RHEUMATOID ARTHRITIS AND AMYLOID DISEASE

REPORT OF A CASE

BY

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[WITH PHOTOGRAVURE PLATE]

The occurrence of amyloid disease as a complication of chronic sepsis is well known. It can also occur as a primary systemic disease process. As a complication of rheumatoid arthritis it is still rare enough to warrant the publication of the following case, especially as the majority of cases published in England where amyloidosis has been associated with rheumatism have been in children with Still's disease.

As Trasoff *et al.* (1944) have reviewed the literature no attempt will be made to do so here. Suffice it to say that the first mention of the association of these two conditions was in 1903, when almost simultaneously Whitman and Spitzy each reported a case where arthritis was complicated by amyloidosis. The next case to be reported was by Carroll and Nelson (1927). Since then just over thirty cases have appeared in the literature.

Clinical History

The patient was a female, unmarried, aged 28, and weighed 7 st. 12 lb. (50 kg.). She was admitted to the Royal Bath Hospital for the first time on June 27, 1946. She had no unusual illness as a child, and there was no history of "growing pains." There was no family history of rheumatism. She left school at the age of 16 and worked in an office until she was 22, when in March, 1940, her knees began to swell, and she was treated with rest in bed, first at home for two months and then in hospital for six months. In January, 1941, she had an attack of acute appendicitis and her appendix was removed. In November, 1941, her left hip became painful and she was given injections of gold, about fifteen in all, and her knees and legs were put in plaster.

In 1943 the patient had a severe attack of "enteritis." No details of this illness are available, but she seems to have had attacks of diarrhoea and to have been confined to bed for some weeks. After recovering from this she was reasonably well, apart from the rheumatic condition, until April, 1945, when she had a severe uterine haemorrhage. She stated that she was given an anaesthetic and taken to the operating theatre and afterwards had a transfusion of 3 pints (1.7 litres) of blood. It would thus appear to have been of considerable gravity. The uterus was not removed. After this her periods were very irregular, and in fact ceased altogether for several months. She had a slight menstrual loss just before admission to the Royal Bath Hospital.

At this time she was not emaciated. She had a peculiar leucodermic pigmentation over the face and was obviously very anaemic. The joints of her arms and legs were affected with rheumatoid arthritis and showed typical deformities. Her hips were fixed in full extension and there was a considerable amount of fluid present in both knee-joints. She was able only to stand or walk with difficulty and generally needed some assistance.

On clinical examination no oedema was found and no evidence of jaundice. Her heart was enlarged to the left, her apex beat being 5 inches (12.5 cm.) from the midsternal line. There were no valvular murmurs and her blood pressure was not raised. The lungs were normal. There was no tenderness over the abdomen. The liver and spleen were both just palpable. No other abnormalities were discovered clinically. It was then obvious that the most important finding was the anaemia, which was out of all proportion to that usually associated with rheumatoid arthritis. This, together with the enlarged liver and spleen and history of haemorrhage, attracted our attention rather than the joint condition, which appeared to be reasonably quiescent.

Examination of her blood on admission gave the following results: haemoglobin, 20%; red blood cells, 1,700,000 per c.mm.; packed cell volume, 12%; white blood cells, 9,500 per c.mm.; polymorphs 70%, eosinophils 7%, small lymphocytes 19%, large lymphocytes 4%. The red blood cells showed slight poikilocytosis and anisocytosis, but there were no immature red cells present. The reticulocyte count was 1.5%. The erythrocyte sedimentation rate was 40% (Spa Hospital method; normal, 0–15%) on admission and remained high throughout her stay in hospital. The red cell fragility was within normal limits, and there was no evidence of haemolysis. The platelets were low, being only 104,000 per c.mm. The bleeding time (Duke's method) was three minutes, and the coagulation time (Lee and White's method) four and a half minutes. The capillary resistance test of Hess was negative. Other investigations included the serum colloidal gold liver function test, which was strongly positive. The urine contained only traces of albumin and a few casts.

At this time something in the nature of a splenic anaemia (so called) or an atypical thrombocytopenia was suggested as a provisional diagnosis. She was given a blood transfusion, large doses of iron, and faradic stimulation to the quadriceps group of muscles and light massage to retain the joint movements which were present. She improved slightly, but on July 15 began to complain of nausea and epigastric pain, and passed dark-coloured stools. Examination revealed the presence of red blood cells in the faeces, and the occult blood test was strongly positive. A fractional test meal investigation was carried out. No charcoal was found in the resting juice, which measured 30 ml. Both the free and combined acid curves were high. There was no bile present in any specimen apart from the fasting juice. A barium meal examination was carried out, and the report from the radiologist (Dr. Hitchcock) was as follows: "Oesophagus normal. Stomach and duodenum—a large gastric residue 7 hours after food. If patient had had no food or drink since taking the meal (I am not sure on this point) it is pathological and due to partial pyloric stenosis. The duodenal bulb is well formed. No colon stasis." A skiagram of the chest taken at the same time showed slight generalized fibrosis of both lung fields.

