that I believe there is such an entity as hemangio-endothelial sarcoma of the penis. Of the 20 odd cases in the literature, at least five have photomicrographs of reasonable quality to document the appearance and in general resemble this tumor. One of these is from Roswell Park and perhaps John Pickren will comment on it. There have been several autopsy reports and these lesions are capable of distant metastases. What is not clear to me is whether inguinal nodes may be involved. I was unable to find a well documented case with inguinal node involvement in spite of the fact that in two recent cases node dissections were done--in both of these the authors neglected to say what was in the nodes! I was also unable to find any good long term follow ups. The longest was three years and the patient died, but the cause was not given. Most of them were followed for periods of several months only or died within a short period to time. So, although I believe there is such an entity, I do not think on the basis of current information that one can say very much concrete about how they should be treated.

There have been other sarcomas reported also, including fibrosarcoma (about an equal number of cases), Kaposi's sarcoma, leiomyosarcoma, and rhabdomyosarcoma both the embryonal and the usual types. There are also some squamous carcinomas and malignant melanomas with spindle cell growth that might case confusion in a biopsy specimen.

CHAIRMAN SEVERANCE: Case No. 10: Hemangioendothelioma ? Kaposi's sarcoma; rhabdomyosarcoma; ? bizarre leiomyoma; Kaposi's sarcoma, corpus cavernosum; Kaposi's sarcoma; Kaposi's sarcoma again; leiomyosarcoma; hemangioendothelial sarcoma; rhabdomyosarcoma; hemangioendothelioma; malignant hemangioendothelioma of corpus cavernosum, and myosarcoma: ? rhabdo or leio (by location should be leiomyosarcoma).

So you have a variety of opinions there, Dr. Totten. Discussion:

DR. TOTTEN: I guess I can summarily dismiss Kaposi's sarcoma since everybody has described today what they are not supposed to look like! (laughter)

Rhabdomyosarcoma; I think these plump cells suggest it very strongly and this was one of the things that we considered. I couldn't find either the fibrillar or cross striations in these cells and I was finally swayed by the presence of these peculiar vascular spaces.

The bizarre leiomyoma I think isn't a bad diagnosis in some areas in this lesion although I think the cells are more pleomorphic and again the vascular pattern is what struck me.

CHAIRMAN SEVERANCE: Did you do a reticulin stain on these, Bob?

DR. TOTTEN: Yes, and it wasn't very satisfactory and didn't really help much one way or the other.

CHAIRMAN SEVERANCE: If these were smooth muscle wouldn't there be considerable reticulin around each of the tumor cells?

DR. TOTTEN: I don't know how reliable that is, but I can say in our preparation in this lesion it showed the reticulin framework around groups of cells, perhaps 15 or 20 at a time in the solid areas and in the vessel areas the cells themselves were without reticulin but

there was a sheath at the outside of the vessel.

CHAIRMAN SEVERANCE: It sounds like it supports your diagnosis. Any comments?

DR. HORN: I thought some of the cells in your photomicrographs were vacuolated. Do you have any dope on what might have been in them?

DR. TOTTEN: No, we don't. We didn't do PAS on it. We did do a fat stain and there is a little lipid in some of the cells, but I don't know how to interpret that.

DR. KAY: A study of the corpus cavernosum with a vascular lesion must give a tremendous amount of problems because the corpus cavernosum itself is so vascular with holes within it and we also know that Kaposi's disease at the periphery can have vascular components that are not really part of the tumor. But so many of the photographs that you did show showed this spindly sarcoma-like area with what I call the vascular slits.

Again one wonders about histochemical studies, whether these things could be helpful or not. We may glibly say this is Kaposi's and the other is hemangioendothelial sarcoma, but there is such a difficulty in diagnosis that I think I for one am a little dismayed in not being able to put my finger on it one way or the other. I, for example, would like to know what Dr. Helwig thought of this lesion and whether he made a comment about it.

DR. HELWIG: I thought of it.

CHAIRMAN SEVERANCE: He wants your diagnosis.

DR. HELWIG: It would not be Kaposi's sarcoma. That is one thing I would rule out. Other than that, all I can do is speculate as to whether this is some sort or kind of a hemangioendothelioma or angiosarcoma, whatever you prefer.

DR. PICKREN: Bob spoke about the case that we saw at Roswell Park. I can't remember who reported it. I know Dr. Woodruff was involved in it. But this patient had a tumor involving the penis and then developed metastasis in the pelvic area and the tumor kept the same pattern all the way through. So we can keep the diagnosis of malignant hemangioendothelioma. I don't know; I can't remember that article that was written, whether the patient had died that time, but subsequently the patient did die with metastasis.

DR. TOTTEN: Mecenas is the first author on that paper, John.

DR. PICKREN: That is a urologist and, as you say, they do rush into print even before the patient is out of the operating room. Dr. Melicow, you don't rush into print before the patient gets out of the operating room, do you?

MEMBER: No; he waits until after! (laughter)

DR. MELICOW: I heartily agree with you that the photographs that are done in urology journals from a pathological point of view are not good and I have often suggested to the Editorial Boards to try and see if they can get a pathologist on the Boards.

When I first looked at the slides and read the history, it's a young man and, of course, I wondered why certain details were left out. I said to myself, a young man of 40, from my point of view, is a young man! (laughter)

Nothing was mentioned about other lesions elsewhere. I put down "hemangioendothelioma" at first. I did think of the possibility of Kaposi's disease but I take that out now because of the absence of slits.

Going through the literature, there was a report by Ball from Canada of quite a number of cases. I noticed in all the cases the patients were of a much older age group than this boy, who was 18.

DR. TOTTEN: 17. He's now 19.

DR. MELICOW: I wonder whether this might not be of some significance, whether it may not have been some form of hemartoma or some form of congenital disease that developed with certain changes.

CHAIRMAN SEVERANCE: Can we go on now?

DR. FARINACCI: Dr. Melicow can be very happy, though. There has been real progress. Back in 1934 when I was in Panama, 62 was really old, and this amputated penis came over with a diagnosis of carcinoma, out of which I obtained Treponema pallidum! (laughter)

CHAIRMAN SEVERANCE: Before I introduce the next speaker, I must tell you a little story. This goes along with this last case--urology.

There was a patient who had carcinoma of the prostate and his urologist decided that he needed orchiectomy. And this old fellow said he didn't want that because those testicles were so dressy he didn't want to part with them. But the urologist said, "Well, we can fix that up so that you can lose the testicles and you could still have a dressy situation there."

So he took the fellow to the operating room and removed the testes and then he put two onions in place of the testes. And some months later he saw this fellow on the street and he says, "Hey, by the way, how is that prosthesis I put in there?" He says, "They're working fine." He said, "The only trouble is when I go down the street and I see a good looking girl, my eyes water!" (Laughter)

Charley Farinacci, next case! That has nothing to do with Farinacci! (laughter)

References:

Ashley and Edwards: Sarcoma of the Penis. Brit. J. Surg. 45:170,1757-58 (Review).

Mecenas and Woodruff: Hemangioendothelioma of the Male Genitalia. J. Urol. 87: 560, 1962

Ramos and Pack: Primary Embryonal Rhabdomyosarcoma of the Penis. J. Urol. 96: 928, 1966

Morgan. Bone Formation in the Penis Associated with Neoplasm. J. Urol. 96: 229, 1966

Case No. 11
Submitted by Dr. Charles J. Farinacci:

A 77 year old woman had been asymptomatic for seven years after radical mastectomy for adenocarcinoma of her right breast (Grade II) with no metastases to the axillary lymph nodes. Then massive raised reddish areas appeared scattered over the entire arm and anterior chest wall. A biopsy was done on the lesion of her right arm.

On cut section the specimen contained a well-circumscribed, hemorrhagic, somewhat translucent firm area measuring 1.5 cm in diameter, surrounded by fat and continuous with the overlying skin.

The history as submitted was somewhat incomplete. This 77 year old woman had been operated upon in 1955 and had not received any irradiation to her axilla. Five years later her right upper extremity became swollen and edematous and a period of another two years passed before she noticed the appearance of the arm lesions. She was treated by cobalt therapy in March, 1962. I don't know how much it was because I could not get any information from her doctor. The records were lost. She was improved both subjectively and objectively according to her surgeon, and he reported that the lesions had decreased in size and some had even disappeared.

X-ray examination of her lungs and bone survey showed no evidence of metastases. She was last examined in October, 1962 by him and her condition apparently was unchanged. When she failed to keep her next scheduled appointment with him, he inquired about her from her family physician, who notified him that she had died in December of 1962 and no autopsy was performed.

