GOUT

AN UNUSUAL CASE WITH SOFTENING AND SUBLUXATION OF THE FIRST CERVICAL VERTEBRA AND SPLENOMEGALY*

RESULT OF ACTH ADMINISTRATION AND EVENTUAL POST-MORTEM FINDINGS

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Introduction

In August, 1946, a young man aged 21, who gave a history of attacks of pain and swelling in his joints since the age of 18, was first seen at the Royal National Hospital for Rheumatic Diseases, Bath. He was already severely crippled. His plasma uric acid was 16 mg. per cent., and there was some hypochromic anaemia. His spleen was just palpable.

His condition was partly controlled by continuous colchicine therapy, there being a fulminant relapse on its discontinuation. Local x-ray therapy caused local exacerbation followed by some improvement. In spite of all treatment, however, his condition gradually deteriorated and by July, 1949, his white-cell count had dropped to 2,500 with only 9 per cent. lymphocytes. In September a splenectomy was performed without material change in his condition; 18 days later he developed a spontaneous partial subluxation of the first cervical vertebra, the result of tophaceous softening. In October he was given a short course of ACTH (adrenocorticotrophic hormone) with general improvement in his condition and startling effect on his appetite. He relapsed again, however, after cessation of treatment, and died on November 30 of a terminal bronchopneumonia. A post-mortem examination was performed.

There are so many unusual features in this case that it is proposed to describe it in detail, and then to discuss it under the headings of clinical features, tophaceous softening of the cervical vertebrae, colchicine and x-ray therapy in gout, splenomegaly and splenectomy, and the use of ACTH.

Case History

Family.—The patient had one brother who began to have attacks of gout at the age of 18. Although a history of gout in the parents was denied, there is room for doubt in the accuracy of this statement.

Previous History.—The patient had always been extremely fit until January, 1943, when, at the age of 18, he awoke one morning when on leave to find his left knee swollen and painful. Complete recovery took place in three days. During the ensuing months

* This paper was presented at the joint meeting of the Ligue Française contre le Rhumatisme and the Heberden Society, held in Paris, June, 1950.

he remained fit, taking part in a Commando course and then in the invasion of Italy, but in November, 1943, five days after the onset of an attack of jaundice, he developed another attack of pain and swelling in the left knee, which lasted for a month. Infective hepatitis at that time was epidemic. In February, 1944, he had another two weeks of pain and swelling in the left knee and then in the fingers. The trouble in the fingers persisted and, after a course of gold, he was invalided out of the Service in September, 1944, as a case of arthritis. During the next two years he had repeated attacks of pain and swelling in many joints, each attack being followed by a complete or almost complete remission. He lost weight and his general condition deteriorated.

In August, 1946, at the age of 21, he was first admitted to the Royal National Hospital for Rheumatic Diseases. He was wasted, anaemic, and debilitated. There was some evidence of involvement of most of the joints of the body and especially of the hands, knees, and feet. There was fusiform swelling of the proximal interphalangeal joints with flexion contractures of the 4th and 5th digits of the left hand, and the knees and ankles were swollen with marked limitation of movement. Tophi were present in the ears. The spleen was palpable, as were glands in the axillae and epitrochlear regions.

Investigations, August, 1946.

Blood Examination

R.B.C. 3,710,000.

Haemoglobin 55 per cent.

W.B.C. 9,800: Polymorphs 69 per cent.

Lymphocytes 22 per cent.

Monocytes 9 per cent.

Suspension stability 58 per cent.

Plasma uric acid 16 mg. and 17.7 mg. per 100 ml.

Cholesterol 125 mg. per 100 ml.

Urea 44 mg. per 100 ml.

Urine showed a trace of albumin, a few red blood cells and uric acid crystals.

X rays showed erosion of cartilage, and translucent areas, such as are commonly found in gout.

Cinchophen produced little clinical improvement, but the pain and swelling were considerably relieved by colchicine gr. $\frac{1}{120}$ three times a day.

