Clinico-pathological Conference

Blood Dyscrasia with Cardiac Complications*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. W., was a sixty-one-year old white divorced bank guard, who entered the Barnes Hospital for the first time on October 9, 1946, complaining of shortness of breath. The family history was non-contributory. The past history revealed that the patient had had pneumonia in 1914 without complications. He had had no other serious illnesses, and the systemic review was negative.

Approximately one year before entry, the patient was told by friends that his eyes were becoming more prominent and from that time on exophthalmos had increased. Shortly after the prominence of his eyes was first noted, the patient became more nervous and developed a slight tremor of his hands. About four and one-half months prior to admission, he became dyspneic for the first time on exertion; dyspnea increased rapidly so that soon it was present when the patient was at rest. Orthopnea and a persistent, non-productive cough occurred. Concomitantly the patient became aware of masses in his neck and in the axillae, and he entered the Washington University Clinics.

There it was recorded that he did not look particularly ill. A patchy maculopapular erythematous eruption was noted over the chest and inguinal regions. There was generalized lymphadenopathy; the nodes varied from ½ to 2 cm. in diameter and were discrete, firm and non-tender. The eyes were prominent. The pupils reacted to light and accommodation and extra-ocular movements were normal. The optic fundi showed only moderate retinal sclerosis; no hemorrhages or exudates were present. The tonsils were enlarged but did not appear inflamed. The lungs were clear to percussion and auscultation. The left border of cardiac dullness was 9 cm. to the left of the midsternal line in the fifth interspace. The rhythm was regular, the sounds were of good quality and there were no murmurs. The spleen was palpable 10 cm. below the left costal margin but the liver edge could not be felt. The prostate was twice its normal size. There was no clubbing or edema and the neurologic examination was within normal limits. Laboratory studies included a normal red blood count and hemoglobin. The white cell count was 173,550 and the differential count showed 1 per cent stab form, 3 per cent segmented forms, and 96 per cent lymphocytes; 6 per cent of the lymphocytes were immature. A chest film was read as follows: "The cardiac silhouette is within normal limits. The hilar markings are prominent on both sides. There is pulmonary infiltration in the second and third anterior interspaces on the right and to a lesser extent along the descending bronchi. X-ray diagnosis: peribronchial infiltration of an indeterminate nature."

A diagnosis of chronic lymphatic leukemia was made and from June 26, 1946, to July 31, 1946, the patient was given

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.

seventeen x-ray exposures. He was then followed in the Anemia Clinic where examination revealed that the spleen and lymph nodes were reduced in size. On September 17, 1946, the following laboratory data were recorded: red blood count, 4,480,000; hemoglobin, 13.2 Gm.; reticulocyte count, 3 per cent; white cell count, 37,400; differential count: 1 per cent eosinophiles, 1 per cent segmented forms, 96 per cent lymphocytes, and 2 per cent monocytes; platelets, 270,000.

During the course of x-ray therapy most of the patient's symptoms had improved considerably but his appetite became poorer. He felt fairly well until one week prior to entry when he again became markedly short of breath and developed nausea, vomiting and diarrhea. Six days before admission he complained of pain in the left chest substernally, associated with marked orthopnea. Three days before admission edema of the legs appeared. Because of the persistence of these symptoms he was admitted to the hospital.

No temperature reading was recorded and the pulse was not obtainable. The respirations were 32 per minute and shallow, and the blood pressure was 85/65. The patient was critically ill and sat on the edge of the bed gasping for air. The arms and legs were cold and clammy and there was cyanosis of the lips and of the finger nail beds. Moderate exophthalmos and lid lag were noted. The mucous membranes of the mouth were cyanotic. The tongue protruded in the midline without tremor. There was marked distention of the neck veins. The trachea was in the midline; the thyroid was normal in size but a small nodule was palpated in each lobe. There was dullness to percussion at the base of the right lung and over this area tactile fremitus, breath sounds and spoken voice were diminished. No râles were heard and the remainder of the lung fields was clear to percussion and auscultation. The cardiac impulse could not be seen or felt and no heart sounds were audible. The heart was enormously enlarged; right border dullness was 3 cm. from the midsternal line in the second interspace, 5 cm. in the third interspace, 9 cm. in the fourth interspace, and 13 cm. in the fifth interspace. The left border of cardiac dullness was 6 cm. to the left of the midsternal line in the second interspace, 8 cm. in the third, 12 cm. in the fourth, and 16 cm. in the fifth interspace. The spleen was palpable 7 cm. below the left costal margin, and the liver 11 cm. below the right costal margin. There was 4+ pitting edema of the feet and lower legs.