This tumor is basically a malignant vasoformative lesion with the neoplastic cells forming vascular channels both within the dermis and

the subcutaneous tissues. The vascular spaces are lined by endothelial cells of variable sizes and their nuclei are hyperchromatic. Many have prominent nucleoli. Mitotic activity varies from field to field, but averages 2-3 per high power dry field. In some of the more cellular areas, the tumor cells have plump spindle shapes and are arranged in a sarcomatous pattern. But even in these areas, vascular spaces containing red blood cells are recognized. There are other endothelial-lined lumina that are empty and there are some channels that appear to be anastomosing with one another. Hemosiderin-laden macrophages, areas of hemorrhage, and collections of inflammatory cells are also present in varying numbers. The reticulin stains show the anastomosing vascular pattern of the tumor, with the tumor cells lying within the reticulin sheaths. No mucicarminophilic material is found within the tumor cells although the supporting matrix in the solid portions of the tumor does stain pink. This differential stain, along with the reticulin stain, helps one to eliminate a metastatic carcinoma.

DISCUSSION:

In their report of 1948, Stewart and Treves emphasized the lymphatic origin of this tumor and soft-pedaled the possibility of a blood vessel origin. In the intervening years, there have been reports in the medical literature that have suggested that the basic lesion is a vasoformative neoplasm involving both the lymphatic and blood vascular channels so that the term "Angiosarcoma" has become acceptable. Even Doctor Frank Foote, of Memorial Hospital, agreed that one can not deny the concept of the dual origin for this lesion. Doctor R. Salm, who wrote an article entitled "The Nature of the So-called Postmastectomy Lymphangiosarcoma" (Journal of Pathology and Bacteriology-Volume 85:445, 1963), had the opportunity of studying only the H & E stained sections of this same case. In his communication to me, he conceded that the tumor looked

"very angiomatous in some areas". But the anaplastic tumor cells looked "carcinomatous" to him, and would do quite well for a primary breast carcinoma. If the reticulin stain would demonstrate an angiomatous framework, he would agree to a diagnosis of angiosarcoma; however, he was pretty certain that the stain would not demonstrate the angiomatous framework (Personal communication from Doctor Salm to Doctor Farinacci, March 9, 1964).

The etiology of the neoplasm remains obscure to this day with the only clinical finding, regularly associated with it, being chronic lymphedema of the extremity. The role that either pre-operative or post-operative irradiation has in the pathogenesis of the tumor is believed to be related to aggravation of lymphatic occlusion rather than being a causative agent because there have been cases of the tumor developing in non-irradiated lymphedematous extremities. This case being discussed is such an example. Hilfinger and Eberle of State University of New York, Syracuse, reported a singular case of a woman who had undergone a bilateral radical mastectomy and who received post-operative irradiation to her left side only. No axillary lymph nodes had been involved in either side. She developed bilateral lymphedema of her upper extremities one to two years following her mastectomies. After a period of nine and three-fourth years, postoperatively, she developed the angiomatous lesions in her upper right extremity (the side that had not been irradiated).

Doctor Frank Foote remarked that a goodly number of these patients did not have any axillary lymph node metastases and, as others have also observed, he noted that the microscopic appearance of the breast carcinoma had no relationship with the occurrence of the postmastectomy angiosarcoma. He commented that if we have a group of women with a low incidence of axillary node involvement, then we are likely to have a larger

reservoir of long-term survivors who will eventually suffer from this disease complication. This opinion is based upon the reports of long-term survival following radical mastectomy and the fact that "the average interval from the mastectomy to the appearance of the angiosarcoma was 9 7/12 years (Range: 1 1/3 to 26 years) and the average interval of the appearance of the postmastectomy lymphedema to the appearance of the lymphangiosarcoma was 9¼ years (range: 1 1/3 to 24 years)."(Quoted from a recent article in THE ARCHIVES OF SURGERY by Doctor Gerald Fine.)

This entity is considered to be invariably fatal although there have been a few cases of long-term survival following irradiation. Southwick and Slaughter reported a case of long-term five year survival (CANCER 8:158, 1955). This same patient, as reported in Gerald Fine's recent article, has survived for 17 years following irradiation to the tumorous extremity. Incidentally, the lesion as seen in their photomicrograph illustrations does not appear malignant to me and even the two authors commented that both their case and that of Rawson and Frank possibly represented a more benign form of the disease. This fact may explain the long survival time in their case. Our patient did not survive more than a year after the appearance of the angiomatous lesions in the lymphedematous arm.

In conclusion, I have presented this case of POSTMASTECTOMY LYMPHANGIOSARCOMA occurring in a lymphedematous extremity that had not been previously irradiated. It is my belief that the tumor process is not simply a pure lymphatic vascular origin but that the blood vessels also are a component in the pathogenesis of the tumor. I should therefore prefer the term "ANGIOSARCOMA" to connote the dual origin as contrasted to the present term of "LYMPHANGIOSARCOMA" which connotes the solitary lymphatic origin.

FINAL PATHOLOGICAL DIAGNOSIS: Postmastectomy angiosarcoma.

Discussion:

This slide is again through the courtesy of Dr. Lattes. He's telling me "If for some reason you're not satisfied with my diagnosis, get some one else to give you another one." This poor befuddled pathologist here has gone to see an oracle, needing some advice, and the oracle told him "To be on the safe side, why don't you check it out with another oracle?" You notice to date we have a lot of prophets and some of us have come away rather confused and befuddled. So I would like to use this to say like Confucius would say: "When you ask the opinion of many oracles, you are likely to become confused." And this is my attitude about vascular lesions today.

CHAIRMAN SEVERANCE: Wait a minute, Charley, and I'll give the diagnoses: ? Kaposi's sarcoma; hemangioendothelioma (malignant); post-mastectomy lymphangiosarcoma: malignant hemangioendothelioma; post-mastectomy lymphangiosarcoma; Stewart-Treves lymphangiosarcoma; post-mastectomy lymphangiosarcoma again; lymphangioendothelial sarcoma; lymphangiosarcoma; lymphangiosarcoma again; post-mastectomy lymphangiosarcoma; metastatic carcinoma, and ? but insufficent evidence for leiomyosarcoma in addition.

Now do you want to comment on any of these, Charley?

DR. FARINACCI: I would like to comment that I considered the possibility of this being a metastatic carcinoma, and that's the reason why we made these special stains, and I don't think I could call it a metastatic carcinoma. I think the reticulin stain certainly shows that there is a definite angiomatous pattern.

The reason why I actually brought this case up, to be frank, is, and again the oracles come in, because you ask too many people their opinion and you get too many answers and you get really confused.

This has been shown to Dr. Frank Foote at the 1963 seminar,

and again there were some people who participated in this seminar who felt it was a metastatic carcinoma, and he wiped it off just by saying "It can't be. This can't be a carcinoma." And he did mention a doctor by the name of Salm who is up in Liverpool, who had written on these cases of metastatic carcinoma. Dr. Salm apparently must have heard what Dr. Foote had said because he wrote to me and asked me to send him a slide. So I did. And Dr. Salm wrote this letter--and this is a letter I must, in all due respect to Dr. Salm, mention that he only had the H & E stain; he did not have the reticulin stain slide:

"I would admit that the features of your case look very angiomatous in some areas (this is quoting) but I have seen this now in three cases I published and in three other cases from this country and the United States. So your case is the seventh of this type."

"You did not tell me whether the nodule was excised from the edematous arm or from the chest wall, but I suspect it was from the arm. If that should be correct, I would think that the unusual features of this growth are due to the separation of the collagen fibers as I described."

"The tumor cells, though, of course, anaplastic, look to me carcinomatous and would do quite well for a primary breast carcinoma. There are abundant small vessels and capillaries which quite obviously do not participate in the malignant process. In my opinion a reticulin stain is essential to prove the issue one way or the other if an angiomatous framework should not be demonstrable in the more solid areas or the angiomatous looking parts." Then he says, "But I do not expect this, then my conclusion would be that this is again a late retrograde metastasis from the original breast carcinoma."

I replied to him; I told him I didn't have any more blocks. So he never got the reticulin stain because at the time I really didn't think I had any more tissue, and it wasn't until the case came up for this Seminar that I was able to find some more tissue, and I think that the reticulin stain rules out that this is a carcinomatous metastasis.

The other reason why I presented this case is that I would like to throw it in with the idea that this is not a pure lymphangiosarcoma but it could be a mixture of both blood vascular and lymphatic vascular origin because I think we have demonstrated pretty well that there are two types of endothelialized spaces, some containing blood and some not containing blood.

I know Drs. Stewart and Treves in their original report sort of pooh-poohed the possibility of this being a dual lesion. They emphasized more than anything else the lymphatic origin. Dr. Frank Foote said he was willing to concede that this could be a dual origin tumor. At any rate, Dr. Gerald Fine, who has just recently written an excellent article with an extensive review of the literature in the February issue, 1967 Archives of Surgery, is here and I think he's likely to present this as being a pure lymphangiosarcoma. Am I right, Gerald?

DR. FINE: I can't speak about your case, Charley, but I have several cases that I think I can show that the evidence is that it is most likely, at least in large part, a lymphatic origin, but again I'm not sure whether I could rule out any participation of the blood vascular endothelium. But in your case I can't say.

CHAIRMAN SEVERANCE: Are you through, Charley?

DR. FARINACCI: Yes, I'm through.