Progress of Disease. *April, 1947.*—He was re-admitted to hospital. He had remained almost free from pain on continuous colchicine therapy, but his general condition had deteriorated and he had lost weight. Blood examination showed little change from before, except that the plasma uric acid had dropped to 13.3 and the cholesterol to 80 mg. per 100 ml. Muscle and skin biopsy showed no abnormality except a slight increase in muscle nuclei.

September, 1947.—He was admitted to another hospital. Colchicine was discontinued and immediately he had a fulminant attack of gout with high fever. After this his joints, especially his hands, became much worse and a bilateral flexion deformity became established in the wrists and knees.

March, 1948.—He was re-admitted to the Royal National Hospital, Bath. His general condition and his joint condition were found to be much worse, but the blood findings were as before. In April, after his discharge, his supply of colchicine ran out. Tincture of colchicum was substituted, but within two days there was an acute exacerbation of gout with fever and vomiting.

May, 1948.—He was re-admitted in very bad condition, but improved on colchicine therapy. The plasma uric acid was 16 mg. again, and the cholesterol had fallen to 50 mg. Both hands and feet were discharging tophaceous material. *X-ray* therapy for the right foot caused a very acute exacerbation, but six weeks later there was a local improvement, sufficient to cause the patient to agree willingly to a similar course of treatment for the left. There was again some increase in pain and swelling for ten days, and after this

regression to the previous state. The dosage used was 4 exposures of 150r using $\frac{1}{2}$ mm. copper and 1 mm. aluminium filter, 180 kv and 10 milliamps.

November, 1948.—There was little clinical change.

Blood Examination

Haemoglobin 60 per cent.
W.B.C. 6,300: Polymorphs 76 per cent.
Lymphocytes 14 per cent.
Monocytes 10 per cent.
Plasma uric acid 13.3 mg. per 100 ml.

FIG. 1(a).—Dorsal aspect of left hand showing discharging tophus.

FIG. 1(b).—Palmar aspect of right hand showing flexion contracture of fingers and discharging tophi.

Investigations, July, 1949.—His general condition had still further deteriorated. He complained of some pain in the left side of his head, and of stiffness in his neck. Examination showed the following results:

Hands.—Fingers were all flexed and swollen and there was inability to open the hands. Tophi were present in all fingers of both hands, discharging on the little and ring fingers of the right hand (Figs 1a and 1b).

Wrists.—Both were almost completely ankylosed.

Elbows.—Gross limitation of movement, range of right 80° to 95°, and of left 90° to 100°.

Shoulders.—Gross limitation of movement.

Hips.—Slight limitation of movement only.

Knees.—Left knee ankylosed at 105° flexion. Right knee showed gross limitation of movement, the range being 110° to 115°. Both knees swollen and the outlines deformed.

Ankles.—Both swollen with gross limitation of movement.

Feet.—Swollen with swollen toes, and tophi.

Numerous tophi were present on both ears, and the spleen was palpable two fingers breadth below the costal margin.

X-Ray Examination

Hands.—Loss of cartilage, osteoporosis, erosion of articular surfaces, subluxation, ankylosis, calcification in soft tissues (Figs 2a and 2b, opposite, show the rapid deterioration which occurred in the right hand between 1947 and 1949).

FIG. 2(a).—X ray of right hand in 1947.

FIG. 2(b).—X ray of right hand in 1949, showing the rapid progress of the disease. Note the bony destruction and calcification in soft tissues.

Elbows.—Osteoporosis and osteosclerosis.

Shoulders.—Osteoporosis and patchy osteosclerosis.

Knees.—Loss of cartilage, osteoporosis, patchy osteosclerosis.

Ankles.—Loss of cartilage, osteoporosis, calcified tophi.

Feet.—Loss of cartilage, osteoporosis, erosion of articular surfaces, subluxation, calcified tophi.

Dorsal and lumbar spine.—No abnormality.

Pelvis.—Patches of increased density in region of left hip joint with some loss of cartilage (see Fig. 3).

