ANEMIA AND ARTHRITIS IN A CASE OF PITUITARY INSUFFICIENCY CONFIRMED AT AUTOPSY

BY

H. HORTLING

Pituitary insufficiency or Simmonds’ disease is found in women more often than in men. The most common cause of this disorder is necrosis of the hypophysis, as a rule due to hemorrhages associated with partus or septic emboli. Less common causes are inflammatory processes of tuberculous or syphilitic origin, and tumours of different kinds. The general symptoms, mentioned in order of frequency, are: diminished sexual function, low basal metabolic rate, loss of hair, cachexia, lowered insulin tolerance, achylia, progeria, atrophy of the mammary glands, anemia, eosinophilia, subnormal temperature and skin pigmentation (Sheehan, 1939, Escamilla & Lisser, 1942, and others). In the following, a case of pituitary insufficiency due to pituitary fibrosis is reported in a male which showed, besides the classical symptoms of Simmonds’ disease, an arthritis with a raised blood sedimentation rate and an anemia of aplastic type.

History. The patient was a sailor, born in 1893. Heredity non-contributory. Cannot recollect any diseases in childhood. Three times gonorrhoea before 1928. Denies syphilis.

In the spring of 1928 the patient was working on a ship sailing on the Atlantic. The journey was difficult and afterwards he felt ill
and tired. He was admitted to hospital at Le Havre, where he lay for a month with fever but without any other noteworthy symptoms. He was removed to hospital at Hamburg. The fever persisted for a further three weeks and the patient was finally discharged after three months in hospital. From time to time he had intestinal bleeding and vomiting, but no abdominal pain. He received large injections in the thighs. As a result of the diseases the hair on the whole of the body fell off. The blood sedimentation rate in December 1928 was 97 mm./1 hour. Ever since this illness the patient felt tired and out of sorts. The right leg was somewhat stiff and it was therefore treated with massage. He regularly visited the dispensary of Maria Hospital, Helsingfors, where a constant hypochromic anemia of moderate and varying degree was recorded. He was admitted seven times to the medical department of the same hospital. Gradually he lost weight and vigour and became unfit for regular work. He was always cold, sometimes had pains in his legs but no fever, and no pains in his joints. The hair on the head and trunk generally returned in a few years but the pubic and axillary hair remained very scanty. The skin was dry. After his illness in 1928 the testes were small and soft and from 1942 he was impotent.

In the summer 1945 the patient was rather better and he even helped with the reaping. He had no special pains nor stiffness in the joints. In the middle of October he fell and hurt his left thigh. At the surgical dispensary of the above mentioned hospital no fracture could be detected. As the leg, however, remained stiff and aching the patient was again admitted on November 16, 1945 and since then he never left the hospital. Gradually the pain in his left leg increased, stiffness in the knee followed and the muscles and tendons of the leg were stretched and sore. In August 1946 the left leg could no longer be straightened. The left knee felt warmer than the right one. The sedimentation rate, which had always been high, showed even higher values and the anemia increased in spite of treatment. As a consequence of an attempt to correct the left knee in the surgical department by immobilizing the leg after straightening it by force, his already weak general condition got worse. Death occurred on October 10, 1947 at 54 years of age.

State. In the following a detailed report is given of the state of the different organs as examined during the patient's admissions to hospital. The hospital diagnoses were: 1929 Encephalitis chronica?; 1933 Infectio acuta, Anaemia secundaria, (Hypogenitalismus); 1941 Anaemia secundaria, Dysendocrinismus; 1944 Dysendocrinismus, Achylia gastrica, Anaemia secundaria; 1945 Dysendocrinismus Anaemia secundaria.
The patient was of slender constitution, weight 1929: 52 kg., 1934: 59 kg. and after that gradually declining, in November 1945: 48 kg., in July 1947: 38 kg. Height 165 cm. He looked more than his age, his face was wrinkled, complexion yellow pale with small dirty-brown stains. Mucous membranes without pigmentation. Sclerae not icteric. No enlarged lymph nodes. No edema. Thyroid gland palpable, small, containing no nodules. Metabolic rate at five determinations during the years 1941—1947: 21, 24, 29, 26, and 9 per cent below zero. Serum cholesterol 1946 290 mg. per cent. Repeated administration of thyroid preparation in large doses did not affect the patient's general condition nor his anemia. Thyrotrophic hormone was tried in the form of the preparation Ambinon Organon but without apparent effect. — Serum calcium 1945 11.6 mg. per cent (10.9—12.4).