References:

Eby, C.S.; Brennan, M.J.; and Fine, G.: Lymphangiosarcoma: A Lethal Complication of Chronic Lymphedema: Report of Two Cases and Review of the Literature. Arch. Surg., Vol. 94: 223-230, Feb. 1967

Foote, Frank, Jr.: Unpublished Proceedings of the 1963 San Antonio Society of Pathologists Tumor Seminar (conducted by Doctor Frank Foote, Jr.- discussion of Case No.2 -Postmastectomy Lymphangiosarcoma.)

Hilfinger, M.F., Jr., and Eberle, R.D.: Lymphangiosarcoma in Postmastectomy Lymphedema. Cancer 6:1192, 1953

Rawson, A.J., and Frank, J.L., Jr.: Treatment by Irradiation of Lymphangiosarcoma in Postmastectomy Lymphedema, Report of a Case. Cancer 6:269, 1953

Salm, R.: The Nature of the So-called Postmastectomy Lymphangiosarcoma. J. Path. Bact. 85:445, 1963

Salm, R.: Personal Communication, March 9, 1964

Southwick, H.E., and Slaughter, D.P.: Lymphangiosarcoma in Postmastectomy Lymphedema -Five-year Survival with Irradiation Treatment. Cancer 8:158, 1955

Stewart, F.W., and Treves, N.: Lymphangiosarcoma in Postmastectomy Lymphedema. Cancer 1:64, 1948

CHAIRMAN SEVERANCE: I want to go on to the next case and withhold any questions you are going to ask Charley until after the next case.

Dr. Pickren, Case No. 12.

Case No. 12
Submitted by Dr. John Pickren:

This patient, a 55 year old woman, had a right radical mastectomy in 1957 for a carcinoma of the breast. This operation was performed at the Millard Fillmore Hospital in Buffalo and the diagnosis was "carcinoma of right mammary gland with metastasis to right axillary lymph nodes".

Following surgery she was given ionizing radiation to the right axilla. The amount of radiation is not available. In July, 1966, she developed a nodular painful hemorrhagic area on the volar surface of the right forearm. The lesion persisted and she was referred to this hospital in September, 1966, for treatment.

Physical examination disclosed an obese individual weighing 260 lbs. Her right arm was massively swollen. At the biceps of the right arm her measurements were 57 cm. while the left arm measured 37 cm in diameter. In the midportion of the forearm, the right side measured 45 cm. and the left side 30 cm in diameter. Along the radial aspect of the forearm, just above the wrist, there was an indurated area which was hemorrhagic and nodular.

Radiographs of the lungs were not remarkable. Following biopsy a disarticulation of the right arm was performed. The patient has been followed in our clinic. She was last seen on January 19, 1967, at which time she had no evidence of recurrent tumor.

Dr. Lattes and I talked over the telephone and he said to me, "What if I told you I found mucicarminophilic material in this case?" I said, "I would be surprised." He didn't say whether it was in my case or in Charley's case, but one of these cases has mucicarminophilic material in it, I think, and we will have to find out.

The case I am presenting is a very similar case to Dr. Farinacci's. It's a 55 year old woman who had a radical mastectomy nine years before she developed other lesions and then she had very severe edema in the arm all the time prior to this.

Slides:

This is a gross photograph of the amputated arm and you can see in this area there are these bluish masses but this, or course, is nowhere near the picture that was shown by Dr. Farinacci in his case. This apparently is the only lesion we can see from the outside. A biopsy had been taken, as you can see where the sutures are, and the diagnosis we had submitted was post-mastectomy lymphangiosarcoma.

Here is a black and white photograph made of one of these lesions, and I think this is a very characteristic type of picture that we see in these cases of raised rather bluish-violet lesions, not circumscribed but an ill-defined mass and this discoloration of the whole area.

When we cut through this mass we find that this lesion is not only in the skin but in the subcutaneous fat right down on the fascia and in fact we have seen some of these lesions in the muscle itself. Here, of course, you can see where the skin all over is bluish and here we can see way down deep in the fat. And this is the sort of gross picture I'm sure that we have all seen in other cases as well.

Microscopic observations: The several gross lesions have similar histologic patterns. A glomerate of spaces are lined by cells of varying heights and anaplasia. These spaces are lined by flattened endothelial cells, by obvious malignant cells, or by cells that are intermediate between the two extremes. The spaces vary in size, but all are enclosed by reticulin fibers. Mucicarminophilic material is not present. In the more anaplastic areas, the lumens of the spaces contain large

histiocytes which have centrally located and indented nuclei. The cytoplasm of these cells contain granular material and vacuoles. These cells contain PAS positive material which is partially digested by diastase. They also contain fat. Neoplastic cells lining some of the spaces also contain cytoplasmic Oil-Red-O positive material but most do not. The histochemical studies are consistent with a tumor of either endothelial or epithelial cells.

The primary tumor in the breast has been reviewed. The breast cancer has a histological and cytological pattern that is different from this arm lesion. The patient was living and well when last seen in April, 1967.

Discussion: This tumor seems to fulfill the criteria of post mastectomy lymphangiosarcoma.

In 1948, in a classical paper, Stewart & Treves vividly described this lesion. It was not recognized as a specific disease entity before that time. They concluded that the tumor arose from lymphatic endothelial cells from both gross and microscopic abnormalities: (1) the neoplastic nodules contained fresh blood that was under pressure even after amputation (2) large cysts were filled with blood (3) gross features simulated Kaposi's disease (4) transition from numerous dilated lymphatic spaces lined by typical endothelial cells to spaces lined by malignant cells (5) presence of lymphoid follicles and (6) thick cuffs of lymphocytes around some neoplastic spaces. Others have questioned their interpretation of the histological derivation, feeling that the lesion represents recurrent carcinoma growing along preformed channels. Nevertheless, these authors do not give satisfactory evidence to me that the lesion is not of endothelial origin. Furthermore, case reports of lymphangiosarcoma have occurred in edematous extremities of patients without a known epithelial cancer.

Eby et al also mentioned unpublished information that histochemical and electron microscopic studies confirm the endothelial nature of the lesion. In addition, these lesions have not been reported to respond to hormonal therapy or chemotherapeutic agents for any significant period. Thus, the lesion differs from breast cancer. Also, metastases from breast cancer generally retains a histological pattern similar to the primary tumor, although skin recurrences usually are more anaplastic than the primary lesion. Nevertheless, a comparison of the growth pattern of the arm lesion should be made with the pattern of the primary cancer. It should be re-emphasized that in this case, the histologic and cytologic appearance of the primary breast cancer is significantly different from the histologic and cytologic pattern of the lesions in the arm. I believe that the disease represents a specific entity. Whether, in fact, the tumor arises from epithelial or endothelial cells must await additional proof.

Diagnosis: Post-mastectomy lymphangiosarcoma of arm.

FURTHER DISCUSSION:

I have taken the photographs from Dr. Stewart's article; and the reasons why he says that this is a lymphangiosarcoma. One is he said that there are proliferating lymphatics in the subcutaneous tissue. Then he notes that the neoplastic quality is questionable. As we can find here, these are these dilated lymphatics, and certainly they do not look very malignant to me, but they are dilated.

Then he goes on. And this picture, by the way, Dr. Farinacci, looked very much like the one you showed; very definite hemangiomatosis in the subcutaneous tissue. Yet again these cells lining this are definitely malignant.

We go to a field like this and we find cells which are much more bizarre. And here he is showing a transition from the normal cells to the malignant cells.

Then he comes to an area that looks like this, which is very highly anaplastic, so that he says he can find transition between these cells. This is one of the reasons he says this is a malignant tumor of the endothelial cells with lymphatics.

In addition to that, he says that there are, in association with this tumor, germinal centers, and often times another thing he says is that there are cuffs of lymphocytes around the tumor. Whether this truly means that this is a tumor of lymphatics I am not sure.

This is a photograph taken from Dr. Ewing's book in which he makes the diagnosis of endothelial sarcoma. Dr. Stout has pointed out-- and this is the reason that I knew that this was an interesting thing-- that when you take this slide and look at it, most of us would make the diagnosis of metastatic carcinoma to the bone from kidney, and in this Dr. Stout has pointed out that often times you will find blood inside of these spaces. So that the presence of blood inside of a space alone does not mean that it is a tumor of blood vessels. And so, Dr. Farinacci, just because you have blood in your case, I don't think you can say that that is definitely a tumor of blood vessels.

I would now like to summarize this case by saying that whether or not in fact this tumor is a tumor of blood vessels or whether it is a tumor of epithelium or lymphatics, I am not quite sure; I don't know. I'm going to have to wait further.

Dr. Fine mentioned in the article-- a very fine article, Dr. Fine, that there was some proof that these lesions histochemically and from electronmicroscopy are definitely of endothelial origin. I haven't seen that material, so I can't say for sure whether it is so or not. But I have read the articles that he refers to, particularly the French articles, in which it says that these tumors are all of epithelial origin rather than endothelial, and they don't come up with any good reason to me

as to why it is definitely epithelial. They may be right, but they also may be wrong.