On July 29 the blood count had again fallen, the figures being: haemoglobin, 47%; red blood cells, 2,700,000 per c.mm. Blood transfusion was again indicated. The patient improved slightly after this, but on Aug. 1 she became much worse. She began to vomit small quantities of blood and dark-stained food material almost continuously, and a few days later profuse bleeding from the gums started. The patient was kept alive by blood transfusions; large doses of vitamins C and K were given and the gums were painted with snake venom. Vitamin C was given in excess because an ascorbic acid estimation of the blood showed a very low figure. The diagnosis was still much in doubt, and on account of the possibility of the case being one of acute essential thrombocytopenic purpura she was seen by a surgeon (Mr. T. V. Pearce) and transferred to the Harrogate General Hospital for a possible splenectomy.

On admission she was still bleeding profusely from the gums and appeared weak and collapsed. A blood urea estimation showed 96 mg. per 100 ml. of blood. There was, however, no clinical evidence of renal failure, breathing was normal, and there was no diminution of consciousness. Unfortunately the plasma proteins were not estimated, and since amyloid disease was not suspected the congo-red test was not performed. Continuous intravenous blood transfusions were given, but the patient died a few hours later.

Post-mortem Findings

Necropsy was performed six hours after death. The body was not emaciated and there was no oedema or jaundice. There was an old abdominal scar in the right iliac fossa. The gums

were oedematous and there was some ulceration. The tongue was normal. The tonsils were not enlarged, but were slightly inflamed though not grossly septic. The thyroid was of normal size, and section showed the structure to be homogeneous and of normal appearance. The oesophagus contained blood-clots, but the walls were not thickened and no ulcers were present. There was no evidence of enlarged blood vessels around its cardiac end. A large blood-clot was found in the larynx, but neither this organ nor the trachea was inflamed. The bronchi were also filled with blood. The lungs were congested, especially at the bases, and blood was present in the smaller bronchioles; there were some areas of patchy consolidation throughout both lower lobes. The pleural spaces were free and there was no excess fluid in the pleural cavity. The pericardium was normal and contained no pericardial effusion. The heart was slightly enlarged and dilated; it weighed 320 g. The myocardium was pale but was otherwise normal. The enlargement was due chiefly to left ventricular hypertrophy. The heart valves were all normal. There was some slight atheroma in the aorta throughout its course. The coronary arteries showed no gross degenerative change.

There was no free fluid in the peritoneal cavity and no evidence of inflammation. The stomach was distended with blood. The gastric mucosa was rather atrophic but there was no evidence of definite ulceration; there were, however, small pinpoint areas of haemorrhage scattered over the mucosa. The intestines were filled with dark faecal matter but contained no fresh blood. The bowel wall was of normal thickness and there was gross evidence of disease.

The liver was enlarged and weighed 1,920 g. It was pale and was definitely waxy. There were no glands at the hilum and no evidence of portal obstruction. The spleen was of normal size and weight; it was also rather pale but was not really waxy. In the cut surface the Malpighian corpuscles were rather prominent. The kidneys were contracted (weight, 110 g. each); the capsule was adherent and the surface very granular. On section the cortex was also seen to be contracted. The vessels were prominent and the pelvic fat was increased. The suprarenals were of normal size and shape.

The uterus was small and the endometrium appeared to be atrophic. The ovaries were of normal size and structure and the Fallopian tubes were normal. The bladder was distended but the walls appeared normal. There was no evidence of cystitis. The pelvic vessels were normal.

Macroscopically the brain was normal. The cerebrospinal fluid was clear. The vessels at the base of the brain were not thickened or atheromatous. The meninges were normal.

The significant findings, then, at necropsy were the contracted granular kidneys, the left ventricular hypertrophy, the enlarged liver, and evidence of intestinal haemorrhage. When tested with iodine for amyloid degeneration the kidney, liver, and spleen gave a positive reaction.

