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CARCINOMA OF THE PANCREAS WITH UNUSUAL CENTRAL NERVOUS SYSTEM COMPLICATIONS. CLINICAL PATHOLOGICAL CONFERENCE

ROBERT K. NIXON, M.D.* BOY FRAME, M.D.* AND JOSE BEBIN, M.D.**

CASE PRESENTATION — (Dr. Nixon)

A 61 year old white male parking lot employee was seen in the Henry Ford Hospital Emergency Room complaining of "blind staggers". He gave a history of having pain in the sacral region during the preceding 3 months. The pain did not radiate. Three weeks before admission the patient had a head cold with a cough which aggravated the numbness of the anterior aspects of both legs down to the knees. One week before admission the patient began to experience a spinning sensation while standing on a ladder painting with his head in a hyperextended position and this the patient referred to as "blind staggers". He had continued to notice this sensation and it was usually associated with looking upward. Approximately 2 days after the onset of the dizziness, the patient noted a frontal headache and this gradually increased. At the time of admission, the patient stated that he felt "sea sick and nauseated". There had been no vomiting. He had taken a considerable number of aspirins without relief. There had been no tinnitus or hearing loss, no aphasia, dysarthria, bowel or bladder disturbance, or seizures and no weight loss.

Past history: In 1939 patient was in V. A. Hospital for 3 months with a diagnosis of "nervous neuritis". In 1921 a T & A was done and afterwards he spent 3 months in the V. A. Hospital because of albuminuria. There was no history of high blood pressure. The patient was known to have a mediastinal mass for the past 19 years which had been checked frequently at Herman Kiefer Hospital and was thought to be of no importance.

Physical Examination: Blood pressure 140/92, pulse 20 to the quarter and regular, temperature normal, thyroid not enlarged, lungs clear to P & A, heart not enlarged, N.S.R., no murmurs heard. Abdominal examination negative, rectal examination showed prostate enlargement of 1 plus.

Neurological examination: Gait normal. Patient able to do heel and toe walking well and tandem walking fairly well. On Romberg the patient had a sway but did not fall. Funduscopic revealed normal disc with grade 1 angiopathy. No hemorrhages or exudates were present. The first cranial nerves were intact. A definite positional nystagmus in the lateral plane which changed direction on turning the patient's head to the opposite side was noted. A minimal vertigo element was present with the nystagmus on one occasion. Visual fields were grossly intact. The pupils round, regular and equal and react to L & A. There was a questionable diminution of the right corneal reflex. 5th, 7th, 8th, 9th, 10th, 11th and 12th cranial nerves were intact. The deep tendon reflexes were all 3 plus active with the exception of a questionable decrease in the left biceps. Hoffman sign was positive bilaterally. Abdominal reflexes, Cremasterics were present. Both plantars were down-going. The

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Nixon, Frame and Bebin

muscle strength was good in all extremities. There was some adiadochokinesis of the right hand and slight impairment of the heel-shin test on the right was present. No bruits were heard. There was some definite percussion tenderness over the left frontal area. Position, light touch, pain and vibratory sense were intact. No evidence of atrophy or fasciculations was seen.

The patient was admitted and the following studies were obtained: Hemoglobin 15.4 gms., WBC 8,600 with normal differential, urinalysis negative, BSP 4%, liver flocc. negative, bilirubin total .32 mgms. Sed. rate 10, cold agglutinins negative. Psittacosis complement fixation titer negative, febrile agglutinins negative. VDRL negative. 3 L.E. preps. negative. Three stools for occult blood negative. Platelet count normal. Skin tests for monilia, mumps, and histoplasmin positive. Mumps complement fixation test neg. Two lumbar punctures were done. The first contained 23 WBC with 18 polys and 5 monos, protein 106, sugar 75 with a simultaneous blood sugar of 180. Second L.P. showed: protein 37, cell count 84 with 77 monos and 7 polys.

