Gase Recurds of the Massachusetts General Hospital

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICO-PATHOLOGICAL EXERCISES

EDITED BY

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CASE 9441

A PORTUGESE-AMERICAN druggist of thirty-five entered April 17, 1923, for study.

F. H. Unimportant.

Occupational History. He had been a sailor and had come in contact with people from all over the world, although he had never been away from the New England coast.

- P. H. Negative except for constipation for years, accompanied at times by occasional dizziness and visual disturbance with light in front of the eyes and headaches lasting for a week; compound fracture of the right leg nineteen years ago; and an occasional cold.
- Two years ago he slowly developed a generalized eczema. His skin was dry and flaky, with occasional small boils and blisters and considerable itching. It cleared up partially at times. A year ago small firm nodules appeared on the legs from time to time and disappeared. For the first year he was treated with salve. Then he had vigorous treatment with the Alpine lamp for several months until his skin peeled. He seemed to improve a little at first, but later became worse. Then he had intravenous treatment at weekly intervals for three months ending four months ago, and improved considerably. This was followed by one intramuscular injection two months ago. The following week he received an intravenous injection (some form of arsenic). The next day he had a chill. He did not return for more treatment. A week after this, seven weeks ago, he noted some nodules on his right leg. Some disappeared, some persisted and grew larger. Others began to appear on his face, arms and body, so that within three weeks he was pretty well covered. Since then some of the lesions had broken down, including one on the right eyelid, and others had grown quite large and were covered with crusts. There was not much itching. His general health had not changed until a week ago, when he "caught cold." Since then he had been hoarse and had had a great deal of unproductive cough. He had taken Fowler's solu-

tion. He brought a negative Public Health Wassermann report dated April 5.

P. E. A poorly nourished man with hoarse voice and dry cough. Skin of forehead, lips and cheeks dry and scaling, with some crusting. Below the right ear a rounded doughy nodule in the skin the size of a plum, freely movable on the subcutaneous tissue. Similar growths on the inner end of the right eyebrow and right upper eyelid, the latter ulcerated, presenting a raw seropurulent granulating surface. Many flattened nodules not so well defined infiltrated the skin at the right corner of the mouth (where a fissure ran through it), the chin and neck near the midline and over the center of the left clavicle. The intervening skin of the neck especially presented in places a lichenoid infiltration. The scalp showed crusting and infiltration at the posterior hair border. On the left chest many flat pink scarcely palpable, scaling papules. sharply demarcated, round, oval or irregular in outline, several running together in places, looking not unlike faded psoriatic lesions. The right chest was clear except for one flatbroken-down paptened. slightly \mathbf{raised} ular lesion three and a half inches in diameter from which oozed foul-smelling seropurulent secretion. The abdomen showed three small flat oval patches. Just below the umbilicus were several irregular soft projections in the skin, which became more prominent when the patient stood. The back was much more extensively involved than the front, showing many dark-colored, almost macular, confluent patches, others pink, raised and well defined. Three had ulcerated areas. The skin on top looked macerated. Arms markedly involved, swollen. Forearms practically covered with pink tumor masses of various sizes up to three inches in diameter. Hands involved, extensor surfaces more than flexors, although there was a large ulcerated mass on the flexor surface of the left forearm, and one on the right upper arm. Right hand deformed by the nodules. Right leg extensively involved in front. Left leg showed the process in its most malignant form. On the back of the thigh was an area six inches in diameter, deeply excavated, with firm thick raised somewhat undermined edges and a black necrotic base with much pus. Below the knee was a similar smaller area. Teeth, many missing and broken, leaving black stumps. Marked pyorrhea, with much foul smelling detritus. Throat, chronically inflamed tonsillar pits and fauces. A few discrete pea-to-hazel-nutsized cervical and supraclavicular glands. One hazel-nut-sized \mathbf{right} submaxillary Groups of six to seven round and oval discrete firm elastic glands in the axilla from the size of a pea to an inch in diameter, not adherent. Three to four glands in each groin ½ to ¾ of an inch in diameter. Chest hyperresonant.

Lungs negative except for a few bronchial râles. Heart. Impossible to percuss borders. Apex impulse not found. A rough systolic murmur at the base. Pulses and arteries normal. Abdominal wall infiltrated. Considerable rigidity. Palpation not satisfactory. Extremities. Right leg slightly atrophied, bent. Foot deformed (equinus). Pupils and reflexes normal.