Blood Examination

R.B.C. 3.38×10^6 per c.mm.

Haemoglobin 60 per cent.

Colour Index 0.9.

Mean corpuscular diameter 7.5μ .

Reticulocyte count 0.5 per cent.

Haematocrit 37 per cent.

W.B.C. 2,500:

Polymorphs

79 per cent.

Lymphocytes 9

per cent.

Monocytes 12

per cent.

Eosinophils nil.

Basophils nil.

Platelets 310,000 per c.mm.

Sedimentation rate 15 mm. in one hour (corrected Wintrobe).

Suspension stability 79 per cent.

Plasma viscosity 189.

Coagulation time 4 minutes.

Prothrombin time 10 seconds.

Fragility same as normal control.

Plasma uric acid 10 mg. per 100 ml.

Cholesterol 60 mg. per 100 ml.

FIG. 3.—X ray of left hip joint showing calcified uratic deposit (July, 1949).

Urea 40 mg. per 100 ml.

Creatinine 1.7 mg. per 100 ml.

Urine Examination

S.G. 1010.

Reaction neutral.

Albumin 0.3 g. per l.

Sugar absent.

Acetone absent.

Bile absent.

Deposit: no pus cells, no red cells, no squamous epithelial cells, no casts.

Splenectomy.—As splenectomy was now contemplated, on August 22 the patient was given a transfusion of two pints of packed red cells with no reaction and a control observation period was commenced. From August 29 total and differential white counts were performed three times a day, fasting blood sugars were estimated daily, and 24-hour specimens of urine were analysed for creatinine and uric acid output, fractionated ketosteroids, and corticoids (for details see the Table and Figs 6-10). In all differential counts, eosinophils and basophils were less than 1 per cent.

On September 5, 1949, a splenectomy was performed, and at the same time a bone-marrow biopsy was carried out. The spleen weighed 200 g. and showed little histological abnormality. There was proliferation of the endothelium of the sinusoids at the expense of the lymphoid tissue, which was small in amount. There was also a little fibrosis.

FIG. 4.—X ray of 1st and 2nd cervical vertebrae (A. P. through open mouth) showing destruction of atlas vertebra by uratic deposits (September, 1949).

Examination of the sternal-marrow smears showed some hypoplasia of the red-cell series but no other abnormality.

On the day of the operation the patient was given two injections of colchicine gr. $\frac{1}{100}$ in 10 ml. distilled water intravenously to replace the oral intake. He was also given prophylactic penicillin. He stood the operation quite satisfactorily.

Later Developments.—During the subsequent 10 days his condition deteriorated and with some vomiting he became dehydrated.

Blood Examination, September 15

Haemoglobin 103 per cent.

W.B.C. 17,000: Polymorphs 90 per cent.

Lymphocytes 5 per cent.

Monocytes 5 per cent.

Plasma uric acid 2 mg. per 100 ml.

Cholesterol 50 mg. per 100 ml.

Plasma proteins 6.7 g. per 100 ml. (albumin 4.6, globulin 1.4, fibrinogen 0.7 per 100 ml.).

Urea 53 mg. per 100 ml.

Sugar 111 mg. per 100 ml.

Chlorides 497 mg. per 100 ml.

He was therefore given 2,000 ml. normal saline, 800 ml. plasma, and then 500 ml. whole blood, with improvement in his general condition.

On September 23 the patient developed a sudden pain in the neck, especially on the left side. Angulation to the left with rotation of the chin to the right was noted, and x rays (see Fig. 4) confirmed the presence of a subluxation forward of the atlas on the

axis, together with destruction of the transverse process of the atlas vertebra. Traction was applied with relief and a plaster collar was fitted three days later. During this period the patient's general condition deteriorated and he became slightly jaundiced with fever. His appetite was very poor and he could only eat spoonfuls of semi-fluids. The white blood-cell count rose to a peak of 67,000 with 92 per cent. polymorphs, and on October 4 his right shoulder was painful. On October 7 his right elbow became more painful, red, and swollen, and was described by him as being typical of his previous gouty attacks (see Fig. 5). In view of the pyrexia and leucocytosis, penicillin was administered prophylactically from September 21 to October 12, although no infection was discovered. On October 15 he was started on control injections of sterile saline, and, with the belief that he was having a special drug, his spirits rose. He improved a little and he began to take a little food.