The laboratory findings were as follows: Red cell count, 4,550,000; white cell count, 96,000; differential count: 8 per cent segmented forms, 92 per cent lymphocytes. Blood Kahn reaction: negative. Venous pressure: 310 mm. NaCl. Circulation (arm to tongue with Decholin): 78 seconds. Roentgenogram of the chest: "The cardiac silhouette is enlarged to the right and left. The hilar shadows are prominent and there is fluid in the right pleural cavity." An electrocardiogram revealed low voltage in leads I, II and III, moderate slurring of all ventricular complexes, inversion of the principal component in I with upright principal components in II and III. There was a Q wave in CF_{IV}. Interpretation: "right bundle branch block and low voltage."

Immediately on entry the patient was given oxygen through a positive pressure mask and his cyanosis was relieved; however, he could not tolerate the mask and it had to be removed. Because the signs were thought to be those of cardiac tamponade, pericardial paracentesis was attempted; a No. 18 needle was introduced in the left fifth interspace at the outer border of cardiac dullness. No resistance was met and after the needle had penetrated 4 cm. blood was easily aspirated. Fifty cc. were withdrawn and the procedure was terminated. The

patient tolerated it well. The count on the bloody fluid obtained revealed 4,810,000 red cells, 13 Gm. of hemoglobin and 80,600 white cells. As a result of these findings it was concluded that the patient had acute cardiac dilatation rather than cardiac tamponade and he was given 1.6 mg. of lanatoside C intravenously over a period of five minutes. Shortly after the injection was completed, he slipped backward from his sitting position, had a mild generalized convulsion, took a few deep gasps for breath and expired. Death occurred approximately one and one-half hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Two features of this case deserve discussion, namely, the hematologic diagnosis and the etiology of the heart disease. Because the patient died so soon after admission to the hospital, the data are somewhat limited. Dr. Moore, would you comment on the hematologic problem?

DR. CARL V. MOORE: This patient probably had chronic lymphatic leukemia. I qualify my statement because neither a lymph node biopsy nor a bone marrow aspiration was recorded, and rarely a leukemoid reaction, characterized by a great increase in cells of the lymphatic series, may result from a chronic infection such as tuberculosis or from wide-spread neoplastic disease.

DR. ALEXANDER: Could lymphosarcoma be associated with a peripheral blood picture such as that seen in this case?

DR. C. V. MOORE: Yes, but I believe it can be excluded here. As you know, there is considerable interest among members of the hematologic division in the occurrence in lymphosarcoma of a peripheral blood picture simulating that of lymphatic leukemia. Not one of the members of the division who examined this patient's smear thought that the cells were those of lymphosarcoma.

DR. ALEXANDER: Is it true that x-ray therapy may lead to the development of a leukemoid peripheral blood picture in lymphosarcoma?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: Does pulmonary infiltration occur in leukemia?

DR. ALFRED GOLDMAN: It is seen not infrequently. I do not believe that the x-ray findings in this case are necessarily due to infiltration with leukemic cells however; they may have represented the changes of low grade pneumonitis.

DR. ALEXANDER: Is it possible to distinguish Hodgkin's disease from leukemia by the nature of the pulmonary infiltration?

DR. C. V. MOORE: I do not think so. In general, approximately one-third of patients with lymphosarcoma, Hodgkin's disease, and chronic lymphatic leukemia have some form of pulmonary involvement equally divided between pulmonary infiltration, mediastinal adenopathy and pleural effusion. Given one of these changes, however, I do not believe that the correct hematologic diagnosis can be made on the basis of the x-ray film.

DR. ALEXANDER: This patient received seventeen x-ray treatments and it was noted that the size of the spleen diminished. Are the cells of lymphatic leukemia quite sensitive to roentgenotherapy?

DR. EDWARD H. REINHARD: They are definitely radio-sensitive although not to as great a degree as the cells of leukosarcoma.

DR. ALEXANDER: Apparently the pulmonary infiltration cleared after x-ray therapy. Would you have expected the spleen to return to normal size?

DR. REINHARD: Usually there is a greater decrease in the size of the spleen than was noted in this case. However, the response to x-ray therapy depends to a considerable extent on the duration of splenic enlarge-

ment; the longer the spleen has been enlarged, the less likely is there to be a good response to x-ray therapy.

DR. DONALD S. BOTTOM: It should be pointed out that this patient did not receive x-ray therapy directly to the spleen but only to the inguinal, axillary and cervical nodes. Frequently, however, the spleen is reduced in size even though radiation is not directed toward it.