T. 97.1°-102.8° with daily evening rise. P. 95-132. R. 22-32, with a terminal rise to 42. Urine 3 17-97. Sp. gr. 1.010-1.025. Cloudy at five of seven examinations, the slightest possible trace of albumin at five, a few leucocytes to loaded with leucocytes at four, rare to many red blood corpuscles at two. Blood. April 17, hgb. 80%, leucocytes 30,000, polynuclears 57%, lymphocytes 6%, eosinophils (somewhat large and atypical) 30%, unclassified 7%, platelets slightly diminished, reds normal. At five later examinations leucocytes 33,200-44,200, polynuclears 45%-82%, lymphocytes 3%-6%, eosin-ophils 18%, 48%, 26%, 19%, 9%, unclassified 3%-7%, red count normal, slight achromia twice, platelets increased once, slightly diminished once, normal once. Bleeding time three minutes. Nasal smear negative for lepra bacilli. X-ray of heart and lungs normal.

The dry lesions were treated with salicylic acid ointment*, the ulcerations with Dakin's solution. After x-ray treatment the lesions on the right arm flattened definitely and some almost disappeared. The throat was better. Further x-ray treatment was given to the right leg, the face and the right arm. After treatment a nodule on the right wrist broke down and discharged foul smelling material. May 9 and 10 sodium cacodylate gr. ss was given s.c. once i.d., May 11-17 twice i.d. It was discontinued because of the appearance of red blood cells in the urine. May 18 the patient complained of sharp pain in the left ankle at times. The ulcerated areas stopped sharply at the muscle layer, so that large areas of muscle were exposed. Much pus could be squeezed out of the ulcers on the right leg. An area beneath the left jaw also suppurated. He looked remarkably well considering the enormous amount of pus formation in the various lesions. He slowly but steadily went downhill, however. May 27 Fowler's solution was given, three minims t.i.d., increased by one minim daily. June 1 there were large moist and bronchial râles in the chest. The left chest was dull posteriorly. . The pulse was very poor in quality. That day he died.

DISCUSSION

BY DR. RICHARD C. CABOT

NOTES ON THE HISTORY

"For study" means that they did not know "Salicylic acid, gr. x; bismuth subnitrate, 1 oz.; amyl, 2 ozs.; oil of rosewater, 1 oz.

what the diagnosis was when they sent the patient in, or did not want to commit themselves. We have to send a patient into this hospital for something, but when we do not want to commit ourselves we send him in "for study," which does not involve one in any embarrassment whatever.

The most definite disease hazard we think of when we think of a sailor is syphilis.

A part of his past history sounds like migraine, which is so often accompanied by those disturbances of light in front of the eyes.

We start the present illness without any special clues obtained from the past history as to what he is going to suffer now.

Dr. Oliver, is it common for a generalized eczema to show itself for the first time as late in life as this?

DR. E. L. OLIVER: I should not say it was very uncommon.

Dr. Cabot: But it is commoner to show a tendency of the system to that sort of thing by something in childhood or youth. You would be a little surprised, though not much, if a man came with the first appearance of eczema at thirty-three.

DR. OLIVER: Yes. The diagnosis of eczema at times is pretty difficult to make. Perhaps it was wrong here.

DR. CABOT: But if we could not call it anything else than that we might have to say "eczema," I suppose. This being a dermatological case up to this point I am going to ask Dr. Oliver to help me. Is there any intravenous treatment that will help eczema?

Dr. Oliver: Sometimes arsenic will.

Dr. Cabot: So that treatment does not prove that he did not have eczema?

DR. OLIVER: No. Especially in the dry scaly cases it does sometimes help.

Dr. Cabot: What are the chances of his getting arsenic intramuscularly?

Dr. Oliver: It is more likely to have been mercury in some form.

DR. CABOT: That is what I thought. It seems as if he were being treated for syphilis now rather than for eczema. As to chills following arsenic preparations, don't they usually come sooner than the next day?

DR. OLIVER: Yes; we expect them in five or six hours. But if he had arsenic late in the afternoon he might go to sleep and wake up with a chill the next morning.

Dr. Cabot: There has been some question of nodules before, also. Is it true, as I should suppose, that this last act cannot be called eczema?