Respiratory organs. Lungs normal except that X-ray examination revealed a sharply limited spot, the size of a finger tip, in the left infraclavicular region. No tubercle bacilli were found in the sputum. Circulation organs. Pulse normal. Blood pressure 1929 was 80 mm. Hg, 1939 90 mm. Hg and subsequently between 110/60 and 145/75 mm. Hg. After subcutaneous injection of 0.7 ml. 1 per mille adrenaline solution the blood pressure showed no rise 5, 10, 15, 30 and 60 minutes after the injection. On the contrary it rather showed a tendency to fall (125/80—100/55 mm. Hg) while the blood sugar as well as pulse rate increased. An increase of the neutrophil granulocyte and the lymphocyte counts within one hour after the adrenaline injection was also noted. An X-ray revealed cor parvum. Electrocardiogram 1946: Right axis deviation, P small, hardly detectable, PQ O. 15, T 1—2 positive, T3 negative, small deviations, rhythm regular. No clinical symptoms of heart disease. Digestive system. Liver and spleen not enlarged. At four Ewald's test meals free hydrochloric acid was absent. X-ray of the ventricle revealed nothing pathological except ptosis. The patient sometimes complained of mild dyspeptic troubles. Meulengracht's icterus index in the years 1943, 1946 and 1947, 1:7, 1:4 and 1:2, respectively. In the urine, Schesinger's test (urobilin) was negative in 1945 and 1947. In the stool there were no worm-eggs and no evidence of blood. Takata's reaction negative 1946. Carbohydrate metabolism. Adrenaline test (0.7 ml. Exadrin Astra intramuscularly): Blood sugar level increased from 0.061 mg. per cent before injection to 0.113 30 minutes later and 0.065 after 2½ hours. Glucose tolerance test on March 3, 1945: blood sugar rose from 0.071—0.127 (after ½ hour) — 0.103 (1 hour) — 0.089 (1½ hours) — 0.065 (2½ hours); April 6, 1945: blood sugar rose from 0.063—0.099 (½ hour) — 0.096 (1 hour) — 0.054 (2½ hours). The rise in blood sugar was less than normal, a fact which can easily be correlated with a disturbance of the function of the anterior lobe of the hypophysis. Insulin tolerance
test, March 20, 1943 (6 units insulin were injected intravenously): blood sugar fell from 0.084—0.050 (1 hour) (nausea) — 0.040 (2 h.); April 12, 1945 (6 units insulin intravenously): blood sugar fell from 0.099—0.028 (20 min.) — 0.030 (40 min.) — 0.084 (3 h. 20 min.). The insulin effect appeared to be more than normal. Nervous system. X-rays 1933 and 1945 of the skull revealed a normal looking sella turcica. In the report of 1933 it was called small. No apparent neurological changes were noted. The face was poor in movement, the movements of the extremities slow (compare joint state). Lumbar puncture January 10, 1946: Nonne —, Pandy —, Cells 8/3 and March 3, 1946: Nonne —, Pandy —, cells 4/3 per mm. Urine never contained protein or other pathological constituents. Nylander, Gerhardt and Lange negative. At a dilution test in 1945 with one litre of water the specific gravity rose from 1010 to 1016 and later the concentration fell to 1008 (apparently a delayed excretion); in 1947 the specific gravity dropped at dilution from 1022 to 1013. The sodium chloride content in the serum was in 1946 590 mg. per cent, 1947 604 and 610 mg. per cent. The sodium chloride excretion in the urine was on Feb. 21, 1946 0.48 per cent of the urine volume per 24 hours or 7.2 gm. The volume of urine was usually normal. At exploration per rectum the prostate gland was of normal size. As already mentioned, the testes were small, about the size of a finger tip, and soft. After treatment with testosterone propionate (Neo-Hombreol Organon) 25 mg. every second day during the period June 26—Aug. 7, 1947 together with desoxycorticosterone acetate (Doca Organon) 10 mg. every second day it was observed that the patient was getting more active and interested in the future. On July 14, 1947 he had an erection, which had not happened for several years. The testes also grew much harder during this treatment. The anemia was not affected, though a small increase in reticulocytes was recorded.