DR. ALEXANDER: If x-ray therapy was directed primarily to the spleen, would the lymph nodes be expected to decrease in size?

DR. BOTTOM: Occasionally such a response is seen.

DR. ALEXANDER: What has been your experience, Dr. Reinhard, in this regard?

DR. REINHARD: I agree with Dr. Bottom. If x-ray is directed to large lymph nodes, they will decrease more rapidly and to a greater extent than if the therapy is directed, for example, to the abdomen, but they usually decrease to some extent even if they are not subjected to direct radiation.

DR. ALEXANDER: You have used radio-active phosphorus in a large number of cases. Do you feel that it should have been used in this patient?

DR. REINHARD: Radio-active phosphorus could have been used, but if reduction in the size of specific lymph nodes or the spleen is the prime objective of therapy, x-ray is preferable.

DR. ALEXANDER: Would you comment on the use of other isotopes?

DR. REINHARD: With the information available to date, I do not believe that any other isotopes have any real advantage over x-ray therapy or radio-active phosphorus.

DR. ALEXANDER: Would you comment on the duration of lymphatic leukema. Does the prognosis vary with age?

DR. REINHARD: In general, the course of chronic lymphatic leukemia in older patients is more benign than it is in patients in the younger age group. The former are more likely to have evidence of the disease as indicated by peripheral lymphadenopathy for a considerable period of time before general systemic effects are noted, and after the diagnosis is made, the older patients survive for a longer period of time. The average duration of life in patients between the ages of twenty and fifty is approximately three years. In a patient over sixty the predicted duration is about four years.

DR. ALEXANDER: Would you comment on the duration of life in myelogenous leukemia?

DR. REINHARD: With the most successful treatment the average course of the disease covers three and one-half years; without treatment the duration is three years. It is important, however, to emphasize that adequate therapy increases the period of useful activity greatly; that is, the patients remain essentially symptom-free until very near the time of death.

DR. C. V. MOORE: I think that Dr. Reinhard's estimate for the average duration of life in myelogenous leukemia was too short. Patients with myelogenous leukemia may live for ten years; this summer Dr. John Lawrence told me that in his experience the average duration of life for patients with myelogenous leukemia, treated with radio-active phosphorus is now over four and one-half years and he thinks that ultimately such patients may be expected to survive for more than five years.

DR. REINHARD: My estimate was based on results in patients with both acute and chronic myelogenous leukemia.

DR. ALEXANDER: Dr. Moore, would you comment on chronic lymphatic leukemia occurring late in life.

DR. C. V. MOORE: Patients with chronic lymphatic leukemia may live for twenty years; such instances are the exception rather than the rule. Dr. Lawrence's

statistics for duration of life in chronic lymphatic leukemia averaged about six years; our results have not been so favorable.

DR. ALEXANDER: Approximately four and one-half months before his death, this man noted dyspnea on exertion and soon thereafter became orthopneic. Dr. Smith, do you believe that these symptoms arose because of cardiac insufficiency?

DR. JOHN R. SMITH: Certainly cardiac disease is the most common cause of dyspnea and orthopnea.

DR. ALEXANDER: When the patient was examined in the clinic, his heart was not enlarged, the sounds were of good quality and there were no murmurs. Unfortunately no blood pressure reading was recorded. The chest x-ray showed no cardiac enlargement. Do you think those findings are compatible with a cardiac basis for the dyspnea and orthopnea?

DR. SMITH: Yes.

DR. ALEXANDER: With x-ray therapy, apparently all of the patient's symptoms improved and he did fairly well until one week before death when he had substernal distress and a rapid progression of the cardiac symptoms—dyspnea, orthopnea and edema. Dr. Massie, what is your interpretation of that sequence of events.

DR. EDWARD MASSIE: Two possible causes for the symptoms seem plausible; either the patient had a myocardial infarction or he developed a pericardial effusion.

DR. ALEXANDER: Do you believe that the dyspnea and orthopnea which the patient had before he received x-ray therapy were suggestive of cardiac insufficiency.

DR. MASSIE: No, I believe that they more likely were based on an extracardiac factor.

DR. ALEXANDER: What extracardiac causes would you consider?

DR. MASSIE: Either pulmonary infiltration or severe anemia could have been responsible for the symptoms. In this case the anemia was only slight and therefore I would consider pulmonary infiltration as the major factor.

DR. ALEXANDER: Do you believe that the x-ray film indicated sufficient pulmonary infiltration to give rise to dyspnea and orthopnea?