Dr. Oliver: I don't see how it can be.

Dr. Cabot: He has certainly got something else than eczema now.

The "cold" is put in quotation marks because we all know how many diseases are mistakenly covered up by such a term as that.

Let us sum up what we have to say about this

from the present illness before physical examination. We have to say that he had a long, itching, scaling disease, which, because it itched so much, probably was not syphilis at the beginning.

Dr. Oliver: No. Itching in syphilis is very rare.

Dr. Cabot: Then he had something which in all probability was treated for syphilis, which was characterized by nodules breaking out in all parts of the body, and which we certainly suspect of being syphilis. At the end he has a cold, cough, and hoarseness. I do not think we can argue much from that,—possibly some little respiratory infection of the type we call a cold. The only fundamental things we have are these skin lesions, the skin lesions very probably of syphilis.

NOTES ON THE PHYSICAL EXAMINATION

Anybody having syphilis who develops hoarseness, especially if it is a long-standing hoarseness, always makes us think of aneurism, because aneurism is a result we are always fearing in syphilis.

The distribution of the lesions is mostly on the head, some on the chest, very few, only three, on the abdomen.

I do not see how they can tell that his throat is "chronically inflamed" by the appearance.

We certainly have glands in the axillae and groins as well as in the neck, though I do not know that we need anything more than these widely distributed lesions to account for them.

There is nothing particularly significant about the heart.

The foot deformity accounts for the right leg's being bent, I suppose.

One of the things I have been looking for is the spleen. When a patient has general glandular enlargement which may or may not be due to superficial lesions we want to know whether the spleen takes part or not. No evidence here.

He had a pyrexia a good part of the time.

From the urine I do not see any reason to suppose a nephritis. We can have all these from various affections of the genito-urinary tract.

In the report of the blood examination the polynuclears are only fifty-seven per cent., an unusual state of things with leucocytosis, and the eosinophils are high in all counts.

Is the negative nasal smear enough to exclude leprosy, Dr. Oliver?

Dr. OLIVER: We often find the bacilli in nasal smears, perhaps in fifty per cent.

Dr. CABOT: Is there much in this case to suggest leprosy so far?

Dr. OLIVER: No. I think it should, so far as possible, be ruled out, but there is not much to suggest it here.

Dr. Cabot: This does not attack the fingers or the face in the way that leprosy usually does.

Dr. Oliver: No.

DR. CABOT: Many of the nodules in other places not treated by x-ray broke down and discharged, so there is no reason for blaming the x-ray.

Sodium cacodylate is a form of arsenic which many doctors like. The red blood cells in the urine may have had something to do with the use of arsenic, though I do not see how we can be sure.

DIFFERENTIAL DIAGNOSIS

I am incompetent to make any proper differential diagnosis on this case, but for my own good I will say the little I know first, and then ask Dr. Oliver to discuss it.

In the first place, syphilis of course is in our minds. It was in the minds of those who treated him. Can it have been syphilis from start to finish, and nothing else? I never knew a case of syphilis to die so quickly with skin lesions alone and no evidence more than this patient has of internal lesions.

If it was not syphilis, what else could it have been? Well, it might have been some form of ulcerating neoplasm. He had lesions in his glands in various places. We do not know about his spleen. We have nothing to suggest any foci in his internal organs. His blood is perfectly consistent with a lymphoma with skin lesions, malignant lymphoma, which we often call Hodgkin's disease. I do not see any way in which that can be excluded. I think it would be my diagnosis if I had no one to advise me.

The excess of eosinophils has been a feature throughout. Eosinophilia is one of the most picturesque and mysterious pictures in the whole of medicine. It occurs in five great groups of cases: (1) In the first place, after any infectious disease. During infectious disease eosinophils usually disappear from the blood and then appear in increased numbers afterwards. So that we have been in the habit of saying that they have something to do with immunity. (2) Then it is very common in animal parasitic disease, either in the intestines or elsewhere, the commonest being trichinosis, then hookworm, and including the hydatid of Australia and other countries. (3) Then the great group of chronic skin diseases in which it used to be thought of some diagnostic value because it seemed to appear in certain ones, but in which I think it has very little value because we know it appears in so many. (4) Then it is common in neoplasm, especially in the particular type of neoplasm we call leukemia, which is neoplasm with circulating metastases. And finally (5) it has a mysterious way of appearing in enormous degree in bronchial asthma.