As already mentioned, the right knee joint had been somewhat stiff ever since his severe illness in 1928. The leg was bent slightly outward at this joint, so that some limping was caused. The patient sometimes had pains in his legs, so that antineuralgics were often given during his earlier admissions to hospital. Real joint pains or joint swelling were, however, never observed before 1945, when he fell and hurt his left thigh. After this, stiffness and pains gradually appeared in this joint and the corresponding knee joint, until the knee finally became fixed at about 120° flexion. After August 1946 it could not be straightened either actively or passively. The left knee looked somewhat swollen as compared with the right one (28 cm. against 25 cm. in August 1946). The left knee felt slightly warmer than the right one. The ankle and the hip joint of the left leg had good mobility. Treatment with testosterone propionate, thy-
roid preparations, Doca and pituitary anterior lobe preparation had no apparent effect on the joint symptoms (regarding doses see later). It is remarkable that during the various admissions to hospital the patient had fever only very occasionally in spite of the raised blood sedimentation rate. The values of the blood sedimentation rate during the first hour varied in 1933 between 37 and 70, in 1941 between 81 and 104, in 1943 between 65 and 95, in 1945 between 29 and 120, in 1946 between 104 and 141, in 1947 between 71 and 157 mm. on Oct. 17. It should be noted that the patient had a markedly raised blood sedimentation rate long before his joint troubles developed. During his admissions to hospital no trouble of this kind worth mentioning in the diagnosis occurred. X-ray examination of the thoracic and sacrolumbar vertebrae and the left knee in the years 1946—47 revealed a small arthritic point in one of the lower thoracic vertebrae and atrophy in the bone of the left knee. The formolgel reaction was negative in the serum, but positive 45 minutes in plasma in December 1945. Serum proteins determined in the years 1946—47 varied between 5.9 and 7.7 gm. per cent while the globulin at three determination (Biuret method) varied between 3.1 and 4.27. The alkali reserve was 44.8 vol. per cent.

Hematopoiesis. Ever since the patient was admitted to Maria Hospital for the first time the presence of a normochromic anemia was recorded; it gradually increased and on Sep. 24, 1946 reached the lowest count: hemoglobin 35/41 per cent Sahli, erythrocytes 1.970 millions per cmm., colour index 1.04 (see the diagrams). The erythrocyte diameter was 7.57 and 7.58 μ when measured in 1945 and 1946. As previously mentioned, Meulengracht's icterus index was normal and the urobilinogen reaction in the urine was negative. The reticuloocyte values usually remained below 1 per cent (25 determinations). As a result of treatment small increases in reticulocytes occasionally occurred (maximum 3.4 per cent). Thus there was no evidence of blood destruction, but it should be mentioned that the blood cell resistance was not determined. Hematocrit 21 vol. per cent at two different determinations June 26 and July 16, 1947. Serum iron at two determinations 1946 0.102 and 0.114 mg. per cent. According to L. E. Tötterman, who was kind enough to undertake the determinations, these values fall within the limits of the normal variation. The leucocyte count showed a tendency towards depression and in the last years clear leucopenia appeared. In 1929 the average of 3 determinations was 7300/cmm., ranging from 5000—8500, in 1933 the corresponding figures were 4, 5420, 4600—6180; 1941: 8, 4400, 3100—5300; 1943: 1, 3700; 1945: 6, 4300, 3000—5000; 1946: 46, 3600, 2100—5700; 1947: 12, 3700, 2400—5000. The differential count showed
nothing pathological except a slight tendency to relative lymphocytosis. Eosinophilia was not proved. The leucocytes looked normal. The thrombocyte count also showed a tendency towards low values. The average of 12 determinations in 1946 was 81702/cmm. (only one value exceeded 100,000, namely 307,972; the lowest value was 31000) and of 17 determinations in 1947 the mean value was 84057 (5 determinations gave values above 100,000; the lowest value was 39000/cmm.). The bone marrow was examined in 1941, 1945 and 1946. The first two times the bone marrow picture resembled the peripheral blood picture. This fact appears to indicate a strong addition of blood. The test in 1946 gave a specimen with few cells and single normoblasts, myelocytes and metamyelocytes and otherwise rather resembling the peripheral blood picture. The presence of anemia, leucopenia and thrombocytopenia without macrocytosis or raised colour index appears to indicate an early aplastic anemia. The therapeutical results are partly described in the diagrams, where hemoglobin (Hgb), erythrocytes (E) and in some cases reticulocytes and the blood sedimentation rate (SR) have been indicated (Figs. 1—2). As partly demonstrated by the diagrams, no apparent effect