Histological Report.—The tissues were fixed in a solution of formaldehyde (10% concentration) and in Zenker's fluid. The stains used were haematoxylin and eosin, congo red (method of Bernhold), and methyl violet. Turnbull's stain for iron was also employed for certain organs. The muscles of the tongue were separated by oedematous fluid and there were small areas of haemorrhage. The epithelium was regular. There was no amyloid present. The mucous membrane of the gums was ulcerated. There was an infiltration chiefly of round cells, but no evidence of an acute ulcerative process. The oesophagus was normal. The gastric mucosa was extremely congested. The mucous membrane was destroyed in places, but there was no inflammatory exudate. The process appeared to be a simple necrosis rather than infective ulceration. There were also small areas of mucous membrane erosion scattered along the small intestine, but again no definite ulceration. The mucous membrane of the large intestine was normal. There were no amyloid deposits anywhere along the course of the alimentary tract, except for some slight deposits in a few of the blood vessels in the pyloric region.

The heart muscle showed fatty degeneration, but there was no amyloid degeneration. The aorta was the seat of early atheromatous degeneration, and the coronary arteries showed slight atheroma.

The kidneys (Plate, Fig. 1) showed marked amyloid degeneration. The afferent arterioles were universally affected. Their walls were thickened and their lumina narrowed. The capillaries of many glomeruli were more or less converted into a homogeneous bloodless mass of thickened and often obliterated capillaries. The glomerular tufts were swollen, at times completely filling Bowman's capsule. The interlobular arterioles were also involved, as were some of the glomerular arterioles. The tubules showed advanced degeneration, and most of them contained fatty and hyaline casts. The interstitial tissue was atrophic and infiltrated with round cells.

In the liver (Plate, Fig. 2) the hepatic arterioles were thickened and the walls contained a heavy deposit of amyloid. As seen in the photomicrograph, the deposit of amyloid had spread in from the periphery of the lobule along the hepatic sinuses. In places the liver cells had completely atrophied and were replaced by amyloid deposit. In the centre of the lobule the cells showed fatty degeneration.

The spleen (Plate, Fig. 3) showed a patchy type of amyloid degeneration. The sinuses and pulp had to some extent escaped, and the deposit of amyloid was chiefly confined to the Malpighian bodies. The reticular fibres of the Malpighian corpuscles had become thickened and filled with amyloid deposit, so much so that in many corpuscles the lymphocytes had disappeared and nothing remained but a solid mass of amyloid. In many cases the central arteriole was affected. The suprarenal (Plate, Fig. 4) also contained amyloid deposit, the vessels of the cortex being affected. In places the amyloid had infiltrated into the tissues, causing degeneration of cortical cells. In the pancreas the amyloid was confined to the vessels; the normal structure of the pancreas was maintained throughout. The histological structure of the brain was normal, and there was no amyloid to be detected in its vessels.

The joints of the limbs were the seat of typical advanced rheumatoid arthritis. The bone marrow was active and showed normal normoblastic proliferation, though this was not as pronounced as the degree of anaemia would warrant.

Discussion

Our knowledge of the aetiology of amyloid disease still remains incomplete. Its association with chronic infection is well known, but the exact causative factor is ill understood. The fact that it occurs in multiple myeloma gives us a clue as to what this factor may be, as in myeloma we get an increase in the plasma globulins. Such a disturbance may account for the deposit of amyloid material in other diseases. Reimann and Eklund (1935) suggest that amyloid disease may follow long periods of hyperglobulinaemia, and have produced experimental results to support this idea. These workers also report a case which suggests that amyloidosis may follow prolonged vaccine therapy. Since our case was not diagnosed clinically no study of the plasma proteins has been made, but there is no history of vaccine therapy. There was nothing in the clinical history of the arthritis or in its morbid anatomy to give an aetiological clue in this case.

Various classifications of amyloid disease have been adopted. Many writers speak of two groups of cases—atypical and typical amyloidosis. The so-called typical amyloidosis occurs after prolonged suppuration or following such chronic diseases as syphilis and Hodgkin's disease. The organs chiefly affected are the liver, spleen, kidney, and possibly the intestinal tract. In atypical amyloid disease there is no recognizable cause and the tissues affected are different. There may be a localized tumour in the tongue, nose, lung, skin, or heart, or a generalized involvement may occur, the mesodermal tissues, such as the intestinal tract or the heart, being affected. Reimann *et al.* (1935) suggested the following classification: (1) primary amyloidosis; (2) secondary amyloidosis; (3) tumour-forming amyloidosis; and (4) amyloidosis associated with multiple myeloma. Tumour-forming amyloidosis really belongs to the primary group.