Culture of cerebrospinal fluid negative. No acid fast bacilli seen on smear. Cytology of the cerebrospinal fluid negative, for malignant cells. Special smear: platelets adequate, 1 band, 72 neutrophils, 1 eosinophile, 16 lymphocytes, 10 monocytes, essentially normocytic. No hematuria. PPD positive. Serum proteins 6.6 with 3.84 albumin and normal globulin fractions. Two repeat urinalyses negative.

Chest x-ray: large calcified node in subcranial area. Fairly well circumscribed infiltrate in the left upper lobe which was present on film taken 1 year previously and non-increased in size. Skull film essentially negative. Sinus films: soft tissue mass in the nasopharynx. Lumbar spine films; mild rotoscoliosis involving the lumbar spine. Defect involving the pars media of the 5th lumbar vertebrae seen on the right. Laminograms of the left hilum showed slight elevation of the left bronchus. Repeat chest x-ray 1 month later showed no change.

Pneumoencephalogram: mild cortical atrophy. EEG: negative. Biopsy of nasopharyngeal mass revealed chronic inflammation of nasal mucosa. Repeat biopsy — same report. Muscle biopsy from left leg showed fibrofatty tissue and muscle. Bronchoscopy: negative. Bronchial washings negative on Pap. smear and negative culture for AFB. Gastric washings negative for AFB on culture. Sputum negative on smear and culture, for AFB. Fungus cultures of sputum negative. Bacterial culture of sputum showed normal flora.

Course in the hospital: The patient was anorexic and seemed to stagger when he walked. He complained of persistent headaches and general malaise. He was noted to lie in bed with his legs drawn up on the abdomen as if this was the position of maximum comfort and complained of backache. Toward the end of the hospital stay some fasciculations were noted in the left calf.

Following discharge the patient became worse and was admitted to a V. A. hospital four weeks later. There he complained of an increasingly severe pain in the back and hip and difficulty in swallowing. He was noted to have slurred speech and shuffling gait and was ataxic. The left pupil was larger than the right and did

Carcinoma of the Pancreas

not react to light and accommodation. There was slight ptosis of the left lid. The uvula and soft palate deviated to the right on phonation. The tongue also deviated to the right. Liver palpable 1 finger breadth below right costal margin. Poor rectal sphincter tone. Bilateral inguinal nodes and soft nodes in the left axilla were noted. A positive Romberg was present. Reflexes were present and bilaterally equal. A slight adiadochokinesia was present bilaterally. No anesthesia noted. X-rays at the V. A. revealed streaky densities resembling fibrotic deposits in the left upper lobe. X-ray of the lumbar spine revealed a fracture of the upper plate of the body of L3 on the right. Laminograms of the left upper lobe revealed an irregular cavitating mass.

At the V. A. hospital, the patient noted increasing difficulty in starting his urinary stream and passing feces. He developed inability to swallow and intubation was necessary. He expired quietly following what appeared to be a bout of aspiration pneumonitis.

DISCUSSION — (Dr. Frame)

For today's Clinical Pathologic Conference, we have a 61 year old male with apparent pathology in the mediastinum, the lungs, central nervous system and bones. In addition, there was a mass in the nasopharynx, which was negative for malignancy on two biopsies. Our problem is to define the pathology in each of these areas and, if possible, try to connect them into one etiology.

A large, calcified mass had been present in the superior mediastinum for at least 19 years. There were no characteristic calcifications of a teratoma. The features of the mass with the diffuse calcification suggest the possibility of a large calcified node, due to chronic infection, with tuberculosis and histoplasmosis, as the best possibilities. This mediastinal mass may or may not be related to the pulmonary pathology.