Those whose minds run to theory like to try

to bring all these things together and describe some x behind them all, but I do not think successfully. In this case it may be a feature of Hodgkin's or malignant lymphoma with skin infiltrations, or the consequence of some other chronic skin disease which I do not know enough to recognize. Being a sailor he may have got all sorts of rare skin diseases which we do not see in this part of the world, which I do not know anything about.

Is this a case you took care of in life, Dr. Oliver?

Dr. Oliver: Yes.

DR. CABOT: Then will you take us at this

point?

Dr. OLIVER: The story in this case and the patient's appearance make the dermatologist think of one disease and of almost no other,that is granuloma fungoides, which is one of the most horrible diseases or perhaps the most horrible to see and take care of that I know. This disease is pretty well mixed up in some eases with Hodgkin's and what we call leukemia of the skin, of which we had some examples at the same time in Ward G. In those cases the medical men said—although the lymphocytes were in some of the cases I think in the hundreds of millions, a very large percentage of lymphocytes —the medical men said that the cases were entirely different from the lymphoid leukemia that they see. But we recognize it as a definite skin disease. Some of the leukemias of the skin which we see have an appearance very much like leprosy. They show the wrinkled, leonine appearance that we associate with leprosy. saw a case in New York recently which we all thought was probably leprosy, but which furned out to be a leukemia. This case, however, is more typical of granuloma fungoides in that it ulcerated rather early. The course of granuloma fungoides is divided into four periods The first is a period of generalized erythema or perhaps scaly lesions, psoriasiform lesions, usually with a good deal of itching. That may last for five years perhaps before anything else happens, the lesions being perfectly fixed and more or less unchangeable. It may clear up and return. The second stage is one of infiltration of the skin either in patches or generalized. The third stage is that of tumor formation, with nodular tumors varying from the size of a pea to that of an orange. The fourth is the terminal stage, when the tumors become ulcerated. The course of the disease is very variable. It may last from five to ten years or it may run a very rapid course. have seen one case that died I think within four months of the appearance of the first lesion of the skin. The first lesion, in fact, was a tumor which broke down rapidly; others appeared, and he was covered with these ulcerating tumors inside of a month or two, and died in four months. That is certainly unusual.

The cases that last longest have occurred since x-ray has been used, because x-ray is of very definite value. It heals the ulcers entirely in some cases, and the patient may stay well for a number of years without further treatment, or he may have to have treatment to keep the tumors in check. Some patients who were expected to die within two or three years have lived eight years or more under constant treatment. Unfortunately most of the cases we have had here have come to us so late in the ulcerating stage that x-ray has not been of great use.

This is a typical case, and the only other diseases to consider I think are leukemia of the skin, Hodgkin's disease, and multiple sarcoma. In the case I spoke of as being so rapid Dr. Mallory examined a specimen and said it was typical small round-cell sarcoma. But the lesion he examined and every lesion healed absolutely under x-ray without a trace except a scar where they had been, and other lesions broke out. That is not the history of sarcoma. Granuloma fungoides is a malignant disease of the skin without doubt. It acts like cancer and it is always fatal. No permanent recoveries are on record.

Many of these cases show towards the very end an increase of lymphocytes in the blood. The eosinophilia, as Dr. Cabot said, is so common in so many skin diseases that I do not think it counts for very much. This patient did not at any time show any great increase of lymphocytes, as I remember it. That is the only way we can differentiate between granuloma fungoides and leukemia of the skin; but the course in this case is more in keeping with what we associate with granuloma fungoides. I should not suppose the glands were anything more than we should expect in any chronic itching skin disease where there is scratching all the time,—simply hyperplasia.

Dr. Cabot: That is a point of great importance, I think, and we shall probably be able to

verify it post mortem.

Dr. OLIVER: I have no idea what the postmortem was. Most of these cases who have died here and been necropsied have shown practically nothing except the skin lesions and hyperplasia of the glands.

This was a horrible case. These lesions went down to the muscle, and the odor was frightful. The man was extremely cheerful and seemed to feel pretty well as a matter of fact, but he

simply rotted to death.

A Physician: May I ask how you ruled out sarcoma?