The only thing I can say about this, and I think Cushman should remark on this, is that regardless of whether they are epithelial or endothelial, that this is a different disease entity because it acts usually different from a carcinoma of the breast; it looks different; it spreads different, and the only thing is they do not respond the same to the various chemotherapeutic drugs or to the ablative hormone therapy as carcinoma of the breast. So, regardless of the origin of the cells, it certainly is a different lesion from the usual carcinoma of the breast.

CHAIRMAN SEVERANCE: Are you ready for the diagnoses?

DR. PICKREN: I'm ready for the diagnoses, and I think I will ask Dr. Farinacci to come back here and do all the answering of the questions.

CHAIRMAN SEVERANCE: Hemangiosarcoma; post-mastectomy lymphangiosarcoma; angiosarcoma following radiation and radical mastectomy. (A) predominantly lymphangiosarcoma; (B) hemangiosarcoma (endothelioma); post-mastectomy lymphangiosarcoma; Stewart-Treves lymphangiosarcoma; post-mastectomy lymphangiosarcoma; lymphangioendothelial sarcoma; lymph-angiosarcoma; lymphangiosarcoma again; post-mastectomy lymphangiosarcoma arising in an irradiated arm; (A) adenocarcinoma, (B) adenocarcinoma, and in addition, suggestion of malignant hemangioendothelioma (special stains might help).

Discussion:

Chairman Severance: Ready for questions. Now you may ask either Dr. Farinacci or Dr. Pickren.

DR. PICKREN: Or Dr. Fine, because he's really the expert.

CHAIRMAN SEVERANCE: Jerry, do you want to start off? Are you going to pick these boys apart?

DR. FINE: I just happened to bring a few slides. I think it might be better than all the words I have.

We've only had the opportunity to study several cases. We studied one with the electronmicroscope and two or three with a battery of enzymes, both oxidative and hydrolytic enzymes. In one of the two cases we only had the opportunity to look at an alkalinephosphatase stain. On the other two or three cases we did a large variety of oxidative and hydrolytic enzymes, and I think the important findings are in the phosphatase splitting group.

The ultrastructure of this tumor has been published already in the Bulletin of the Johns Hopkins Hospital and there was a paper given at the Academy meeting recently from the University of Illinois group, and our findings are similar to theirs. That is, the ultrastructural features are those of endothelial cells and not of epithelial cells. These tumors have pinocytic vesicles. Basement membranes can be demonstrated although not necessarily in every area, and I think these are features of endothelial and not epithelial cells.

Slides:

You see, I came prepared. The problems that we thought we were faced with was (1) is this a carcinoma or is it an endothelial cell tumor and (2), if it is an endothelial cell tumor, is it lymphatic or is it of blood vascular origin? I already mentioned the ultrastructure features and I am not going to show any electronmicrographs.

This is an alkaline phosphatase stain from a lymphangioma. We studied four lymphangiomas. Some of them were very cystic and you could classify them as cystic hygromas. You will notice that there is no

staining. You can take my word for it, for those of you who are not familiar.

This is a 5-nucleotidase stain done at pH 9.2, and I think it is obvious. This is the cobalt method, the only method that I know of for 5-nucleotidase, and I think you can appreciate that there is a good deal of activity in the tumor and much of it, as you can see, is within cells that are lining spaces. I am not sure whether they are spaces, but I would surmise that they are, and they have just collapsed.

This is an imprint which demonstrates the 5-nucleotidase from the same lymphangioma or cystic hygroma, if you wish. The imprint is very nice to use because often in these cobalt techniques there is a diffusion of enzyme and we do not get the same type of diffusion in the imprint. So that we are not confusing the diffused enzyme and the connective tissues. Here we have just cells that come away and you only have cells staining.

This is the lymphangioma in one of our cases. This is the alkaline phosphatase done at pH 9.2. It is the cobalt method and you do see some activity. The other case that we had was only a small biopsy. This is the autopsy case and we did this on autopsy material which works perfectly satisfactorily. The surgical specimen that we had didn't even show or didn't show any activity in the sections that we ran. So this specimen is really unique. This is as much as we saw in the sections that we studied. So there is some alkaline phosphatase activity. The question is is this in blood vessels that are accompanying this tumor or does it represent a participation of malignant blood endothelial cells. Many of the tumor cells you can see in the background are in this area here.

This is the 5-nucleotidase stain done at pH 9.2 of the same section. It's almost a serial section. You can see again the same vascular channel; you can see again that there is much more 5-nucleotidase activity, no alkaline phosphatase activity in this hemangioendothelioma, which we felt was a hemangioendothelioma, and this is the alkaline phosphatase stain done at PH 9.2, and I think you can appreciate the tremendous amount of alkaline phosphatase activity in this tumor, and this holds true in all the hemangioendotheliomas that we have studied thus far.

I might say that if one does the 5-nucleotidase you will fine 5-nucleotidase activity because the alkaline phosphatase will split the adenylic acid, which is the substrate for the 5-nucleotidase so that one to my knowledge cannot distinguish between 5-nucleotidase, but in the case of lymphangioma, of course, we are not bothered with this because we don't have any non-specific phosphatase activity which might split the adenylic acid that we use for the substrate in 5-nucleotidase.

This summarizes the group of lesions that we included in this little study which has not been published yet. We actually had the three lymphangiosarcomas. As I said, one of them just had the alkaline phosphatase; the other two had fat. We only studied four carcinomas of the female mammary gland and we had one malignant hemangioendothelioma that we included, and we included the Kaposi's, which is not our data, which was taken from several articles. One is Lever's work and another is by two British authors the names of whom I have already forgotten.

You will notice the table indicates exactly what I have said, that there is no alkaline phosphatase in the angiosarcoma. There is 5-nucleotidase activity. This is at pH 9.2. This is a little bit of the PAS reagent. As I have already mentioned, the reason for the 5-nucleotidase is the splitting of the 5-nucleotidase substrate by the alkaline phosphatase and notice in the Kaposi's the difference in the alkaline phosphatase,

at least from these people's studies, and lymphangiosarcoma.

As you know, some people have said that the lymphangiosarcoma is a Kaposi's, and I don't think they look alike histologically and I think there is evidence really from the enzymatic cell ultrastructure that they are different lesions.

DR. AZAR: This is fine, except you can't add up the results of someone else on a table because no two histochemists has exactly the same method. So another histochemist or enzymatic histochemist has not found a reaction. This does not mean that the two lesions are not related, although this is quite plausible and you yourself can not compare what you have done since you have used the same techniques, you can't compare it with someone else.

DR. FINE: I would agree with that, Henry. I included this, as I said, the ultrastructure. By that same reasoning, of course, I can't compare our ultrastructural findings with somebody else's. Everybody has to do their own work. But I think when the techniques described are similar to the other individual's, it means something.

I agree with you. We have to do our own Kaposi's; I agree 100 per cent, but I think it's interesting, too, the findings, the differences and the similarities between lymphangiosarcoma and the lymphangioma and the dissimilarities between the lymphangiosarcoma and the mammary gland carcinoma in the female.

DR. TOTTEN: I think your work is helping us along the line of trying to tell lymphatic from blood vessels. I just wondered if anybody has done angiographic studies on these people either in vivo or after the arm is taken off? Are you aware if this has been done?

DR. PICKREN: No. With regard to Kaposi's and the malignant hemangioendothelioma, I had written to Murray in Johannesburg because I

was interested in Kaposi's disease in the heart, and he informed me that radiographically by injection studies there is a definite difference between Kaposi's and the malignant hemangioendothelioma. In the same area he also said that he felt that the Kaposi's and the post-mastectomy tumor are not the same breed. But this is all I know about it.

DR. HAAGENSEN: Fortunately, clinical experience can be different under these circumstances. This disease, this endothelial sarcoma, whether you call it angio or endo, is a separate disease, as John and Charley said, no matter how you trace its histogenesis, and the fact that it's a separate disease not concerned with the original carcinoma is proven very clearly by the cases in which this disease occurs many years after the treatment of the original carcinoma, in which there is no residuum or recurrent evidence of the original carcinoma.

When carcinoma of the breast recurs, it very rarely recurs in one specific area such as the arm. It recurs in many places. So that when you see a patient--and we have seen many with this disease--who has a lesion such as shown here, it involves only the arm and no other evidence of recurrence, it's a strong point that it's a new disease.

This disease certainly has to do with the edema, which must be both long, persistent and severe; otherwise it doesn't evolve this way. It's a disease sui generis. It should not be treated by amputation. Nobody has ever cured one of these patients by amputation. Indeed, they are not cured by any method, of course, but radiation sometimes provides a little palliation.

I have seen the other disease which we are thinking of, namely, carcinoma of the breast, recurring and growing down into the lymphatic channels of an edematous arm. Here the clinical picture is perfectly clear. There is massive recurrence in the axillary area and in the upper arm, and we saw, as far down as the wrist, lymphatic channels

full of solid masses of carcinoma cells such as you see in the breast itself. This was unmistakably carcinoma of the breast. The growing retrograde in the channels are not at all like this other disease that you have been talking about.