Let us next evaluate the infiltrate in the left upper lung field. We are told very little in the way of respiratory symptoms or physical findings, so we will have to concentrate primarily on the x-rays. This infiltration had been present for at least one year and seemed to increase slightly in size and, terminally, cavitation was suggested. The main differential seems to be whether this infiltration was chronic infection or malignancy. The slowly progressive course over a period of a year is perhaps more compatible with chronic infection, such as tuberculosis or histoplasmosis, which may have broken down terminally into cavitation. However, the many negative sputum and culture studies for acid fast and fungi would be somewhat unusual in a progressive active infection of this nature. Secondary to the patient's neurologic disease was moderate dysphagia. This brings up the possibility of aspiration pneumonitis, which occasionally does occur in the upper lobes, particularly in a patient who is confined to bed. The pneumonitis may have broken down and resulted in a pyogenic abscess; or possibly a foreign body with pulmonary abscess could have been present.

The other strong possibility in this patient, to explain the infiltrate in the left upper lobe, is that of pulmonary neoplasm. The negative bronchoscopy and smear for tumor cells is somewhat against this diagnosis but does not rule it out. The absence

of any pulmonary symptoms whatever is somewhat unusual in pulmonary neoplasm. The other consideration would be the presence of a chronic infection, such as tuberculosis plus superimposed pulmonary neoplasm, either primary or metastatic. Such a combination is being described more frequently in the literature. We can only conclude at this point that the available information does not readily separate the diagnosis of tumor from chronic apical tuberculosis and that the presence of both is a good possibility.

At this point, let us consider the pathology of the central nervous system. We have essentially a spotty cranial nerve involvement with signs of cerebellar insufficiency, associated with pleocytosis and a variable elevation of the cerebrospinal fluid protein. There were no signs of meningeal irritation but, nevertheless, the presence of chronic meningitis has to be strongly considered. An infectious agent, such as tuberculosis or torula, could possibly give a basilar meningitis with spotty cranial nerve involvement and the pleocytosis of the spinal fluid. However, the absence of a specific agent on direct smear and culture is strong evidence against the presence of such an infectious meningitis. In addition, the absence of a more striking reduction of the cerebrospinal fluid sugar is additional evidence against such a diagnosis.

Another consideration to explain at least part of the central nervous system involvement would be that of a meningeal carcinomatosis from possibly carcinoma of the lung. The cranial nerve involvement, in addition to the cerebrospinal fluid changes are compatible with this, but ordinarily in this condition, the cerebrospinal fluid sugar is also frequently lower than that reported here. However, to be taken into consideration is the fact that the blood sugar, at the same time the cerebrospinal fluid sugar was determined, was moderately elevated. The patient had quite striking evidence of cerebellar insufficiency. This raises the possibility of metastatic disease to the cerebellum but there were no headaches or signs of increased intracranial pressure. We, therefore, consider strongly the possibility of a cerebellar degeneration, which is being described more and more frequently with various malignancies. This is a strange type of degeneration that may occur in the cerebellum, the long tracts of the spinal cord, the peripheral nerves and muscle in a variety of malignancies without actual metastatic invasion of these organs. The pathogenesis of this condition has not as yet been defined.

We must consider other sources for metastatic spread to the central nervous system. We are told of a nasopharyngeal mass. This must have been quite impressive since the nose and throat consultant biopsied this mass on two occasions. The mass also looked quite impressive on the skull x-ray. We ask ourselves if this patient could have a primary carcinoma in the nasopharynx, the so called Schmincke's tumor, which spread to the central nervous system. The spotty type of cranial nerve involvement and the pleocytosis in the spinal fluid is classic for this type of tumor. The negative biopsy does not disturb us, since it is well known that these tumors may be quite difficult to biopsy and several negative biopsies are not unusual. The lack of local signs relating to obstruction of the nares or internal auditory meatus also should not deter us from making this diagnosis, since tumors are frequently silent and may give no local clue as to their presence. Distal metastases to bone

Carcinoma of the Pancreas

are common in this type of malignancy and this might well be the explanation of the persistent progressive back and hip pain. The negative skull x-rays are somewhat disconcerting but, again, this tumor may invade the various foramina at the base of the skull impairing the function of one or more cranial nerves without causing any actual erosion of the skull. Ordinarily, these tumors spread locally to the cervical lymph nodes; none were described in this patient. However, about a third of these patients in some series have no cervical lymph node involvement. So on the basis of the information, we would have to strongly consider the possibility of a nasopharyngeal carcinoma with spread to the central nervous system, bone and possibly lung.