Blood Examination, October 17

R.B.C. 2,430,000.
Haemoglobin 44 per cent.
W.B.C. 31,100:
Polymorphs 94 per cent.
Lymphocytes 3 per cent.
Monocytes 3 per cent.
Sedimentation rate 40 mm. in one hour (corrected Wintrobe).
Plasma uric acid 12.0 mg. per 100 ml.
Cholesterol 50 mg. per 100 ml.
Plasma proteins 6.2 g. per 100 ml. (albumin 4.0, globulin 1.1, fibrinogen 1.1 per 100 ml.). Sugar 105 mg. per 100 ml.

At 15.00 hrs on this day he was given 5 mg. ACTH and this was repeated 6-hourly until October 22 (105 mg. in all). His appetite became ravenous so that each patient in the ward as he passed his bed gave him some morsel of food. The effect on the blood count was not dramatic, but whether *post* or *propter hoc* the white count gradually fell. (For details see Figs 6-10 and the Table overleaf.)

Blood Examination, October 21

Haemoglobin 45 per cent.
W.B.C. 19,520:
Polymorphs 84 per cent.
Lymphocytes 11 per cent.
Monocytes 5 per cent.
Sedimentation rate 37 mm. in one hour (corrected Wintrobe).
Plasma uric acid 7.3 mg. per 100 ml.
Cholesterol 42 mg. per 100 ml.
Plasma proteins 6.5 g. per 100 ml. (albumin 3.5, globulin 2.2, fibrinogen 0.8 per 100 ml.).
Sugar 116 mg. per 100 ml.

FIG. 5.—Right elbow showing gross swelling and complete loss of normal outline (July, 1949).

Final Stages.—On October 24, exactly two days after stopping the ACTH, the patient said he felt less well, started to sweat, ceased to eat, and began to twitch a little, especially in his neck. The blood count and other blood examinations showed no real change.

By October 27 the plasma uric acid had risen to 13.3 mg. per 100 ml., the white count had dropped to 15,400, and he was beginning to improve again a little in himself. This

FIG. 6.—Plasma uric acid, cholesterol, haematocrit, and white-cell levels, August, 1946 to July, 1949.

FIG. 7.—Urinary steroid excretion, August 30 to October 27, 1949.

FIG. 8.—Plasma proteins, September 15 to November 7, and sedimentation rate (corrected Wintrobe), September 5 to November 7, 1949.

TABLE
URINARY URIC ACID, CREATININE, AND STEROID ESTIMATIONS

Date	17-ketosteroids						
	Total (mg./24 hrs)	Non-ketonic (mg./24 hrs)	Ketonic (mg./24 hrs)	α Fraction (mg./24 hrs)	β Fraction (mg./24 hrs)	α in Ketonic (%)	β in Ketonic (%)
Aug. 29-31 ..	12.0	3.7	8.3	8.05	0.25	96.9	3.1
Aug. 31-Sept. 2 ..	10.9	3.4	7.5	Almost 7.5	Trace	Almost 100	Trace
Sept. 6-7 ..	14.7	5.6	9.1	8.98	0.12	98.7	1.3
Sept. 7-8 ..	18.0	6.5	11.5	11.4	0.10	99.1	0.9
Sept. 8-9 ..	22.7	6.8	15.9	15.69	0.21	98.7	1.3
Sept. 13-14 ..	18.2	7.6	10.6	10.6	nil	100	nil
Oct. 2-3 ..	6.7	3.6	3.1	3.04	0.06	98.1	1.9
Oct. 11-12 ..	6.1	3.3	2.8	2.73	0.07	97.5	2.5
Oct. 14-15 ..	4.05	—	—	—	—	—	—
Oct. 15-16 ..	2.82	—	—	—	—	—	—
Oct. 16-17 ..	5.06	—	—	—	—	—	—
Oct. 17 (10 a.m.-10 p.m.)	3.0	3.0	nil	nil	nil	nil	nil
Oct. 17-18 (10 p.m.-10 a.m.)	3.3	1.9	1.4	1.4	nil	100	nil
Oct. 18-20 ..	4.6	2.4	2.2	2.19	0.01	99.4	0.6
Oct. 23-24 ..	12.7	3.3	9.4	9.26	0.14	98.5	1.5
Oct. 24-25 ..	10	—	—	—	—	—	—
Oct. 26-27 ..	4.2	1.0	3.2	Almost 3.2	Trace	Almost 100	Trace