DR. MASSIE: No, I do not. However, I have seen, on occasion, patients who presented themselves because of dyspnea and orthopnea and although careful study revealed no cardiac cause of the symptoms, eventually a blood dyscrasia was uncovered as the basis of the symptoms.

DR. ALEXANDER: Dr. Moore, what is your experience?

DR. C. V. MOORE: Dyspnea and orthopnea on the basis of pulmonary infiltration is rare, even in cases in which there is also marked involvement of the mediastinum.

DR. REINHARD: I agree with Dr. Moore. It should be pointed out, however, that in lymphatic leukemia the myocardium may be heavily infiltrated with abnormal cells.

DR. ALEXANDER: Do you believe that the patient improved after his x-ray therapy because of the destruction of abnormal cells in the myocardium.

DR. REINHARD: I do not know.

DR. ROBERT A. MOORE: Heavy pulmonary infiltration in blood dyscrasias is rare. Likewise infiltration of the myocardium to a marked degree is not common. Infiltration of the endocardium with abnormal cells, however, is a common manifestation of leukemia.

DR. ALEXANDER: Dr. Massie, is bundle branch block usually attributed to coronary-artery disease?

DR. MASSIE: Yes. In this case, however, the pain in the left chest may have been associated with pericarditis or pericardial effusion rather than with coronary insufficiency. The bundle branch block may have been existent for many years and its presence in a single electrocardiogram would not

allow one to differentiate between coronary-artery disease and pericardial disease as the cause of the chest pain.

DR. ALEXANDER: This patient developed progressive exophthalmos and a tremor of the hands; on physical examination a nodule was felt in either lobe of his thyroid. No basal metabolic rate was recorded. Dr. Futcher, do you believe that histologic evidence of hyperthyroidism will be found by the pathologists?

DR. PALMER H. FUTCHER: It has been pointed out frequently that the symptoms of hyperthyroidism are often present in leukemia. It has been suggested by one writer that thyrotoxicosis and leukemia both may arise from stimulation of the sympathetic nervous system and he has treated leukemic patients with iodine in the hope of controlling the course of the disease. I should like to ask Dr. Moore how often a hyperplastic thyroid is found in leukemia.

DR. C. V. MOORE: I cannot answer that question, Dr. Futcher. I have always assumed that the increased metabolic rate in leukemia was related to the number of abnormal cells circulating rather than to the thyroid gland *per se*.

DR. ALEXANDER: The question arises as to whether this patient had a bloody pericardial effusion. The physical signs were classical of those seen in pericardial effusion.

DR. MASSIE: I agree that blood was probably present in the pericardium.

DR. FUTCHER: I believe that a more likely explanation is that the needle was in the ventricle.

DR. ROBERT J. GLASER: When we saw this patient, the clinical picture was thought compatible with pericardial effusion and cardiac tamponade, and because of the patient's critical condition, pericardial paracentesis was considered justified. The needle was inserted very slowly but at no time was resistance encountered to suggest that the needle had pierced the ventricular muscle. As soon as bloody fluid was obtained, the procedure was terminated and cell counts were done. The counts indicated that pure blood had been withdrawn.

DR. ALEXANDER: Are there possibilities other than that the ventricular cavity was entered?

DR. W. BARRY WOOD, JR.: Rupture of the auricle or ventricle could explain a bloody pericardial effusion.

DR. ALEXANDER: Yes, the patient may have had a myocardial infarction one week before entry when he first complained of substernal pain with subsequent rupture at the site of infarction.

DR. WOOD: It is also possible that there was pericardial infiltration by leukemic cells with a secondary bloody effusion. Such a finding is not uncommon when carcinoma extends to the pericardial sac.

DR. ALEXANDER: Dr. Moore, is pericardial infiltration and a bloody pericardial effusion common in leukemia?

DR. C. V. MOORE: I do not know, Dr. Alexander. However, Dr. John Tinsley told me of a case report describing infiltration of the auricular wall in leukemia with subsequent rupture and cardiac tamponade. In another case the aortic wall was infiltrated with leukemic cells and subsequently ruptured.

DR. ALEXANDER: It is said that invasion of the pericardium by lymphomas is rare.

DR. R. A. MOORE: I have seen it in a few cases, and in some of these, bloody pericardial fluid was present.

DR. ALEXANDER: The physical findings certainly suggested a pericardial effusion. The heart was tremendous and the signs were classical.

DR. C. V. MOORE: Dr. Robert Moore mentioned that lymphomas may involve the pericardium. I have seen that happen with lymphosarcoma or with Hodgkin's disease, but I do not understand its occur-

rence in lymphatic leukemia. Pleural effusion and ascites are not uncommon in lymphatic leukemia and yet in such instances involvement of the serous membrane with abnormal cells is not found.