Another possibility is that a primary pulmonary neoplasm, which has already been discussed, could metastasize to the nasopharyngeal area and then spread to the central nervous system, as outlined for primary nasopharyngeal tumor.

In addition to the above considerations, we would like to list several possibilities which one might consider as he reads the protocol but for which information is not sufficient to make a definite diagnosis:

1. A malignant degeneration of a teratoma with spread to the left upper lung and central nervous system, but again, the calcification in the mediastinal mass is not that of a teratoma.
2. We considered the possibility of a granulomatous process in the nasopharynx and lung, something in the nature of a necrotizing vasculitis or Wegener's arteritis but, ordinarily this gives an ulcerative process in the nasopharynx in association with peripheral neuritis and a terminal glomerulitis.
3. One must consider unusual fungus infections involving the nasopharynx, the lung and the central nervous system. We are told of one elevated blood sugar but are given no other information with regards to the possibility of diabetes-mellitus. Nevertheless, one particular type of fungus, namely mucormycosis, has a predilection for the nasopharynx, as well as lung and seems to occur more frequently in the presence of diabetes.
4. Terminally, inguinal and axillary nodes were described, which raises the possibility of a lymphoma which could spread to the central nervous system in such a fashion depicted.
5. We are told that the patient preferred to lie with his legs drawn up over the abdomen, as the position of maximum comfort. This unusual position raises the possibility of a retroperitoneal neoplasm, especially in the pancreas, which might then spread to bone, lung and central nervous system, as already described. However, with no further information given, we can only offer this as speculation.

We must then, of the various possibilities suggested, try to make a final diagnosis in this case. It is difficult to be dogmatic, but two possibilities seem to be foremost: *One*, that the patient had a primary pulmonary neoplasm with metastatic spread to the meninges of the central nervous system, bone and possibly the nasopharynx; the tumor then spread from the nasopharynx to the base of the brain giving rise to the

cranial nerve involvement. The *second* possibility would be a primary nasopharyngeal carcinoma which spread to the lungs, bones and central nervous system; statistically, the former would be the more common. We believe that, in addition, the cerebellar symptomatology in this patient is on a degenerative basis, secondary to malignancy without actual metastatic invasion of the cerebellum. Since the pulmonary picture, particularly the radiologic findings, seem somewhat more compatible with an infectious process, we wonder if the patient did not have additional infection in the upper lobe, either reactivation of tuberculosis or terminal aspiration pneumonia and abscess.

DISCUSSION AFTER PATHOLOGY

This case demonstrates how silent carcinoma of the pancreas can be. Ordinarily, with this neoplasm one expects greater weight loss and abdominal pain, but obviously, it can occasionally behave in a fashion as described by Dr. Bebin. Unfortunately, the nature of the nasopharyngeal mass, indeed if there even was one, must remain an enigma since this area was not examined at autopsy.

FINAL PATHOLOGICAL DIAGNOSES — (Dr. Bebin)

Aspiration pneumonia and multiple lung abscesses (cause of death); Left pleural effusion; Adenocarcinoma of the head of the pancreas with carcinomatosis: Meningeal, Cerebrospinal, Lung, Adrenal, Bone (lumbar spine); Generalized arteriosclerosis; Multiple retention cysts of the left kidney.