![Graph showing blood sedimentation rate, hemoglobin, and erythrocytes during iron, thyroid, and liver therapy.](image)

*Fig. 1.*

Blood sedimentation rate (SR), hemoglobin (Hgb) and erythrocytes (E) during iron, thyroid and liver therapy.
**Fig. 2.**

Blood sedimentation rate (SR), hemoglobin (Hgb), erythrocytes (E) and reticulocytes (Ret. c.) during gonadotrophin (21 injections), thyroid, liver and iron therapy.
on the erythropoiesis could be noted in spite of continued administration of iron in the usual doses together with or without dilute hydrochloric acid, liver therapy in the form of Heptomin forte Medica injections at three periods with 2 ampoules × 2, respectively 3 days after each other as well as combined with liver preparations per os, 3 injections Campolon at an interval of a week, Thyreoidin Medica in doses of 0.1—0.3 gm. 2—3 times a day for about 5 months as well as for periods, Ambinon Organon 15 ampoules for a month, testosterone propionate Neo-Hombreol Organon 18 ampoules of 25 mg. for 6 weeks together with Doca Organon 15 injections of 10 mg. and iron per os, a gonadotrophin preparation Antex Leo 21 ampoules for 5 weeks (the dose is unfortunately not indicated in the hospital records), Testoviron 10 mg. × 12 for a fortnight, etc. The hormone preparations were tried both alone and in combination with iron or liver. A, B, C and D-vitamins were also tried. The figures also revealed that the blood sedimentation rate and Hgb and Er-values respectively often ran parallel, though lower values for Hgb and Er with higher values for SR might well have been expected, since this is usual in chronic infections. It must be stated that the doses of liver and hormones may have been too small.

Record of autopsy, done by Professor I. Wallgren about 27 hours after death had occurred (brain and hypophysis were taken out and placed in 10 per cent formalin about 8 hours after death): Gyri of the brain were somewhat flattened. The formalin treated brain substance appeared macroscopically normal. In the ependyma of the IVth and IIIrd brain ventricles there was a slight fine granulation. The hypophysis looked like a transversal whitish string about 1 cm. long. Heart weighed 200 gm., otherwise normal. In the right lung there was much edema, the left one appeared normal. Liver weighed 1050 gm., otherwise normal. Kidneys weighed 200 gm., capsule somewhat adherent, surface smooth, structure plain. Stomach normal. Prostate and testes small, in aorta moderate sclerosis. Thyroid small, weighing 12 gm., firm with grey spotted surface on section. The bones of the skull and the right femur diaphysis were remarkably firm. In the sternum yellow bone marrow, in femur red.

Parts of hypothalamus and the region about aqueductus Sylvii, nucleus ruber and pedunculi cerebri embedded in paraffin wax were examined histologically. The sections were stained with hematoxylin-v. Gieson, toluidin blue and the marrow sheaths were stained according to a method suggested by Woelcke, 1942. Serial sections of the hypothalamus were made. In the hypothalamus no signs of
Fig. 3.
Ganglion cells in the region of nucleus paraventricularis stained with toluidin blue. Magnification 240 X.

Fig. 4.
Cross section of hypophysis stained with hematoxylin–v. Gieson. Magnification 31 X.
abnormal cell infiltration or of injury to the cell bodies were present. No ependyme granulations were noted. Substantia nigra was well preserved. Fig. 3 shows ganglion cells from hypothalamus from the proximity of the IIIrd brain ventricle. The cell body count in nucleus paraventricularis and nucleus supraopticus appeared to be somewhat reduced, but it was difficult to form an adequate opinion in this respect in a single case. — Serial sections of the pituitary body were made, all of which revealed considerable changes in this organ. Enormously increased connective tissue appeared especially in the periphery (Fig. 4). Most of the cells were small, dark, with a minimum of cytoplasm and without vacuoles, with round or oval nucleus. Only occasionally did larger cells of a lighter shade of eosinophilic or basophilic type occur. (Fig. 5). The anterior lobe