So I believe there are these two diseases. But the common one certainly is the one which John and Charley showed, which is a disease arising in endothelium as a result of long continued stasis and what goes with stasis.

I believe you know that edema can be largely avoided in the arm by a careful, meticulous surgery. I can't tell you how you do it, but it can be done. We have never had one of these cases in our patients, but we have less edema than most people.

CHAIRMAN SEVERANCE: Thank you.

DR. PICKREN: I meant to mention, and I forgot, that actually we saw it in the literature, but Carl points it out in his paper very well. I mean all of you I'm sure got his paper and you should read it, his case, that lymphangiosarcomashave been reported in fifteen cases of patients who have not had carcinoma; they just had lymphedema from either a congenital origin or another type of origin, but no carcinoma, and these patients have developed a lymphangiosarcoma.

In response to Dr. Haagensen's statement about no patient has ever been cured, we have had four cases in our hospital. Two patients died less than a year later. This patient that we have now is still well, but it's only been less than a year. But one patient, Dr. Haagensen, had an amputation in 1960 and in 1967 she is still living and well without any evidence of recurrence, and this is conclusively one of these types of cases. So we have had one case that's been cured for seven years so far.

CHAIRMAN SEVERANCE: Dr. Haagensen is glad to know that.

Any other comments?

DR. FLYNN: What is the incidence in patients with filariasis?

CHAIRMAN SEVERANCE: Dr. Pickren, do you know the incidence of this disease in the people with filariasis?

DR. PICKREN: It must be extremely low, but I don't know about any case. I didn't look them all up. Jerry, you must have read all the papers.

DR. FINE: You are giving me more credit than I deserve. There are two other authors on this thing and I'm only the pathologist on the thing. I can't answer that, John, to be honest with you. I did not read all the papers.

DR. LURIE: I've had one case which developed in the duodenum in a case of Hodgkin's with massive involvement of inguinal nodes.

CHAIRMAN SEVERANCE: Following Hodgkin's?

DR. LURIE: Yes.

CHAIRMAN SEVERANCE: Any other discussion or comments from the audience?

MEMBER: Dr. Farinacci was looking for another oracle when he wanted to know what to do. Perhaps the German philosopher Schopenauer could help us on what to do. He said the task is not to see what no one has seen yet but to think what no one has thought yet about what everybody sees.

CHAIRMAN SEVERANCE: Jerry, I think we better go on.

MEMBER: I would like to know what Rafe had in mind with his mucicarmine?

DR. LATTES: We just wanted to scare John! (laughter)

CHAIRMAN SEVERANCE: He used a lot of special stains.

DR. LURIE: Just very briefly that I don't think that the picture that somebody asked about filariasis is the same as you get in post-mastectomy. In filariasis you get a tremendous degree of fibrosis of the tissues rather than dilated lymphatic spaces and I wonder whether the radiation does not play a significant part in this?

CHAIRMAN SEVERANCE: Somebody mentioned that some of the cases had not been irradiated and still developed this disease. Didn't you mention that, John?

DR. PICKREN: Dr. Farinacci's case had not been irradiated, but most cases have been irradiated.

References:

Stewart, F.W. and Treves, N.: Lymphangiosarcoma in Post-Mastectomy Lymphedema . Cancer 1:64, 1948

Eby, C.S., Brennan, M.J. and Fine, G.: Lymphangiosarcoma: A Lethal Complication of Chronic Lymphedema. Arch. Surg. 94: 223-230, 1967.

CHAIRMAN SEVERANCE: We have to go on because time is moving. The next one is Dr. Nash, Case No. 13.

Case No. 13
Submitted by Dr. Artemis Nash:

A 60 year old white Russian-born male began having progressive exertional dyspnea for $1\frac{1}{2}$ years, and orthopnea and ankle swelling for six months prior to admission to the hospital. Except for inguinal herniorrhaphy and symptoms of chronic peptic disease he had a healthy past history.

On admission he was found to be in moderate congestive heart failure with a Grade III-IV presystolic crescendo apical murmur and x-ray evidence of cardiomegaly with left atrial and right ventricular enlargement. It was felt that he had mitral stenosis due to old rheumatic disease, and a cardiac catheterization and cineangiography confirmed this demonstrating, in addition, pulmonary hypertension with no evidence of mitral insufficiency or aortic valve disease.

After symptomatic improvement on cardiotonic and diuretic regime, an exploratory cardiotomy (bypass) for an intended mitral commissurotomy was performed. Upon entering the left atrium, a large tumor was found filling the entire chamber and attached near the annulus of the mitral valve between the annulus and the left atrial appendage. The tumor was easily removed by blunt dissection in a subendocardial plane.

The gross specimen was an 8 x 5 x 4 cm. lobulated soft mass with a smooth yellow to red surface and a soft, semi-liquid, bright yellow to dark red cut section.

It is noteworthy to add to this history that the mitral valve was entirely normal and there was no gross evidence of pre-existing rheumatic disease which had been the supposition of the surgeon.

Now with your permission I would like to reverse the format of the presentation and discuss briefly the diagnosis of this case and then show the slides, hoping to illustrate some of the points that I would like to make beforehand with the slides.

I don't think this case presents a great diagnostic problem and I am not presenting it as such. We made the diagnosis, which is sort of convential in these lesions, of myxoma of the left atrium. However, we were not entirely satisfied and felt rather insecure about it. So I am presenting it as a sort of questionable pathological entity, hoping to learn something about it from your comments.

The textbooks tell us for the last many years that there are such lesions which are generally considered to be benign neoplasms, referred to as myxomas; that they are a myxomatous connective tissue composition and, however, they usually have been sort of quaint post-mortem findings. It was not until after 1955, with the advent of very advanced procedures for diagnosis and surgery on cardiovascular organs that these lesions have been diagnosed in life and have been successfully operated upon. So I also on that ground felt that as surgical pathologists we may be seeing more of them and they deserve further consideration.

Even though they are supposed to be rare lesions, however, as I said, there have been more and more coming to light with the advent of surgery. Up to 1966, in the last review I read, there have been over 300 cases reported. However, there are probably more, because I don't think they are reported as frequently now except from a surgical point of view.

The controversy around these lesions in the literature centers around two differential diagnoses. One school of thought contends that these are merely peculiarly organizing thrombi and not neoplasms, and the other point of view maintains that they represent in fact benign neoplasms.

The theory on the nature of this lesion is that people have observed myxomatous degeneration, so-called, in organizing thrombi. In trying to look up the reports, I found it very unsatisfactory in that I found very few illustrations that at least resemble my case, and the few

pictures that I have seen or the cases discussed show very small areas of non-specific sort of myxomatous tissue with connective tissue cells in a loosely woven stroma only in local areas in an otherwise typical laminated organizing type of thrombus. I would be interested to know if other members of this group have seen such degenerations, so-called.

The neoplastic theory, however, I think has the greater weight of evidence for the argument, and they pointed out that, first of all, these lesions, which are usually pedunculated, are usually smooth; they have a shiny endothelial covering and do not present the dull fibrinous appearance of the usual thrombus. Secondly, that their substance is gelatinous and soft, malleable and not friable nor laminated as thrombi are. Thirdly, they point out the hemorrhages which the thrombus theory uses as being evidence of thrombus rather than neoplasm and, indeed, there are hemorrhages in these lesions, but these lesions can be extremely vascular so that this could actually represent hemorrhage from a rupture of a vessel; that neoplasm need not imply the pre-existence of a thrombus. However, fibrin, which is heavy and extensive in the thrombi, is not very common in these lesions.

Fourth, there are usually, in the reports that I have seen, demonstrable mucin positive areas which are rather predominant in the substance of these tumors, whereas there are usually none in thrombi.

Another important finding I think is the location of these tumors. The great majority (over 75 per cent) of them occur in the left atrium and the great majority of those occur in the fossa ovalis area, which is not a common site of thrombosis. The usual site of thrombosis, of course, is the auricular appendage. Also, the next most common location is the right atrium, and very few cases have been reported in the ventricles proper, whereas we know that thrombosis in the ventricles is quite common although it is not quite as common as in the auricles.

Finally, they contend that--and it is true--if one looks at the reported cases, that even though some of these lesions are associated with rheumatic heart disease, the majority of them are not associated with any kind of an underlying endocardial or myocardial pathology. Therefore, there is no basis to surmise that there is a reason for thrombosis.

Having sort of favored the neoplastic origin of these lesions, I looked at the various opinions as to what is their structure. I notice Dr. Stout in his articles on myxoma in the adult and in childhood avoids this lesion. He mentions it but he avoids it on the grounds that it is a controversial one and, as I understand it, that he then does not consider it as a representative of an ordinary pure myxoma.