Dr. OLIVER: I think the multiplicity of the lesions and the rapid ulceration are very much against that; also the previous skin trouble. Sarcoma usually does not begin after this long period of chronic skin disease. It appears rather suddenly, out of a clear sky. There is a

multiple sarcoma, sarcomatosis, that may spread all over the body, but its history is usually different.

A Physician: Has a causative factor been found?

Dr. OLIVER: No. It is considered by many to be an infectious disease, but if it is the infectious element has never been found. It seems to me it is more like cancer. It comes in women and men equally, almost always after the thirtyfifth year, we might say in the cancer period. It is unknown in childhood and in youth. I do not think I have ever seen any case reported under thirty-five. This man was just on the borderline.

Dr. Cabor: Years ago I began to be interested—and should have kept on if I had kept more actively in medicine—to reform our medical terminology, and especially in the attempt to get together the terms started by different specialties like dermatology and laryngology each for its own purpose and with the idea that there is such a disease of its locality alone. I think the sort of getting together that we have done a little of here today is very valuable. For instance, if this thing is pathologically the same as Hodgkin's disease, then, it seems to me, to keep up a special name for it, like "granuloma fungoides" merely when it happens to appear on the skin a great deal, is not desirable. I do not know how to settle these questions except by necropsies and consultations at necropsy between a general clinician and a dermatologist. Of course clinicians see cases which everyone 1. would call Hodgkin's disease—long-standing glands in the neck and enlarged spleen-sometimes complicated by itching, by scaling, by cutaneous lesions which break down. Typical leukemia also, as Dr. Oliver has said, may have 2. ulcerating skin lesions. It would be a great thing, therefore, if we could come to a common terminology and say, "There is a special form of cutaneous lymphoma which we have called 'granuloma fungoides,' " or to say that we will not give such names to special localizations of one underlying disease. The microscope, so far as I see, is the only thing that can settle it. The facts of treatment are all in favor of that unification that I am trying for. Among tumors I do not know any that yields more readily and rapidly to x-ray than Hodgkin's. That fact would tend to make us rather unify this case with the other forms of lymphoma than separate it from them.

Dr. Holmes, is there anything to say about the x-ray treatment of the disease which this case exemplifies?

Dr. Holmes: Not much more than Dr. Oliver The tumors of this disease are susceptible to radiation. The same is true of Hodgkin's. As Dr. Oliver has pointed out, we should get them before the tumor has broken

does not require a very large dose to affect them successfully. I think it is advisable to keep well under the dose that would give erythema. think a good many unsuccessful results are brought about by giving too large a dose. We have found recently in the treatment of Hodgkin's disease that we can get satisfactory results by giving about one-eighth of the erythema dose, not over one-tenth of what we give to the carcinomata. Such a dose ought to be absolutely safe locally and also generally. As has already been said, they do respond very rapidly to the treatment.

Dr. Cabot: The issue Dr. Richardson is going to be able to decide for us is parallel to the issue that for years made people call tuberculosis on the skin "lupus," in the lungs "consumption," in the bone "hip disease," without recognizing that they were all one thing. If we can unify these different forms of lymphoma it is very desirable.

CLINICAL DIAGNOSIS (FROM HOSPITAL RECORD)

Mycosis fungoides. Bronchopneumonia?

DR. RICHARD C. CABOT'S DIAGNOSIS

Malignant lymphomata of the skin.

ANATOMICAL DIAGNOSIS

Primary fatal lesion

Mycosis fungoides (malignant lymphoma of skin.)

Secondary or terminal lesions

Degeneration of marrow of femur. Abscesses in the retroperitoneal tissue (left) and in the anterior abdominal wall. Suppurative pneumonia. Serofibrinous pleuritis, left. Acute pericarditis. Fatty metamorphosis of the liver. Wet brain.

Historical landmarks

Slight chronic pleuritis. Chronic hyperplasia of the spleen.

Dr. RICHARDSON: The skin of the face, neck, body, extremities, showed numerous smaller and larger tumors discrete and confluent, and smaller and larger areas of necrosis and ulceration in what was apparently tumor tissue. Some of these areas were very large and extended deeply into the subcutaneous tissues. The skin condition in this case very much resembled that in down; after that we do not get good results. It the previous necropsy, the difference being that in the other case the spleen, liver, and lymphatic glands were markedly involved. The main lesions here were in the skin, and it is rather a typical picture of malignant lymphoma of the skin, for which the old name is mycosis fungoides.