The autopsy was performed at the Veterans' Administration Hospital in Dearborn, Michigan. There were no unusual findings on the external examination of the body. The left pleural cavity contained 200 cc. of clear, bloody fluid and a few fibrous adhesions in the apical regions. The protocol does not mention the mediastinal mass found in the x-ray examination. The lungs were described as being heavy and firm. They did not collapse on opening of the chest. The pleural surface of both lungs were thick and opaque. On section of the lungs, the cut surfaces were marred with many red-yellowish areas of increased density. Multiple abscesses were also present throughout the lung fields; these were filled with a semi-solid yellowish pus; however, the exudate was odorless. Only the upper lobe of the right lung contained a substantial amount of air. On microscopic examination, almost the entire lung parenchyma was replaced by a diffuse aspiration type of pneumonitis and multiple abscess. In some areas between the inflammatory processes there were foci of metastatic neoplasm with the characteristics of an adenocarcinoma very similar to the one found in the pancreas.

The heart and vascular system were considered normal except for a moderate degree of arteriosclerosis. The gastrointestinal system, the liver and the spleen were normal on microscopic examination. The pancreas was normal in size and shape. The head of the pancreas appeared to be much more firm than the remaining portions of this organ. The parenchyma of this portion has lost its normal architecture, contrasting with the normal appearance of the body and the tail of this organ. On microscopic examination, the parenchyma of the head of the pancreas was replaced by a neoplasm made up of duct-like structures lined by columnar and sometimes cuboidal cells, supported by a dense, fibrous stroma. In some of the nerves of the

Carcinoma of the Pancreas

peri-pancreatic tissues there was marked invasion by neoplasn. This tumor was classified as a ductal adenocarcinoma arising from the head of the pancreas.

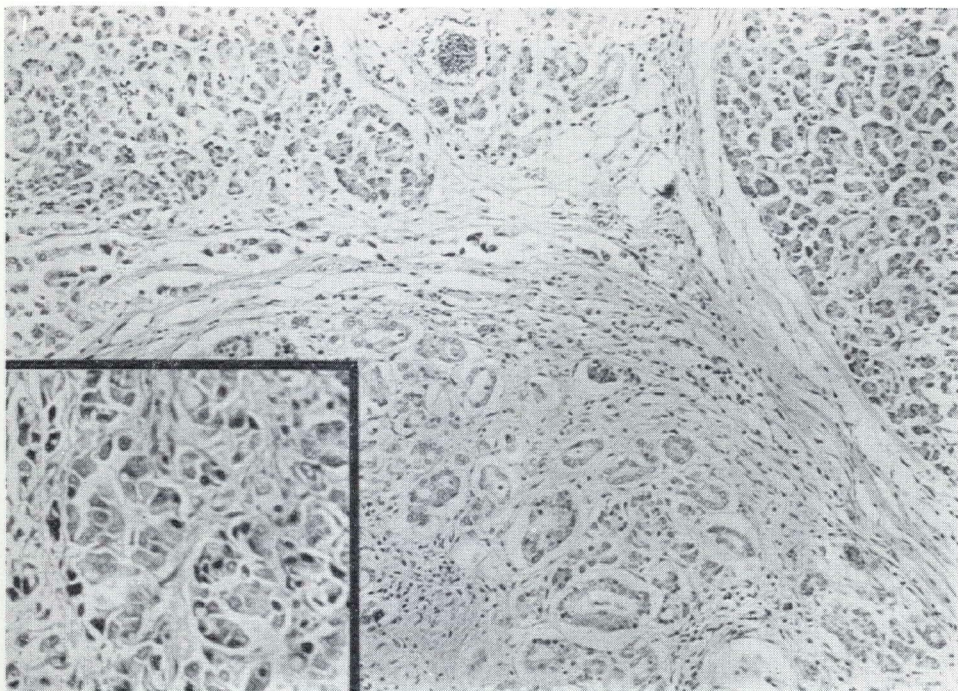


Figure 1

Ductal Adenocarcinoma of head of pancreas.