DR. R. A. MOORE: I was speaking primarily of lymphosarcoma but occasionally pericardial involvement is seen with leukemia.

DR. GLASER: I should like to justify the use of lanatoside C here. Because of the character of the fluid obtained on pericardial tap, it was concluded that the patient had cardiac dilatation rather than pericardial effusion, and because nothing else seemed to offer any hope, rapid digitalization was attempted.

DR. WOOD: The decision to digitalize this patient was motivated somewhat by a previous experience in which a similar problem faced the staff when a pericardial tap was attempted and blood was obtained. A diagnosis of cardiac dilatation was made in that instance, the patient was digitalized and responded dramatically. It was believed in the present case that digitalis should not be withheld. If the diagnosis of pericardial effusion could have been substantiated, lanatoside C would not have been given.

DR. ALEXANDER: In summary, it is clear that this patient had chronic lymphatic leukemia. The etiology of his heart disease cannot be definitely established; pericardial effusion is apparently ruled out leaving as the most likely possibility coronary artery disease or thyrotoxic heart disease. The patient very possibly had thyrotoxicosis although, as has been pointed out, leukemia and thyrotoxicosis have certain clinical features in common.

CLINICAL DIAGNOSIS: Chronic lymphatic leukemia and cardiac insufficiency due to either coronary artery sclerosis or thyrotoxic heart disease complicating hyperthyroidism.

PATHOLOGIC DISCUSSION

DR. FRANK VELLIOS: At the time of autopsy, the veins of the face and neck were markedly distended and there was edema of the lower extremities. One thousand cc. of fluid were present in the peritoneal cavity, 150 cc. in the right pleural cavity and 300 cc. in the left pleural cavity. The pericardial sac contained 50 cc. of serosanguineous fluid. The heart weighed 700 Gm. and was large, pale and flabby. Near the tip of the left ventricle there was a needle puncture which extended into the cavity. All four chambers were greatly dilated but the ventricular walls were not particularly thickened. The right ventricle measured 5 mm. in thickness, the left, 14 mm. The coronary arteries showed a few arteriosclerotic plaques but none of these encroached upon the lumina of the vessels. The thyroid gland weighed 28 Gm. A small, firm, encapsulated nodule was present in the left lobe; in the right lobe there was a cyst, 1.5 cm. in diameter, containing yellow material. The lungs weighed 2,300 Gm. and were large and firm. The liver weighed 2500 Gm. and was large, firm and purple in color. The spleen, which weighed 900 Gm., was firm and red. The kidneys were not remarkable. Petechiae and ecchymoses were present in the serous membranes.

DR. R. A. MOORE: To answer the questions outlined in the discussion, let us first consider the problem of the hematologic disease. On the basis of the gross observation of enlarged lymph nodes, splenomegaly, hepatomegaly, petechiae and ecchymoses in a number of organs, the diagnosis of chronic lymphatic leukemia can be confirmed.

To turn to the cardiac disease, it was noted that the heart was hypertrophied and dilated. Either valvular disease or hypertension could have explained the heart findings but the absence of changes in

the kidneys would effectively rule out the latter and no valvular abnormalities were noted. The 50 cc. of pericardial fluid was slightly blood-tinged, but other than the identification of the site of the needle puncture in the ventricular wall, there was no evidence of any significant sequellae of the pericardial paracentesis. Attention should be called to the fact that in the laboratory ventricular puncture is a common procedure which is almost always innocuous.

During the clinical discussion the question as to whether the pulmonary infiltration was responsible for the cardiac symptoms was raised, but this explanation must be rejected because the hypertrophy and dilatation involved not only the right ventricle but also the left, and indeed the left ventricular involvement was more marked. No lesion was found in the lung either grossly or microscopically to have accounted for the cardiac symptoms. The amount of coronary artery disease was insignificant. Only a few plaques were found in the vessels and these did not significantly impinge on the lumina. Anemia should be considered as an explanation for dilatation and hypertrophy of the heart, for 50 per cent of patients with pernicious anemia exhibit hypertrophy of the myocardium without apparent cause other than the anemia. In such instances, however, fatty degeneration is found and the classical "tigered" papillary muscles are seen. Another possible cause of cardiac disease is the lesion called Fiedler's myocarditis or isolated myocarditis. These diagnoses must be based on microscopic findings and will be considered subsequently. One must consider the possibility of thyrotoxic heart disease in view of the presence of an adenoma in the thyroid gland. The lesions noted in the gross, however, would not be expected on microscopic study to give evidence of thyrotoxicosis. The histopathologist finds it difficult to correlate gross and microscopic findings in such an instance as this. Other improbable causes of the cardiac findings include so-called beriberi heart and radiation effect. When a sufficient dose of radiant energy is directed to the heart, the myocardium may be injured and feasibly such changes might lead to dilatation and hypertrophy. This patient, however, did not receive radiation to the cardiac area and that possibility must be excluded.