![Image](https://example.com/image)

**Fig. 5.**

Cells of the hypophysis anterior lobe (stained with hematoxylin—v. Gieson). Magnification 240 X.

appeared to contain almost exclusively head cells. Some preparations revealed a tissue in the proximity of the anterior lobe consisting of fine red threads arranged in a net-like pattern with a few spool-shaped or star-shaped cells and brown refractive lumps. This was obviously part of an abnormal posterior lobe. Near this tissue single lymphocytic infiltrations appeared. — In the thyroid increased tissue and a good deal of lymphocytic infilrtration were noted. Acini were poor in colloid, the cells cubical. — Liver and pancreas revealed normal histological structure. — The adrenals also revealed normal histological structure. In the prostate much smooth muscles and many cavities covered with cells and resembling sinus
structures in urethra. — Pathological-anatomical diagnosis: Fibrosis hypophysis et glandulae thyreoideae. Splanchnomicria. (The histological preparations were also examined by Professor I. Wallgren, and the preparations from the brain stem were also examined by Dr. K. v. Bagh, and I wish here to thank them for their courtesy). The cause of death was probably a general endocrine deficiency.

Summary of the case history. After a four months admission to hospital in 1928 in France and Germany, during which the patient had fever for nearly two months, there was hair loss, testis atrophy leading to impotence in 1942, lowered basal metabolic rate and other symptoms suggesting pituitary insufficiency. During this period a slowly progressive normochromic anemia with aplastic features was present. In consequence of a trauma in the left thigh in 1945, soreness and stiffness in the corresponding knee developed until complete ankylosis set in. The patient’s condition became progressively worse. The anemia reached the lowest count 39/41 per cent for hemoglobin and 1.970 millions for erythrocytes. Attempts to affect the anemia produced no apparent results. The sexual function and progeria seemed to be affected by Doca + testosterone propionate. The patient died of general cachexia in 1947. Autopsy revealed splanchnomicria and an abnormally small hypophysis, transformed into connective tissue. Microscopic examination revealed marked fibrosis of the pituitary body and reduction of eosinophilic and basophilic cells in the anterior lobe. Increased connective tissue, though in a less degree, was also present in the thyroid. Hypothalamus appeared to be normal.

DISCUSSION

Common symptoms of Simmonds’ disease, all of which were present in this case, are asthenia, underweight, loss of hair, dry skin and, more rarely, skin pigmentation. Further signs are lowered basal metabolic rate and, probably as a consequence of this, increased sensitivity to cold. These symptoms were not affected by thyroid medication. In the present case thyrotrophic hormone was also administered in
the form of Ambinon Organon, without any apparent effect on the symptoms mentioned or on the blood picture. It should, however, be noted that the patient's general condition was then already very bad. It is interesting that desoxycorticosterone acetate in combination with testosterone propionate had a beneficial effect on the progeria as well as on the sexual function. One result of this was an erection, which had not occurred for several years. This is of interest when considering the relative efficacy of the doses in attempts to affect the patient's anemia. — The results of substitution therapy in Simmond's disease are on the whole negative, as indicated by cases confirmed at autopsy (Escamilla & Lisser, 1942), but good results with testosterone propionate, desoxycorticosterone acetate and thyroxin have recently been reported (Luft & Sjögren, 1949). — This patient also revealed obvious symptoms of disturbance of the carbohydrate metabolism of a type different from that associated with diabetes mellitus. This is not uncommon in Simmonds' disease (Escamilla & Lisser, 1942). — Symptoms of the nervous system such as apathy and incapacity for regular work as well as deficiency of facial and other movements have also frequently been observed in Simmonds' disease (Sheehan, 1939) and were also noted in this case. It might be assumed that the patient had suffered from an encephalitis localized to the brain stem in connection with his severe illness in 1928. The histological examination, especially of the hypothalamus, appeared to indicate that at least this region had escaped inflammatory processes. Considering the great change revealed in the hypophysis, it hardly seemed probable that the basal ganglia had been subject to changes caused by a chronic encephalitis, as the inflammatory process would then have »jumped over« the hypothalamus. The possibility of minor degenerative changes due to partial elimination of the pituitary body cannot, however, be excluded.