The association of amyloid disease with multiple myeloma has been stressed by Magnus-Levy (1933). In the cases he described the amyloid either was localized or had affected the tissues characteristically involved in atypical amyloidosis. It is better, then, to speak of two types—primary or atypical, and secondary or typical. Indeed, the simple terms "primary" and "secondary" seem better. Primary amyloidosis occurs without any known cause, with the apparent exception of multiple myeloma, affects mesodermal tissue, and may be localized, forming a tumour, or generalized. It is possible that the deposit is not really true amyloid. Secondary amyloidosis follows certain well-known chronic diseases, and affects the abdominal organs, such as liver, spleen, and kidneys; true amyloid is present. Our case belongs to this secondary group, following as it does the chronic disease of rheumatoid arthritis.

The clinical findings in this case conform in general to those of the other reported cases. The history of enteritis at the age of 25 is interesting, as attacks of diarrhoea are common in these cases. The poor general condition with marked loss of weight is to be noted. The anaemia is also to be expected, but the tendency to haemorrhage is in some ways unusual. In most of the cases reported where haemorrhage has taken place the bleeding has been from organs affected by the amyloid process. Haematemesis, for instance, has occurred in systemic amyloidosis of the alimentary tract. In this case bleeding started sixteen months before death and took the form of a severe menorrhagia. When in hospital haematemesis occurred, ending in a terminal severe bleeding from the gums. None of the organs concerned had amyloid deposits. The liver and spleen were clinically enlarged. At necropsy the spleen had contracted and its weight was within normal limits. The liver, however, was definitely waxy and slightly enlarged. Albuminuria is generally regarded as a definite sign of amyloid disease of the kidneys but is not always present. In our case it appeared to be intermittent. This is very surprising in view of the state of the kidneys and the raised blood urea.

Summary

A case of amyloid disease complicating rheumatoid arthritis is reported in a female aged 28.

Several unusual clinical and pathological features of the case are noted.

The post-mortem findings are detailed, and a full report of the histological examination, with illustrations, is given.

The aetiology of amyloid disease is discussed, and a simple classification into "primary" and "secondary" is suggested.

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A useful guide to current French medical literature is published by Editions Cartier, 13, rue Puits-Gaillot, Lyon, in the form of a journal entitled *Diagnostics et Traitements*. Each number contains brief abstracts in French of articles arranged in alphabetical order according to subject. For example, a current number contains abstracts on subjects from "F" to "H," beginning with "ferments" and ending with "hysteria." Presumably the entire alphabet is covered in a year. The majority of articles are from French sources, though foreign literature receives some attention. Some original and review articles are also scattered through the text. Two special journals are also published by Editions Cartier, *Revue de Diététique* (monthly) and *Archives de Rhumatologie* (quarterly). In these greater emphasis is laid on publication of original articles, although abstracts of current literature are included.

CONGENITAL DEFECT OF LEFT DIAPHRAGM WITH VOLVULUS OF STOMACH AND TRANSPOSITION OF VISCERA

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[WITH PHOTOGRAVURE PLATE]

Whilst the various abnormalities which may cause the abdominal organs to be placed in the thoracic cavity have been described by many observers, much confusion exists on the subject, the different types of anomaly being so mixed that a careful study of the reported cases often leaves one in doubt as to which one the author is describing. The clearest classification of the various diaphragmatic abnormalities is that given in several articles by LeWald (1924, 1927, 1928). There are true congenital diaphragmatic hernia in which developmental defect of varying size occurs and the hernia is contained within a sac; false diaphragmatic hernia, either congenital or traumatic, in which no sac is present; eventration of the diaphragm, in which an attenuated half of the diaphragm is arched so high that the abdominal organs are in close proximity to the heart; congenital absence of half of the diaphragm; and the rare condition of thoracic stomach, which, according to Bailey (1919), is a term used to indicate the presence of the stomach in the chest cavity without evidence of any abnormal opening in the diaphragm. The shortened oesophagus opens into a stomach placed above the diaphragm, and the pylorus or duodenum passes through the oesophageal opening in the diaphragm.

The case described below is of particular interest by reason of (1) the difficulty in establishing by radiology the exact size and nature of the congenital defect, and whether the condition was amenable to surgical intervention; and (2) a sudden and inexplicable volvulus of stomach together with equally sudden transposition of viscera—resulting in death, which occurred while the case was under review—whereby the herniated small and large intestines underwent spontaneous reduction into the abdominal cavity, and the dilated stomach, which had previously been normally placed in the abdominal cavity, became transposed into the thorax.