DR. WOOD: Would you comment on leukemic infiltration of the myocardium as a cause for hypertrophy and dilatation of the heart?

DR. R. A. MOORE: The microscopic sections did not show any such infiltration. Figure 1 shows a section of the capsule of a lymph node. The lymphoid tissue is depleted and the cells, which are all of the lymphoid series, may be identified as leukemic cells. There is infiltration in the capsule and in the perilymphatic fat. A section of the lymph node (Fig. 2) shows total destruction of the normal architectural pattern. The cells are all small and uniform in appearance and thus are typical of those seen in chronic lymphatic leukemia.

In the next section (Fig. 3), taken from the bone marrow, there are a few foci of active erythropoiesis but most of the marrow is occupied by leukemic cells of the lymphoid type; there is a decrease in the number of myeloid elements. In Figure 4, a section of the bone marrow under higher magnification shows typical small lymphocytes. The next section (Fig. 5) is from the liver and shows a small amount of leukemic infiltration in the portal spaces and passive congestion of the central areas. The sinusoids are greatly dilated and there is compression and necrosis of the liver cells in the central portions of the lobules. Figure 6 is from the spleen and shows a large follicle. The white pulp is markedly increased in

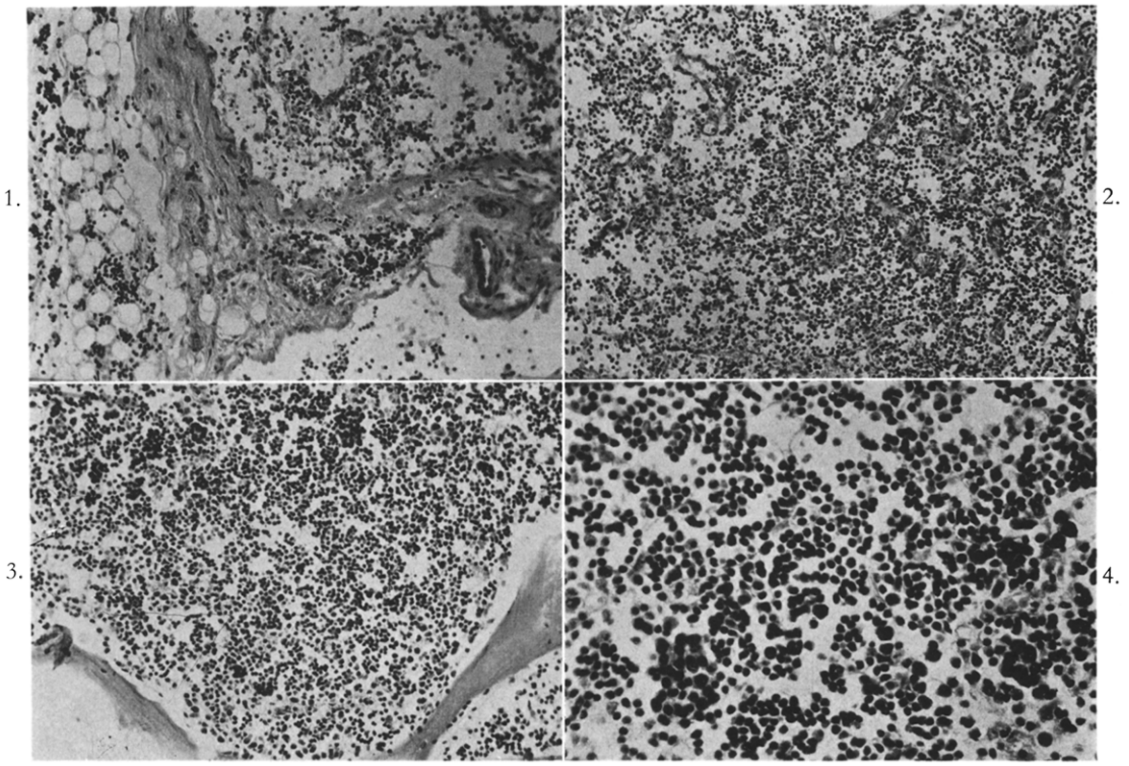

FIG. 1. Section of the periphery of a lymph node showing infiltration of the perilymphatic fat with leukemic cells. × 47.