A predominant feature of the disorder during the final years was the joint symptoms. Are they manifestations of a chronic rheumatic disorder of the joints, independent of the
hypophysis, are they secondary symptoms of pituitary deficiency or are they possibly related to the trauma preceding the appearance of these symptoms? The fact that no real joint signs were observed during the years 1929—1945 in spite of the raised blood sedimentation rate and anemia is evidence against a chronic polyarthritis. Although the patient limped slightly and occasionally had diffuse pains in his legs, he had no fever and during his many admissions to hospital nothing would have justified the diagnosis of polyarthritis. It should, however, be kept in mind that a subnormal temperature is sometimes associated with Simmonds’ disease (in 35 per cent of cases according to Escamilla & Lisser, 1942). Rather interesting is the fact that the joint signs were clinically observed and progressed rather quickly as a result of a trauma in 1945. Jonsson & Berglund (1949) have recently critically examined the relation between trauma and polyarthritis and among 2236 cases of polyarthritis they found only one in which a relation could be assumed. They believe, however, that in some cases trauma might be a contributory cause of polyarthritis. As in this case a possible chronic infection preceding the trauma must be taken into account, only secondary importance, if any, can be attributed to the trauma as a cause of the joint trouble. It is remarkable that with rather marked joint symptoms the patient had no fever during the whole of this post traumatic period. Even previous to the trauma a considerably raised blood sedimentation rate and anemia were present. If a relation between these signs and a chronic arthritis had existed, at least occasional fever or marked joint signs would probably have occurred during the earlier stages of the disease. This, however, was not the case. It should also be noted that the course of the blood sedimentation rate often ran parallel with or independent of the anemia (compare Figs. 1—2), whereas in cases of chronic polyarthritis an increased blood sedimentation rate is usually associated with worsening of anemia (Nilsson, 1948). It is thus difficult to interpret the occurrence of the ankylosing knee affection directly following
on a trauma in the left thigh unless the presence of an endocrine factor is assumed.

Patients with Simmond's disease often have rheumatic symptoms in their limbs and osteoarthritis has been proved post mortem (Sheehan, 1939), though by no means regularly. Escamilla & Lisser (1942) do not mention this symptom in a single instance of their large number of cases i.e. 101 confirmed at autopsy. Joint diseases of the type osteoarthritis deformans occur in acromegaly and Cushing's disease and they are also accompanying disturbances in conditions involving the brain stem and hypothyroidism (quoted by Lichtwitz, 1941, and Selye, 1948). Castration seems to predispose to joint diseases and it has been reported that testis preparations can prevent osteosclerosis brought about experimentally in animals by large doses of oestrogens (Jonsson, 1939). The anterior pituitary hormone may bring about bone and joint changes (Silberberg & Silberberg, 1940). Lowered secretion of oestrogenic hormones (Rasmussen, 1936) and ovarian failure have been noted in cases of chronic polyarthritis (Sjövall, 1944). The so called climacteric arthritis has probably an endocrine origin. Of interest is the recent research on the metabolism of joint cartilage. From the testes of animals an enzyme has been isolated which splits, among others the polysaccharide chondroitin sulphuric acid in joint cartilage (Meyer et al., 1941). With such testislyaluronidase produced from fresh bull's testicles, it has been possible in vitro to affect cartilage from different joints taken from fresh autopsy cases so that histological pictures developed resembling those seen at beginning ma¬lacia in arthrosis deformans (Hirsch, 1947). — Disturbances in the non protein nitrogen balance in connection with pituitary insufficiency (Lee & Ayres, 1936, and others) and reduction of the albumin-globulin quotient after hypophysectomy in animals have been des¬cribed, (Podhradszky, 1940), but are not mentioned in human by a number of investigators. A markedly raised blood sedimentation rate without joint symptoms has been reported in a case of atrophy of the hypophysis (Jersild, 1943).

The experimental investigations up to date appear to suggest a relation between joint changes and endocrine disturbances. In the present case many features differed from the symptomatic picture of rheumatic polyarthritis. The severe endocrine hypofunction revealed in the patient would appear to indicate that this failure was a contributory cause of the
joint disease activated by the trauma. It is, however, hardly possible to discover the exact mechanism with data of a single case.

In this case the anemia also deserves detailed discussion. An account of earlier investigations on this subject is first given.