Case Report

The patient, a male infant aged 8 weeks, was admitted to the Cardiganshire General Hospital, Aberystwyth, on Sept. 4, 1946, stated to be suffering from congenital pyloric stenosis. There was a history of normal delivery, the weight at birth being 6¾ lb. (3.06 kg.). This was the mother's second pregnancy, and a sister aged 2 years was healthy and free from known congenital defects. The mother had noticed that the breathing was very difficult from birth. There were frequent attacks of cyanosis with aggravation of dyspnoea, which appeared to be worse after feeding. The baby was bottle-fed, and vomiting was an early symptom. Sometimes the vomit occurred immediately after the feed; at other times it was delayed and projectile. Invariably the act of vomiting relieved the cyanosis and dyspnoea. The mother had found that nursing usually aggravated the dyspnoea, and that the most comfortable position appeared to be lying down. On admission the baby's weight was 7 lb. 12 oz. (3.5 kg.); its colour was normal; the respiration

RHEUMATOID ARTHRITIS AND AMYLOID DISEASE: W. YEOMAN AND J. V. WILSON

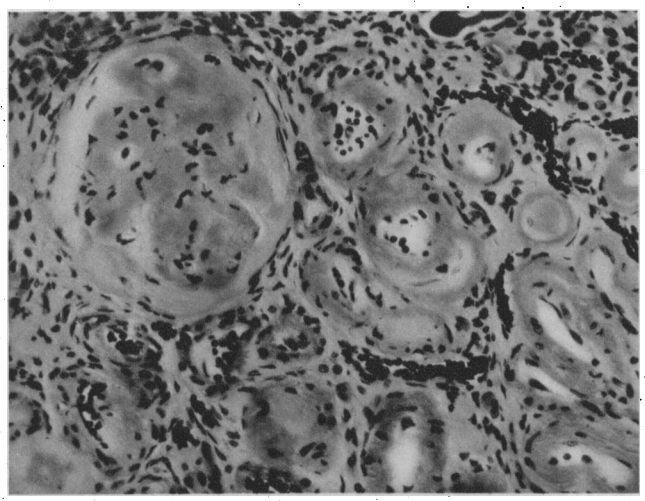

FIG. 1.—Kidney. Showing degenerative changes in glomeruli, tubules, and interstitial tissue.

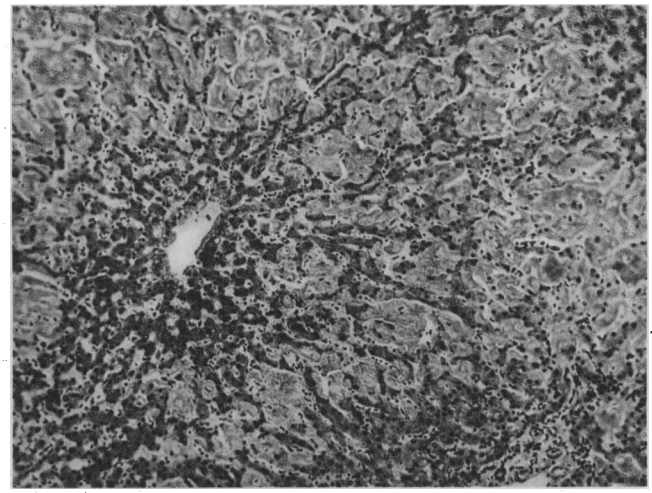

FIG. 2.—Liver. Amyloid spreading in from periphery of lobule. Liver cells show degenerative changes.

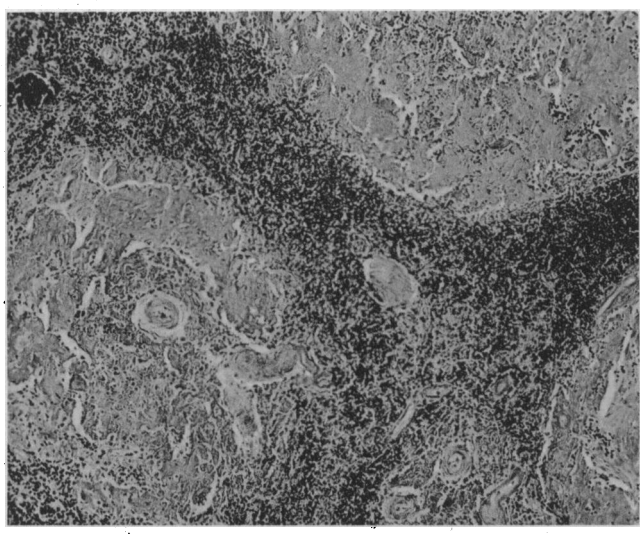

FIG. 3.—Spleen. Malpighian corpuscle showing amyloid infiltration.