FIG. 2. Section of the same lymph node showing destruction of the normal architectural pattern by leukemic cells. × 47.

FIG. 3. Section of bone marrow which shows leukemic infiltration. × 47.

FIG. 4. High power view of same section seen in Figure 3. There are a few foci of erythropoiesis but leukemic cells predominate. × 100.

amount because of the presence of leukemic cells and there is a relative decrease in the red pulp. From these microscopic sections the diagnosis of chronic lymphatic leukemia can be substantiated, and from an anatomic standpoint the disease would appear to have been under good control at the time of death for infiltration into the various organs was not massive.

In a section of the thyroid gland (Fig. 7), it is noted that the cells are cuboidal or flat, but the tall columnar cells, which are usually but not invariably associated with hyperthyroidism, are not seen. Occasionally cuboidal cells apparently are present in hyperthyroidism. There is no totally satisfactory method of correlating the clinical picture with the histologic findings in the thyroid gland. A section from the edge of the adenoma (Fig. 8) shows a number of small acini which are relatively free of colloid and it is seen that the acini are apparently isolated in rather acellular interstitial tissue. These are the characteristics of a fetal adenoma. There is no way to decide definitely whether or not the adenoma was toxic.

Figure 9 shows a typical section from the myocardium. The appearance suggests old destruction of some of the myocardial fibers and there is an actual increase in the amount of interstitial tissue. In the next section (Fig. 10) another region is seen in which edema and recent hemorrhage into the tissue are conspicuous. Whether these findings can be attributed to the digitalis

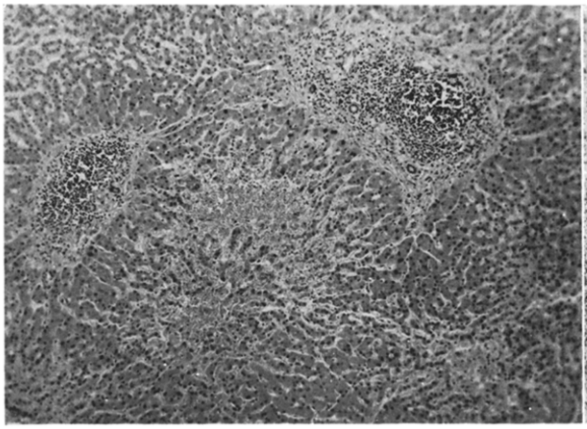

FIG. 5. Section of the liver which shows leukemic cells in the portal spaces and central necrosis. × 47.

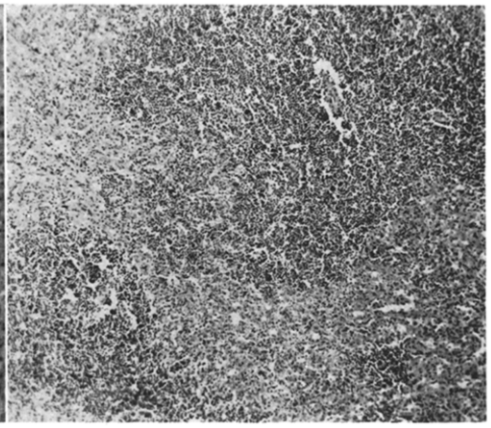

FIG. 6. Section of the spleen showing characteristic changes of chronic lymphoid leukemia. × 47.