From the relevant literature, Sheehan (1939) has compiled 31 cases of Simmonds' disease, caused by necrosis of the hypophysis associated with partus, in which attention has been paid to the blood picture. Of these, 19 revealed anemia and 4 polycythemia while the rest had a normal red blood picture. A table given by Sheehan further indicates that in 9 cases genital atrophy without anemia was present, while 12 cases with genital hypoplasia revealed anemia and 1 case with normal genitalia showed a normal blood picture. All cases of polycythemia had genital atrophy. This survey thus reveals no clear correlation between blood picture and genital function. Sheehan further states that in the material described by him the erythrocyte values during the first five years of the disorder remained about 5—6 millions and the colour index varied between 0.6 and 0.8. During the following five years the corresponding values were 3—4 millions and 0.7—0.9, while in cases of longer duration the number of erythrocytes could be reduced to 2—3 millions and the colour index to 0.95—1.25. He indicates that the hyperchromic anemias are more frequent in cases with signs of hypothyroidism. The leucocyte values were normal. Often a relative lymphocytosis and eosinophilia were noted. Among 6 cases of pituitary insufficiency (Snapper et al., 1937), which included 4 males with hypogonadism as the predominant sign, 5 had achilia and 4 certainly had hypothyrosis, degeneration of the spinal cord of the type funicular myelosis was present in 2 cases, anemia of pernicious type in 2 and hypochromic anemia in 1. Three of the cases were cured by liver therapy, one by the administration of thyrotrophic and gonadotrophic hormone and the hypochromic anemia with the same hormones in addition to iron. A case of hypogonadism and hypochromic anemia has also been described in which preparations of testis and gonadotrophic hormone in combination with iron had a beneficial therapeutic effect while synthetic preparations had none (Gonnermann, 1938), 1 case of a hyperchromic type with pituitary deficiency reacted to liver (Witts, 1942), in 1 case of hyperchromic anemia and 1 of a hypochromic type, testosterone propionate in combination with liver, or iron, had a beneficial effect (Watkinson et al., 1947). A number of other similar cases have been described (Foster & Mc Carter, 1941, Williams &
Whittenberger, 1942). In castrates a slight anemia has been observed (Mc. Cullagh & Jones, 1942). In a survey of 101 cases of Simmonds' disease confirmed at autopsy Escamilla & Lisser (1942) give the average values 65 per cent (min. 40 per cent) for hemoglobin and 3.710 (min. 2 millions) for erythrocytes. The type of anemia is not mentioned in the paper. Of special interest from the point of view of the present case is an observation on a patient with aplastic anemia and with a cyst destroying the hypophysis (Bloom & Bryson, 1948). As is well known, polycythemia has been reported in cases of pituitary disturbance such as Cushing's disease and acromegaly. This question has, however, never been thoroughly analyzed. It is possible that dehydration could be demonstrated in these instances. (Snapper et al., 1937). — In animal experiments some facts have recently been noted which appear to indicate that androgenic hormones stimulate the erythropoiesis (Steinglass et al., 1941; Finkelstein et al., 1941; Arendsen de Wolff-Exalto, 1947). — In connection with hypothyreosis, hypochromic and, though more rarely, hyperchromic anemia have been described. The beneficial effect of thyr-roeidin on anemias of this type is considered characteristic (H. Zondek, 1922; Unverricht, 1923; von Boros & Czoniczer, 1935; Holboll, 1931, and others). Hypothyroidism and anemia in Simmonds' disease are on the other hand not as a rule affected by thyroid preparations (Escamilla & Lisser, 1942).