Even though the majority of them do have this myxomatous element, however, several of the cases are impressively vascular or, rather, vascular features have been described and emphasized by some authors, particularly John Orr from England, a very fine article in 1942, whose case is almost identical to ours here. The people who like to favor the myxoma theory, primarily Ribbert in the old German literature, stated that if you section the fossa ovalis of the atrium you will find a lot of myxomatous embryonal rests which might give rise to this kind of a tumor. However, Pritchard, in a review of the world literature in 1951, had personally studied at least 55 cases, consecutive cases of the fossa ovalis structure. He took serial sections and found that only three cases showed possibly something that might be interpreted as a myxomatous rest and that he therefore does not substantiate this theory.

On the other hand, he does point out and show nice pictures of peculiar inclusion-like spaces beneath the endocardial lining which

are lined by similar endocardial cells in the endocardial cavity, and he contends that perhaps the spotty existence of such sort of endocardial rests might be the site of origin, and I think this is of some interest in our case.

Slides:

This is a gross photograph of the specimen, the outside surface of it, to point out the smooth, shiny surface devoid of any fibrin, and it is evident that there are, of course, areas of hemorrhage, bright red, more recent and somewhat older hemorrhage.

This is a cut section to show again the rather homogeneous and gelatinous appearance of the entire substance of this lesion, with some hemorrhages.

Microscopic Description: The basic architecture of this lesion consists of a pale mucoid and largely acellular stroma which is traversed by a multitude of variously-sized vascular channels and small, often branching vascular buds lined by spindle-shaped cells with ovoid vesicular nuclei. Many of the vessels are lined by similar cells which, on cross section are seen to extend in strands and sheets into the surrounding mucoid space, forming peculiar, spiral-like patterns when the vessel is seen in tangential section.

This feature is reminiscent of the process of penetration of endothelial cells lining the primitive endocardial tube into the acellular "cardiac jelly" surrounding it, to form the endocardial cushion described by Patten, et al.

Finally there are areas of fresh hemorrhage as well as evidence of ischemic necrosis and old hemorrhage with groups of hemosiderin-laden histiocytes and other types of mononuclear inflammatory cells. Very few primitive or mature connective tissue cells are seen.

The histological features seem to indicate a benign neoplasm primarily of endothelial origin, with a propensity to reproduce the structures of the embryonic endocardial tube. Further observations and identification of its elements by electron microscopic studies and histochemical technique would be necessary to confirm this and to elucidate the true nature of this lesion.

DIAGNOSIS: Endocardial myxomatous tumor, benign.

Another thing I failed to point out is that I looked up the embryology of the development of the heart. In Patton's work, he describes very nicely some work that he did on embryos where the cardiac tube is still in a very primitive stage of development and is surrounded by the cardiac jelly. He described that at about 34 hours or so this jelly is completely structureless and that there is merely one layer of cell lining the cardiac tube. However, at 50 hours or so these cells begin to grow out into this cardiac jelly and form a sort of a network pattern which gives it more substance and eventually it becomes the subendocardial cushion.

So I thought that some of these structures that this lesion seems to reproduce are reminiscent of this kind of growth.

In conclusion I would like to state that I believe at least that these are neoplasms. However, rather than being myxomas, perhaps they are of endothelial nature, sort of trying to reproduce the primitive endocardial structure.

CHAIRMAN SEVERANCE: What names are you going to give it?

DR. NASH: I don't know. Maybe you have some good suggestions. I don't want to add to the confusion of names in the pathological literature until their nature is really proven.

Discussion:

CHAIRMAN SEVERANCE: Any comments from the audience?

DR. KAY: Did you see any of those not only in this case but the others that you have had, any of those epithelial inclusions that Dr. Fine has presented at a recent meeting?

DR. NASH: No.

DR. KAY: You seem surprised. Did I hear correctly, Jerry, that this is what you found?

DR. FINE: Not epithelial inclusions; epithelium lining.

DR. KAY: Epithelium lining. All right, put it that way.

DR. HELWIG: I showed this section to Dr. Mannion who has studied some hundred examples of myxomas of the heart, if that's the name you want to use, and he pointed out that these endothelial-like cells are rather characteristic. He thought this was a quite characteristic myxoma, so-called, of the heart.

This is of more than academic interest because those of you who are called to the operating room and examine a thrombus, if you can interpret that thrombus--and you should be able to; it has been done--that this is not thrombus but is actually a part of the myxoma of the heart and then they can go in and remove the myxoma.

CHAIRMAN SEVERANCE: Let me give the diagnoses before you disappear: Myxoma of the heart; myxoma of left atrium; fibrosed myxoma; myxoma, heart. (By some authors considered as a polypoid mural thrombus.); myxoma; cardiac myxoma; myxoma (very vascular); myxoma; myxoma of heart; "myxoma" of heart; primary myxoma of the left interatrial septum with ball-valve obstruction of the mitral valve; "myxoma" with lymphomatous and angiomatous elements: Mesenchymoma.

Pretty much agreed.

DR. NASH: It seems like the thrombotic theory is a thing of the past again. I would be glad to hear that.

DR. FINE: Am I allowed to show slides in two cases?

DR. NASH: Yes. May I ask one question. I would like to ask Dr. Ozzello if he has any experience with tissue culture?

DR. OZZELLO: I have experience only in one case that was very similar to the one that you described. Histologically it did not have so many endothelial-like cells as yours, and in that the culture showed usually fibroblasts.

DR. NASH: So that would seem to support the myxoma theory; is that right?

DR. OZZELLO: Yes.

CHAIRMAN SEVERANCE: Dr. Fine is about to discuss this, Dr. Nash.

DR. FINE: I think some of the members have already heard this, so they can go to sleep! But it might be of interest and I would like to present very briefly what we have done with the myxomas.

We have had a chance to study thirty-three cases;only eight of them our own. The rest have been sent. These authors have been very kind. They have submitted sections to us. We have studied eight of our own cases; we have only been able to study five extensively with multiple blocks and multiple sections. The other three are old cases and we do not have as many blocks on which to comment upon. But again we employed the ultrastructure and histochemistry to see if we could elucidate what this lesion is and, as Dr. Nash has already mentioned, is it a thrombus or is it a neoplasm: If it's a neoplasm, what is the cell origin? I would like to show a few slides of the epithelial or epithelial-like and gland-like pattern that we have encountered in five of our myxomas.

Slides:

The epithelial pattern has been mentioned three times in the literature, the first by Anderson in the early 40s and then by two English authors and then lastly by a Czech, Vasik, and we were able to get slides of the Vasik and English authors, one of which is Axelrod, and I've forgotten the other author. Anderson's slide had been disposed of, so we could not look at that.

In five of our cases we were impressed with the epithelial-like pattern. This actually comes from Vasik's case and I think it shows the cords of cells which I think at first glance, and I think after you look at it a while, they look like epithelium, if you will. There is a rather loose pink staining stroma which is Alcian blue positive as well as PAS positive. Some of these are in a circular fashion and you might say, "Well, are they tubes, are they glands; what are they?"

This lesion Vasik called a hamartomal blastoma, but actually on the right side one sees the more classical picture of a myxoma where you find just single cells or perhaps one or two cells, and this is the usual picture of the myxoma. I think it is confusing when one sees the marked cellularity such as you have on the left.

This is from one of our cases, and this occurred right under the surface of the tumor and we found these structures here. This is actually an ancient section; it looks very pink, but this material stained with mucicarmine stain and again on the outside one has cells some of which are inflammatory, I'm sure, some of which are mesenchymal cells. I don't think you can always identify these, but certainly this suggests a gland-like pattern, if you will.

This comes from Axelrod's case and I think it shows pretty much a glandular pattern, if you will. We had an opportunity to stain this one; he sent us a block. On the other hand, you see a transition

from a lower type epithelium. Here you see a group of cells which look like the usual lepidic cells. "Lepidic" was coined by ORR, that Dr. Nash has already mentioned, and "lepidic" means really "covering cell."

This was from our own case, which we first thought was a metastatic carcinoma. This was an elderly woman and much of the tumor looked like this, very cellular epithelium and suggesting in some areas at least a gland or perhaps you might say are these endothelial lining channels? This woman is alive. This was done in 1956. She is still alive; no evidence of a primary tumor.

This again is from another one of our own cases, showing areas that look epithelial, and these look more like the cells that you saw in the Seminar slide set.

I tried to convey to you what we think the origin of these gland-like spaces is. It has been suggested that the glandular epithelial-like structures may be endodermal rests. By some it has been suggested that these may be mesothelial cells, mesothelial rests. Then the third possibility is that this would be of teratomatous origin.

After studying these tumors and seeing the cellularity, we think that these gland-like and epithelial-like spaces actually come from these small groups of cells, the so-called lepidic cells; just a proliferation, and eventually what happens is that these cells are actually producing a polysaccharide and that they get pushed apart and form these gland-like or tubular spaces.

It isn't easy to find polysaccharide within the cells, but we have found it in a number of instances. We find isolated cells; they are generally PAS positive, which is non-digestible, suggesting or indicating a neutral mucopolysaccharide.