There was deformity of the right tibia, said to be an old fracture. The left thigh was a little larger than the right. There was no definite edema.

Examination of the head showed a wet pia and wet brain tissue.

The marrow of the femur was fatty and showed here and there a few reddish areas. There was no definite infiltration of this marrow with lymphoid cells. There was some degeneration of the fat tissue of the marrow.

The retroperitoneal glands were slightly to moderately enlarged, but examination of specimens taken from the glands showed no evidence of invasion by lymphoid cells. The axillary glands were slightly enlarged, but we found no cells in them of the same nature as those in the skin.

The left pleural cavity contained 1500 c.c. of thin cloudy fluid and fibrin. There were a few adhesions on the left. The trachea and bronchi contained much muco-pus; that is, there was a purulent bronchitis. The bronchial glands except for being slightly enlarged were negative. The right lung was negative at the apex. Scattered through this lung however were areas of what for want of a better name we call suppurative pneumonia,—pneumonia gone on to The left lung had a somewhat suppuration. similar appearance and in addition to that a large abscess in the retropleural tissues which bulged into the cavity. It was 11 cm. by 3 cm. in diameter and 3 cm. deep, and contained pus.

In the anterior abdominal wall there was another collection of pus. The microscopic examination gave no hint as to whether there was any tumor tissue there or not.

The pericardium contained a little cloudy fluid and fibrin,—a slight acute pericarditis associated with the infection present here. The heart weighed 240 grams and was negative. The circulatory apparatus in general was negative.

The liver was large, 2025 grams, but we were unable to make out any infiltration with lymphoid cells. There was a little fatty metamorphosis. The spleen was slightly enlarged, 360 grams, and at one place in the tissue there seemed to be some evidence of the presence of lymphoid cells, but not very well marked,—in contradistinction to the other case, where there were many.

The kidneys microscopically looked all right, but we found one or two foci of lymphoid cells, suggesting that if he had lived longer there might have been many more. There was a little patch of hemorrhagic edematous mucosa in the bladder.

CASE 9442

A Norwegian housewife of thirty-seven, entered March 29, 1910.

F. H. Her father died at fifty-eight, after being ill many years with chronic cough. She was not at home at the time.

P. H. She had the diseases of childhood, and had always been subject to colds. Last year she had "grippe and influenza."

HABITS. Good.

P. I. Four days before admission, after feeling perfectly well, she felt as though she were going to be ill. Her menstrual period began, but there was scarcely any flowing. The next day she had a very severe headache. She had vomited several times after taking medicine.

During the history taking she was dull, apathetic, wandering, and forgetful. She did not grasp questions. Her answers were irrelevant, and very slow and halting.

P. E. Fairly well nourished. Tongue, dry brown coat. Apex impulse of the heart not seen or felt. No enlargement to percussion. Sounds at the apex fair in quality. P₂ greater than A₂. Systolic B.P. 165. Lungs. Slight dullness, a few crackles and consonating râles, vocal and tactile fremitus slightly increased at both apices, front and back, with bronchovesicular breathing in front and bronchial breathing in the back; signs more marked posteriorly. Abdomen. Slight tenderness in the epigastrium. Genitals not recorded. Extremities. No edema. Pupils. Normal reactions. Reflexes. Knee-jerks not obtained. Double Babinski?

T. 100.7°-102°, with slight afternoon rise on three of the five days. P. 110-131. R. normal. Urine. 3 30 on the one occasion recorded. Sp. gr. 1.011-1.013. Slightly cloudy at one examination, neutral at one, alkaline at the other, a very slight trace to a trace of albumin at both. Blood not recorded. Spinal fluid. 2-3 c.c of clear colorless fluid not under increased pressure, not coagulated after fifteen hours. Two hundred leucocytes per cu. mm., 80 per cent. mononuclears, 20 per cent. polynuclears.

The morning after admission the patient was mentally clearer. Fundus examination showed considerable blurring of the edges of both discs with marked tortuosity of the vessels, and in the left eye a hemorrhage in the center of the disc.

The afternoon of April 1 the patient developed a complete left-sided hemiplegia. The white count rose to 13,000. She failed gradually, showing no new signs or symptoms, and died April 2.