Animal experiments have shown that hypophysectomy in rats causes a reticulocytopenia, which regenerates after about a month (Overbeek & Querido, 1939; Meyer et al., 1940; Ruitinga et al., 1940), as well as anemia (Wilson, 1937; Vollmer et al., 1939; Meyer et al., 1940; Crafts, 1946). Hypophysectomy in the rabbit led to the same result (Houssay et al., 1931). The reticulocytopenia has been attributed to decreased erythrocyte destruction (Overbeek & Querido, 1939), but this opinion has been subject to criticism (Meyer, 1940). Flaks et al. (1938) report that they have found a factor which stimulates the formation of erythrocytes and reticulocytes in an extract from the anterior lobe of the pituitary gland, free from growth, gonadotrophic or thyrotrophic hormone. This extract exerts its action only with oral administration. Meyer et al. (1940) could not confirm Flaks' findings, but they were of the opinion that the preparation used by them possibly lacked Flaks' factor. They believe, that the changes in the red blood picture caused by hypophysectomy cannot be attributed to the lack of some specific hormone in the pituitary gland regulating the hematopoiesis, but are due to general metabolic changes associated with hypophysectomy. Crafts (1946) showed that the anemia was microcytic and hypochromic and he was able to prevent it with injections of thyroxin, iron and copper.
The change in the leucocyte picture seems to be slight in the above mentioned experiments involving hypophysectomy. In a recent survey, Doughaday et al. (1948) are of the opinion that the erythropoiesis is not subject to primary hormonal control.

The facts observed appear to indicate that hypogonadism with or without other signs of pituitary deficiency may in some cases cause an anemia which can be successfully treated with gonadotrophic hormone. On the other hand the type of anemia described in connection with Simmonds’ disease appears as a rule to be unaffected by hormone therapy. A case of aplastic anemia associated with injury to the hypophysis has recently been described. A number of animal experiments indicates the possibility that the anterior lobe of the pituitary contains specific hormones regulating erythropoiesis, but the evidence of these experiments has been questioned. In any case it cannot be denied that the anterior lobe might contain specific erythropoiesis regulating substances. The facts observed during the progress of the anemia in the present case, particularly the absence of association between the blood sedimentation rate and the joint signs, the aplastic character of the anemia and the marked signs of pituitary failure, would appear to indicate the existence of a relation between the blood disease and the endocrine disturbance. The presence of increased connective tissue in the pituitary body and to some extent also in the thyroid seemed to suggest a previous inflammatory process, but no signs of actual inflammation were present at the time of post mortem examination. Consequently, a process of this kind could not have been a decisive cause of the raised blood sedimentation rate and the anemia. This view is also supported by the presence of a normal serum iron. — A cerebral factor must also be taken into account. A number of clinical experiments and animal experiments (literature given by Hortling, 1948) indicate the possibility that parts of the hypothalamus, perhaps in the first place in the nucleus paraventricularis, and some adjacent areas (Hess, 1947) play a part in the regulation of the erythropoiesis. The histological structure of hypothalamus ap-
peared, however, to be normal in this case. Nevertheless it is possible that the number of ganglion cells in the nuclei of the hypothalamus was reduced, as has been observed when the pituitary stem has been surgically removed (Rasmussen & Gardner, 1940).

The posterior lobe of the pituitary body in this case showed pathological changes although no clinical signs had been present. Signs of diabetes insipidus were not observed. It should, however, be kept in mind that only 15 per cent of the ganglion cells in nucleus supraopticus are required to prevent diabetes insipidus (cf. Rasmussen & Gardner, 1940). Injection of the posterior lobe hormone pituitrin in the rabbit and guinea-pig is reported to cause anemia of a hemolytic type in some cases (Dodds et al., 1936).

Interesting in this case is also the great reduction of the basophilic and eosinophilic cell counts in the anterior lobe of the pituitary body, while cells of a type resembling head cells were predominant. Similar observations in cases of pituitary fibrosis have previously been made (Langdon-Brown, 1936; Doane et al., 1940; Jersild, 1943, and Øllegaard, 1945). It should be mentioned that increased connective tissue was also noted in the thyroid, suggesting the possibility of a systemic disorder of the endocrine organs. This has previously been described in single cases (quoted by Escamilla & Lisser, Jersild and Øllegaard).

**SUMMARY**

A case of pituitary insufficiency is described, which besides having the classical signs of Simmonds' disease, revealed an ankylosing joint affection of the left knee, developing after a trauma in the left thigh, chronically raised blood sedimentation rate already present before the appearance of the joint disorder and a normochromic anemia with aplastic features. At autopsy, splanchnomicry and an abnormal hypophysis were noted. Microscopic examination revealed considerably increased connective tissue in the hypophysis and moderately increased connective tissue in the thyroid. In the anterior lobe
of the hypophysis cells resembling the head cells were almost exclusively observed. The relation between the joint condition and anemia on the one hand, and the pituitary failure on the other, is discussed; it is considered that such a relation may exist.

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