This I merely show to demonstrate what I think is sometimes confusing, and when you first look at these, the cells often are very closely applied around capillaries and if you think so, they sure are endothelial cells. But I think what they are is they are on the outside of the channels, and in this instance I think they are really pushed aside by the secretion so that they are now in this area. Anyway, you can see that they are actually not lining the capillary channels here.

This just summarizes what we concluded. We feel they are a neoplasm and not a thrombus, and we think we have support for this on the ultrastructural level as well as the enzymatic level.

I might say that with light microscopy I think that there are certain features that have already been pointed out, that these may be endocardial cells or epithelial. There has been one reference that I could find in the literature. It was not a detailed description; it was merely mentioned that the tumor was cultured and it looked like endocardial growth.

As far as the EM is concerned, we found that there are abundant secretory vacuoles as well as desmosomes. Now, the desmosomes would go in very nicely with endocardial or endothelial cells, if you want to use the term "lepidic." The secretory vacuoles and rough endoplasmic reticulum we feel is an indication of secretory activity of these cells. This is not a degeneration of the collagen, as some people have proposed. These cells are actively engaged in secretion. So we now have an explanation for the mucoid material.

We were not able to find pinocytic vesicles or basement membranes. This is against an endothelial origin. So we are still not absolutely sure what the cell origin is.

Histochemically the most striking thing was the richness of these cells in non-specific alkaline phosphatase,which goes in very

nicely with the endocardial or endothelial cells.

If I can be permitted the next slide just to show the ultrastructure. These are two of the cells in the nuclear area and the nucleus here; secretory vacuoles in this area, and this is the separation here. This is the dividing line. This I believe is a desmosome in this area, but again notice the spaces and the granular material in between the cells.

The next one will show a single cell with the stroma, the granular area of the stroma. In contrast, this is not fibrin; it doesn't have the ultrastructure of fibrin or of collagen; just a granular nondescript granular tissue; the nucleus of one of the tumor cells and then these tortuous cisternae, actually endoplasmic reticulum, which are features of active secreting cells.

CHAIRMAN SEVERANCE: Thank you. Anybody got any discussion left down there in the audience?

MEMBER: I was struck by the similarity of the behavior of some of these cells and exactly what Dr. Fine was describing, too, between this tumor and the mesothelioma of the dura where you get epithelial-like structures; you get your spindle cells, you get your Alcian blue, and so on.

I think all that is in keeping with this being of endothelial origin and that the mesothelial cell behaves like the mesothelial cell of the dura.

Do they ever metastasize?

CHAIRMAN SEVERANCE: I think Dr. Nash said no.

DR. NASH: No. I found no such reference.

DR. HILL: We have nine cases in our files and we have no difficulty of differentiating tumors grossly from auricular thrombi.

We don't have any metastases, but we have two patients, one is a 14 year old girl and one is a 17 year old girl who dropped dead suddenly, who have these masses extending from the left auricular appendix all the way down to the bifurcation of the aorta. It's a continuous mass.

DR. FINE: Well, as far as malignancy, I would like to clear up one thing, that Fenster in 1932 reported a case of malignant myxoma of the heart. Fortunately, in writing to the present professor there we received a block of tissue and Bob Horn, the expert on rhabdo has seen this, and this is not a myxoma in the present concept.

DR. HORN: This is a rhabdomyosarcoma. I have the slides here if somebody wants to look at them. But as far as I know there hasn't been a bona fide myxoma of the heart that's metastasized.

With regard to differential diagnosis, I agree with Bill. Generally one does not have any problem in distinguishing these lesions from a thrombus, but I think there can be some difficulty. I don't say we can do it in all instances at first glance. I think sometimes it takes study.

I think we have more trouble in distinguishing these from the botryoid myosarcoma and we got bumped once and the second time we were smarter. But I think if you get stuck, if one uses the electron-microscope or more simply the alkaline phosphatase, we can distinguish between myxoma and rhabdomyosarcoma. The myxoma has abundant alkaline phosphatase; the rhabdo, in the cases we have studied does not have any.

DR. KAY: Let me just state that grossly a myxoma should not infiltrate the wall of the atrium. If anybody knows of one that did, I would like to hear about it, because this is one way you can tell grossly.

Once you get infiltration into the wall, in the mesoendothelium of this tumor, you are dealing now with a malignant tumor.

DR. FINE: One case that I got from Dr. Hazzard is an interesting thing. That lesion was reported also as a malignant myxoma. Bob again has seen this, so he can back me up. It doesn't look histologically malignant but it has multiple foci surrounding it in some of the coronary vessels of this so-called "lepidic cell." To me I interpret this as a multicentric origin for the lesion. In other words, what I'm getting at is the fact you say that it's invading. I think some of these lesions may well arise in a number of areas. So don't jump at malignancy because you may see invasion of the wall there.

I think you are perfectly right, that these generally do not infiltrate the wall.

CHAIRMAN SEVERANCE: The time is moving on and I'm going to shut off any more discussion on this case.

References:

Gould, S.E.: Pathology of the Heart, Charles C. Thomas, 1960

Newman, H.A., et. al.: Intracardiac Myxomas: American Surgeon, 32, p. 213, 1966.

Nichols, J. and Hennigar, G.: Bilateral Multicentric Cardiac Myxoma; Arch. of Path. 67, p. 24, 1959

Prichard, R.W.: Tumors of the Heart (Review); Arch. of Path., 51, p. 98 1951

Orr, J.W.: Endothelioma (pseudomyxoma) of Heart: J. Path. and Bact. 54, p. 125, 1942.

CHAIRMAN SEVERANCE: Dr. Lattes offered to stop the meeting at this point and give us his discussion of his two cases and send them by mail. But I thought we might go on, because there are a few of us that would like to hear about it. But those who want to go I'm sure can. But before you go I want to tell you this story.

There were three men fishing out in the ocean: a minister, a rabbi and a lawyer. And somehow or other they got pretty far from

shore and they lost their oars. And then they decided they ought to choose lots to see who was going to swim ashore for help. Lo and behold, the lawyer was the guy who got the short end of the straw and he had to swim ashore.

So he took off and he began to swim ashore, and finally there were a lot of sharks out there in the water. And the Minister said, "Look at that fellow, He's going right between those sharks and they aren't bothering him. How do you account for that?" And the rabbi said, "O, that's easy. Professional courtesy!" (Laughter)

So before you leave, remember "professional courtesy" and stay and hear Rafe!

Case No. 14
Submitted by Dr. Raffaele Lattes:

This is a fascinating case showing the rare but well-known association of congenital arteriovenous shunts and capillary angioma-like proliferations associated with them. I had pulled out the material from this case in order to select some illustrations for the second edition of the fascicle on tumors of soft tissue for the A.F.I.P. About the same time I had sent around to all the members of the APS Society a notice requesting the submission of tumors of the vascular system for this seminar. John Pickren who in 1952 was a member of our department in New York remembered the case either because he owns a copy of our files or because he owns a private collection made out of our sections or both, and wrote to me suggesting this case as a candidate for the seminar. It certainly is an excellent candidate.

You have read the history. After many attempts at conservative treatment it became obvious that it was impossible to save the arm of this little girl because of the local complications represented by soft tissue swelling, multiple episodes of ulceration and hemorrhage, deformity of the bones as well as because of systemic cardiovascular complications associated with a syndrome of peripheral arteriovenous shunts. The two sections distributed to you represent the "angiomatosis" pattern with multiple lobulated areas consisting of small tortuous blood vessels with slightly prominent endothelial cells. Each one of these lobules is fed by larger veins and arteries. In addition, practically everywhere there are larger malformed blood vessels some of them typically arterial in type others typically venous and some of them representing some kind of a hybrid that is venous vessels with enormously thickened intima and prominent amounts of elastic tissue. Many of these vessels

contain organized thrombi possibly at least in part the results of previous attempts at ligation and sclerosing of these vascular malformations. The "angiomatosis" involved practically every tissue in the amputated extremity, skin, subcutaneous tissue, skeletal muscles. The bones were not involved by angiomatosis. I would like to add a final remark and that is that the foci of capillary proliferation appear to me different from those of the usual capillary hemangioma of children. I don't know how to put it well in words but they resemble more the blood vessels found in granulation tissue. I wonder if any one here has had similar experiences.

DIAGNOSIS: Angiomatosis, diffuse of forearm associated with congenital multiple arteriovenous shunts.

CHAIRMAN SEVERANCE: These are the diagnoses: Hemangiomatosis of arm (as part of VonHippel-Lindau's disease); angiomatosis (Stout's disease, right arm); hemangiopericytoma ? angiomatosis; hemangiomatosis with dyschondroplasia (Maffucci's syndrome); hemangiomatosis of AV communications; infantile hemangioendothelioma; benign hemangioendothelioma; hemangiomas of skin with AV communications; angiomatosis, skin and soft tissue of forearm; "telangectasia elephantiosis" (Virchow-benign); congenital diffuse angiomatosis with associated gigantism of the affected extremity; capillary hemangiomata.

Any comments, discussion from the audience?