The genital-urinary system was unremarkable except for a few small retention cysts filled with clear greenish fluid present in the left kidney. The endocrine system was normal except for the right adrenal gland which, on microscopic examination, showed evidence of metastatic invasion by the pancreatic neoplasm. The vertebral body of the lumbar spine revealed a replacement of the bone marrow by tumor.

Central nervous system; the brain weighed 1300 grams and was described as moderately atrophic and congested throughout. On the left occipital lobe there was a 5 mm. metastatic lesion. No other focal lesions were seen on the cerebrum, brain stem, or cerebellum. The circle of Willis showed moderate arteriosclerosis. The leptomeninges of the brain and, particularly of the spinal cord, demonstrated diffuse infiltration by neoplastic elements mingled with some inflammatory cells. The neoplastic cells were several layers thick around the anterior spinal artery and the spinal meninges. They also infiltrated heavily the spinal roots and the spinal ganglia. Similar neoplastic elements were found infiltrating the meninges at the base of the brain and especially around the brain stem and the cranial nerves.

There was some congestion throughout the brain. In the left occipital lobe around the metastasis there was considerable edema. The tumor itself was very similar to the pancreatic tumor. The cerebellar cortex showed areas with loss of

granular and purkinje cells, and occasional nests of neoplastic cells. There was some degeneration of the marginal zone of the spinal cord, particularly in the areas adjacent to the more heavily infiltrated meninges.

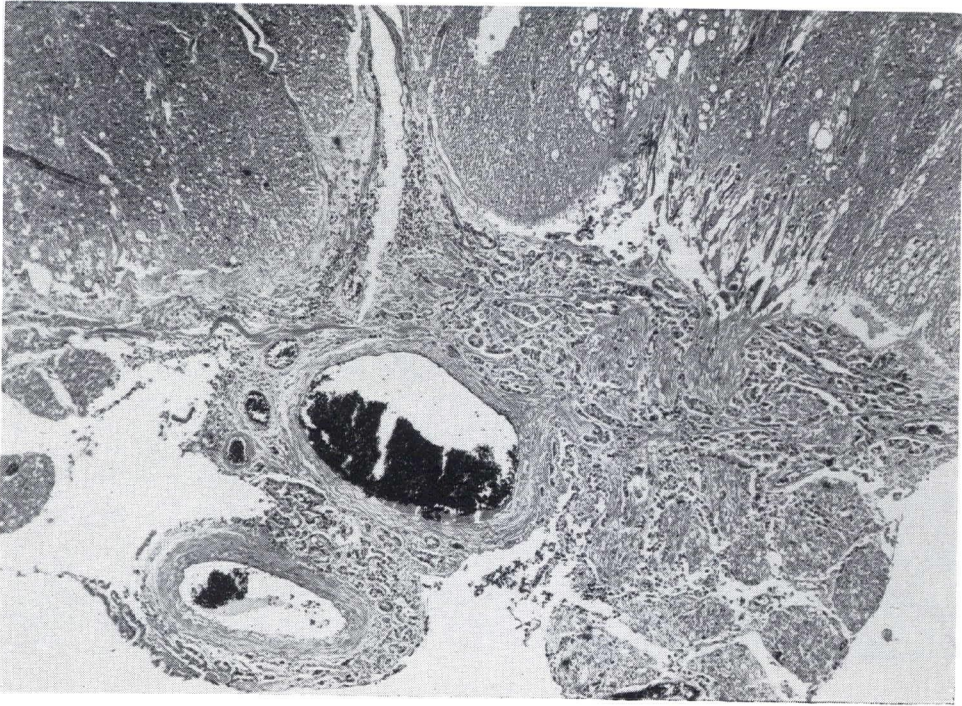


Figure 2

Ventral surface of spinal cord. Invasion of leptomeninges and spinal roots by carcinoma.