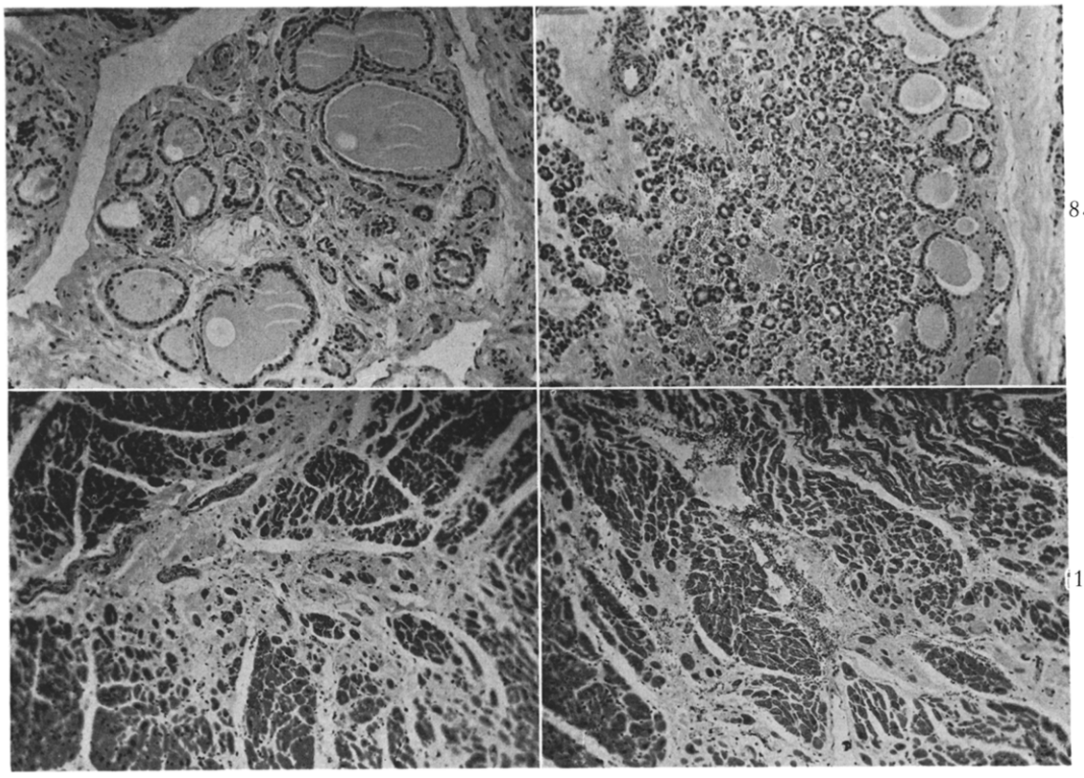

FIG. 7. Section of thyroid gland. No tall columnar cells are apparent. × 47.

FIG. 8. Section from the fetal adenoma of the thyroid. The acini are small and contain little colloid. × 47.

FIG. 9. Section of the myocardium showing increase in the amount of interstitial tissue. × 47.

FIG. 10. Another section of the myocardium which shows edema and hemorrhage. × 47.

glycoside cannot be stated. Occasionally such lesions are noted in the heart muscle of patients who have received a large amount of digitalis.

Returning to the differential diagnosis, many of the suggested possibilities must be excluded on the basis of the microscopic findings. Fiedler's myocarditis is characterized by considerable cellular infiltration, usually lymphocytes and eosinophiles, and such a diagnosis is not tenable here. Had a basal metabolic rate been determined, the existence of thyrotoxic heart disease could better have been established. It is true that in hyperthyroidism destruction and fibrous replacement in the myocardium is seen. Radiation effect and beriberi heart disease seem very unlikely.

DR. WOOD: It was recently brought to my attention that investigation by radiologists has indicated that the myocardium is one of the most radio-resistant organs in the body and that the amount of x-ray necessary to cause myocardial damage is tremendous. For this reason it would appear to me that a diagnosis of thyroid heart disease is much more likely in this case.

DR. R. A. MOORE: Unfortunately, the diagnosis of thyrotoxic heart disease cannot be made without qualification, but it is certainly suggested by a process of elimination.

DR. WOOD: In thyrotoxicosis there is stimulation of the entire lymphatic system which is well recognized clinically. The possibility that the onset of the patient's lymphatic leukemia may have had some relation to the thyrotoxicosis must be considered. Dr. Moore, would you comment on this possibility.

DR. C. V. MOORE: The possible relationship of lymphatic leukemia and thyrotoxicosis has been mentioned in the discussion, and it is true that on occasion total removal of the thyroid has been done in an attempt to alter the course of lymphatic leukemia. The operation has never been successful, however, and more recently the treatment of lymphatic leukemia with thiouracil has not been of value.

DR. FUTCHER: Differential diagnosis of arteriosclerotic and thyroid disease is often difficult and whenever a patient has cardiac enlargement, the basal metabolic rate should be determined.

DR. REINHARD: In this instance a basal metabolic rate would not have been particularly helpful since a reading of +40 to +60 could easily have been attributed to the leukemia.

DR. R. A. MOORE: In summary, from the gross and microscopic findings in this case, the diagnosis of chronic lymphoid leukemia is confirmed; the disease was well controlled at the time when the patient died. Although hyperthyroidism and associated thyrotoxic heart disease cannot be established without equivocation, the anatomic findings are compatible with those diagnoses.

Final Anatomical Diagnoses: Chronic lymphoid leukemia; fetal adenoma and cyst of the thyroid; hypertrophy and dilatation of the heart; chronic passive congestion of the lungs, liver and spleen; hydrothorax, bilateral, and ascites.