DR. KAY: I would just like to ask Rafe one question. Do you ever see these associated with what you are sure are lymphatics so that you can use a combination diagnosis, the same kind of malformation?

DR. LATTES: I'm not familiar with this. It's a rare condition and it's also rare to have the opportunity of studying not a small biopsy but a whole extremity and establishing that indeed there are

associated malformed large arteries and veins as well as proliferation of capillaries.

I believe that those that have been described are essentially blood vessels and not lymphatic vessels. I would have to read again some of the bibliography that I went through rapidly, to see if anybody has suggested that, but I don't believe so.

CHAIRMAN SEVERANCE: Any other questions, comments? If not, Rafe, you can go on with the last case, Case No. 15.

References:

Malan, E. and Puglionisi, A. Congenital angiodysplasias of the extremities: Note I: Generalities and Classification; Venous dysplasia. J. Cardiovasc. Surg. 5: 87-130, 1964

Malan, E. and Puglionisi, A. Congenital Angiodysplasias of the Extremities: Note II: Arterial, arterial and venous, and haemolymphatic dysplasias. J. Cardiovasc. Surg. 6:255-347, 1965

Case No. 15
Submitted by Dr. Raffaele Lattes:

This was a 6½ week old infant with congenital heart disease. The infant was born after seven months gestation, weighing 5 lb. 4 oz. There was rapid weight loss to 4 lbs. 4 oz. Sometime after birth the infant developed a left pleural effusion with mediastinal shift which recurred after repeated taps but gradually decreased in 4 to 5 days on tube drainage. The effusion was chylous, and was re-fed to the baby. Nevertheless, the infant developed hypoproteinemia and was treated with g-globulin when 40 days old. It died after cardiac catherization when 48 days old.

Autopsy findings were body weight, 2425 gm; body length (crown heel): 19-½ inches.

Significant gross findings limited to the chest.

The great veins and arteries are normal except for a persistent left superior vena cava and absent left innominate vein. Drainage of the persistent LSVC into the coronary sinus.

Heart: Enlarged right atrium, marked hypertrophy of both ventricles. Large anterior patency in foramen ovale with communication between atria. Deformity of all valves by many smooth firm nodular excrescences.

The descending thoracic aorta was flanked on each side by a softly nodular purple mass resembling confluent lymph nodes, and measuring 4.0 x 0.6 x 0.3 cm on the left side and 4.0 x 0.7 x 0.3 cm on the right side. Centrally placed behind the aorta, within the crura of the diaphragm, was a thin-walled ovoid shaped sac measuring 1.0 x 0.3 x 0.4 cm. and placed in a horizontal position. This chamber communicated by a probe passable channel with the mass on the left side. Communication

of the sac with the mass on the right side as well as thoracic duct entry into the venous circulation could not be demonstrated. However, numerous minute vascular branches were noted to open into the persistent left superior vena cava at and slightly below the entry of the left subclavian vein.

This last case was a case that was entered at the last moment because it was too beautiful not to introduce it in this Seminar. It is an autopsy finding in the Bellevue pediatric service that was brought to me, as I said, shortly before we completed the Seminar.

I have read to you that it is an infant that lived only $6\frac{1}{2}$ weeks; had a very complex congenital heart disease, and before death it was known that the patient was suffering from recurrent pleural effusions which were chylous in type.

The findings at autopsy which are pertinent to the lesion are represented essentially by a bilateral perivertebral posterior mediastinal mass on both sides of the thoracic aorta and apparently communicating at the dorsal end with a thin-walled sac which presumably was the beginning of the thoracic duct.

Slides:

This is the mediastinal region and the lungs. This is the posterior mediastinum, and on both sides of the thoracic aorta there were these spongy brownish masses.

This is a low power of the same section, showing the esophagus and the aorta and the vertebral bodies here, and these spongy masses are situated here, on both sides and posterior to the aorta (indicating).

The soft mass was grossly spongy and histologically proved to be lymphangiomatous in type and associated with islands of lymphoid tissue. The vascular spaces contain at times extravasated blood and more often mononuclear leukocytic cells and foam cells.

We thought it would be interesting to add this unusual case to the Seminar. Primary lymphangiomatous lesions of the mediastinum are rare. When Dr. Pachter and I in 1963 reviewed the mediastinal tumors in our files we found only six cases that could be considered as primary in the mediastinum three of which were classified as lymphangiomas, one as lymphangiomyoma and two as lymphangiopericytoma. Many years ago in one of these seminars a case of "lymphangiopericytoma" of the mediastinum associated with chylous effusion was presented. I believe that since then the case was reclassified by Dr. Enterline as lymphangiomyoma. His paper in Cancer of 1966 (see references below) gives a good review of the problem. The current case however could not be classified as either lymphangiomyoma or lymphangiopericytoma. Morphologically it is a classical lymphangioma associated with lymphoid tissue. Whether or not had the baby survived, it would have changed its histological pattern and become more complex in its structure would be pure speculation. A good discussion of the sources of chylous thorax can be found also in a presidential address in the August 1966 issue of the Journal of Thoracic and Cardiovascular Surgery by Dr. Herbert C. Maier.

DIAGNOSIS: Lymphangioma, bilateral, congenital, of posterior mediastinum associated with chylous pleural effusion.

This was also a very interesting case from another point of view for, contrary to what some might think, primary lymphangioma limited to the mediastinum is a rare lesion. The majority of the so-called mediastinal lymphangiomas in children are actually cervical lymphangiomas that extend down in the retrosternal region.

I wonder whether anyone here has seen a similar case of a congenital tumor?

CHAIRMAN SEVERANCE: These are the diagnoses, Dr. Lattes: Lymphangioma (congenital malformation); hemolymphglands (hemolymphatic hamartomas); cavernous hemangioma; multiple vascular hamartomas of blood vessels and lymphatics; bilateral lymphangiectatic sacs; lymphangioma; lymphangioma again; lymphangiectasis; hemangioma, cavernous; lymphangiectasia (lymphangiovenous anastomosis); congenital anomaly lymphangiovenous shunt (something similar to the arteriovenous shunt; hemangiomatosis of malformed lymph node; lymphangiomatosis and hemangiomatosis of (another) malformed lymph node.

Discussion:

DR. LATTES: I omitted to say that the credit for this beautiful dissection goes to the pediatric pathology service at Bellevue and Dr. Dishe was positive that she found a direct communication between the cisterna of the thoracic duct and the lymphangiomatous cavernous lesion on the left.

CHAIRMAN SEVERANCE: Are there any comments or discussion from the floor?

DR. HAAGENSEN: I must mention that anomaly which I saw last year, which I never saw before, which is or has a remote relationship except that this may be pursued: A radical mastectomy, nothing abnormal, and the flaps and wound were full of chyle for two weeks until I got things stopped by aspiration. This was without any question, I'm sure, a thoracic duct entering into the axillary vein. It was on the left side and draining into the wound. There is no other possible explanation other than that.

CHAIRMAN SEVERANCE: Any other discussion from the group:

DR. HAAGENSEN: I had a nurse watching me one day as I aspirated and I said, "Can you explain this? What is this?" She said,

"It's milk. You've been operating on the breast, haven't you?" (Laughter)

References:

Cornog, J.L., Jr. and Enterline, H.T.: Lymphangiomyoma, A Benign Lesion of Chyliferous Lymphatics Synonymous With Lymphangiopericytoma. Cancer 19: 1909-1930, 1966

Laipply, T.C. and Sherrick, J.C.: Intrathoracic Angiomyomatous Hyperplasia Associated with Chronic Chylothorax. Lab. Invest. 7: 387-400, 1958

Maier, H.E.: Presidential address-The pulmonary and pleural lymphatics: A Challenge to the Thoracic Explorer. J. Thor & Cardiovasc. Surg. 52: 155-163, 1966

Pachter, M.R. and Lattes, R. Mesenchymal Tumors of the Mediastinum III. Tumors of Lymph Vascular Origin. Cancer 16:108-117

Rienhoff, W.F. III, Shelley, W.M. and Cornell, W.P. Lymphangiomatous Malformation of Thoracic Duct Associated with Chylous Pleural Effusion. Ann. Surg. 159: 180-184, 1964

CHAIRMAN SEVERANCE: Any other discussion? Can you stand one more story?

There was a lady who was cleaning out her closet and she came across a suit of clothes that her husband had had for quite a few years, and she decided to throw it away. And before she did she went through the pockets and she pulled out a tag that represented a little receipt that had been given to her husband when he had a pair of shoes repaired but he forgot to go back for them some twenty years before.

So he said, "My God, what will I do with this? I think I'll pull a joke on this shoemaker." So he went back one day after that, nonchalantly handed the shoemaker the ticket. So the shoemaker goes back into his workshop back there and he looks around and he doesn't find the pair of shoes.

So he comes back and he hands it to the man and he says, "They're not ready yet. Come back tomorrow!" (Laughter)

So we will see you next year. Goodbye! (Laughter and applause.)

(The Seminar adjourned

at 4:30 o'clock)