This case illustrates very well the difficulties in diagnoses of some of the pancreatic tumors particularly when they are not accompanied by jaundice as one of its clinical manifestations. The silent nature of the primary tumor and the frequency of symptoms referable to metastases have been already especially emphasized by Duff.¹ The ductal adenocarcinomas of the pancreas are the most common neoplasm of this organ. They constitute 81 per cent, according to Miller and Bagginstoss,² of all primary carcinomas of the pancreas and they arise more frequently in the head (71 per cent). Jaundice was found to occur in 128 out of 144 cases of carcinoma of the pancreas (89 per cent). The invasion of the perineural lymph-spaces occurs in 73 per cent of all cases.

The neurological manifestations with carcinoma of the pancreas as well as with other visceral cancers are due, in general, to invasion of the nervous system and its meninges. In recent years the association of neurological symptoms with carcinoma without invasion of the nervous system has been emphasized. Three types of pathological changes seem to occur more frequently:

1. Subacute degeneration of the cerebellar cortex described by Greenfield³ in 1934 with degeneration and disappearance of purkinje cells and loss of granular cells;

Carcinoma of the Pancreas

2. Peripheral neuropathy and myelopathy, occurring mainly as sensory neuropathy and described by Denny-Brown⁴ in 1948;
3. Myasthenia-like symptoms described by Denny-Brown⁴ and by Henson⁵ with nonspecific changes in the muscle and with no tumor of the thymus.

The case presented today has combined features of both direct spread of a carcinoma to the other organs as well as the central nervous system and also of the features of a subacute degeneration of the cerebellar cortex.

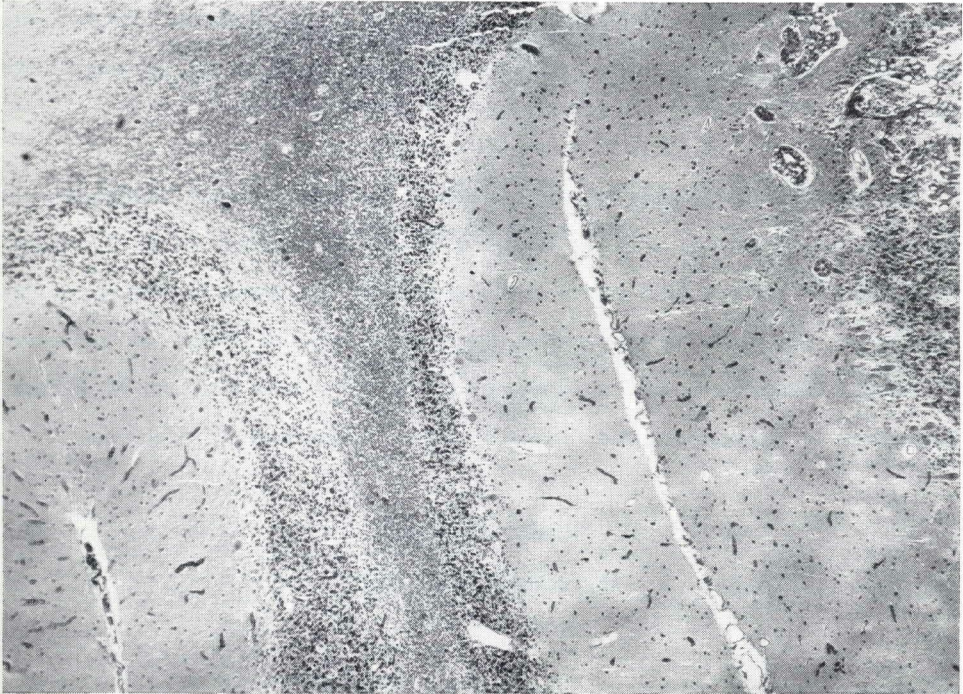


Figure 3

Cerebellar cortex. Loss of Purkinje and granular cells. Nests of neoplastic cells.

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