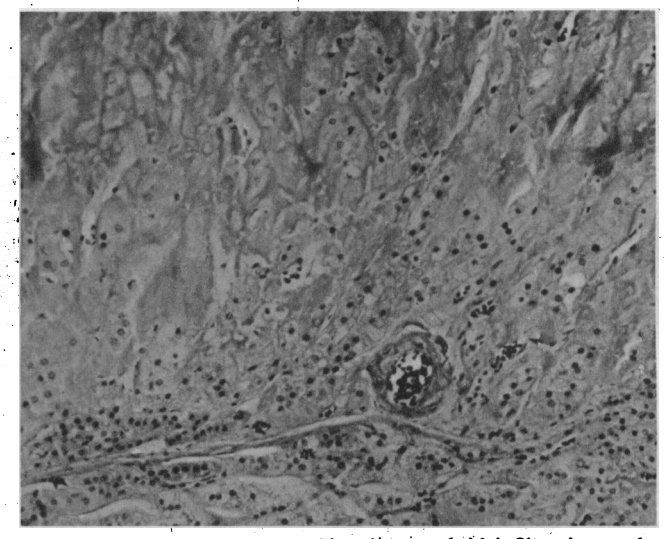

FIG. 4.—Suprarenal cortex. Showing amyloid infiltration and some cellular degeneration.

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AMYOPLASIA CONGENITA ASSOCIATED WITH HYPEROSTOSIS FRONTALIS INTERNA: R. N. HERSON

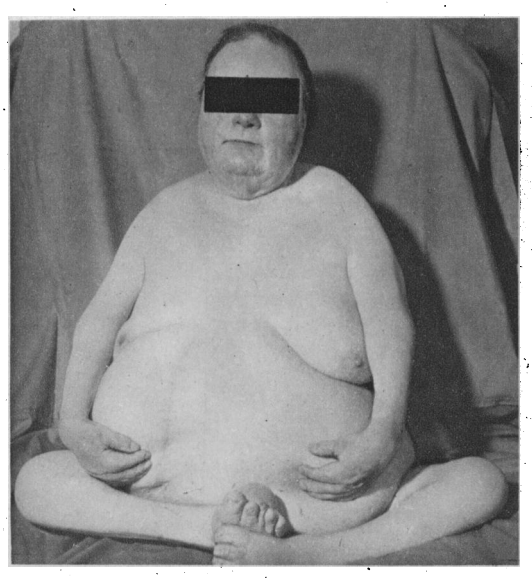

FIG. 1.—The patient at the age of 61.

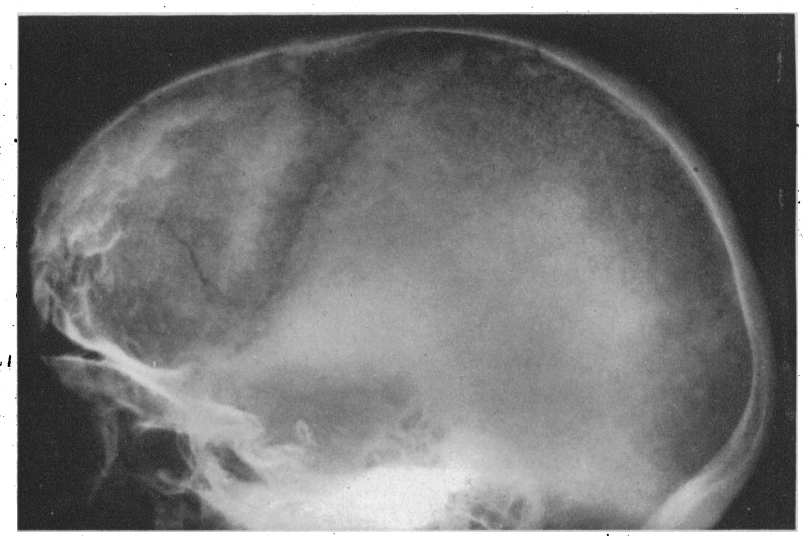

FIG. 2.—Lateral radiograph of skull showing hyperostosis on internal surface of frontal bone and calcification of base of pituitary fossa. The frontal sinuses are large and the mastoids over-pneumatized.