FIG. 9.—Total white-cell and differential white-cell counts, July 15 to November 9, 1949.

TABLE
URINARY URIC ACID, CREATININE, AND STEROID ESTIMATIONS

Date	Cortin (mg./24 hrs)	Uric Acid (g./24 hrs)	Creatinine (g./24 hrs)	Uric Acid Creatinine Ratio
Aug. 29-31 ..	1.3, 1.7	0.92, 1.29	0.78, 0.70	1.2, 1.8
Aug. 31-Sept. 2	2.5, 4.9	0.91, 0.75	0.71, 0.70	1.3, 1.1
Sept. 6-7	—	0.38	0.70	0.5
Sept. 7-8	1.1	0.58	0.80	0.7
Sept. 8-9	2.2	0.88	0.84	1.0
Sept. 13-14 ..	2.5	0.78	0.77	1.0
Oct. 2-3	1.47	—	0.58	—
Oct. 11-12 ..	0.44	—	0.44	—
Oct. 14-15 ..	—	—	—	—
Oct. 15-16 ..	—	—	—	—
Oct. 16-17 ..	—	—	—	—
Oct. 17 (10 a.m.-10 p.m.)	0.85	0.8	0.3	2.7
Oct. 17-18 (10 p.m.-10 a.m.)	0.42	0.5	0.25	2.0
Oct. 18-20 ..	0.7	0.66	0.20	3.3
Oct. 23-24 ..	1.7	1.51	0.51	3.0
Oct. 24-25 ..	—	—	—	—
Oct. 26-27 ..	1.96	3.8	4.3	0.79

FIG. 10.—Plasma uric acid, cholesterol, haemoglobin, and haematocrit levels, July 16 to November 17, 1949.

day he was given one injection of 10 mg. ACTH. He continued to improve, but there was no dramatic change. On October 29 he had an infusion of 1 pint packed red cells with no reaction. During the next 10 days there was little change clinically, or on haematological examination.

On November 17 a new leather collar was worn for the first time and the patient sat up in a wheel chair. He seemed better.

On November 19 he had some haematuria; he also began to run an evening temperature again, and developed a slight cough. Early signs of consolidation at the base of the right lung were noted. Penicillin therapy was started at once, but from this time the patient went downhill, becoming weaker and more drowsy until his death on November 30.

Post-Mortem Examination

This confirmed that death was due to bronchopneumonia. There were many tophaceous deposits in both ears, around nearly all the joints, and over-lying the ribs; a pultaceous deposit was present over the right thyroid cartilage. The bone marrow appeared normal macroscopically.

Examination of the heart showed a little pericardial thickening on the wall of the right auricle; the heart muscle was a little flabby. The aorta and coronary arteries appeared normal. No atheroma was visible anywhere.

The adrenal glands showed a normal pattern but with hardly any lipid in the cortex. The pituitary and thyroid glands appeared normal macroscopically.

The kidneys, especially the left, showed obliteration of the normal pattern and contained in the medulla and in the inner part of the cortex a large number of minute yellow granules. The capsule of the left kidney stripped with some difficulty, but the arteries appeared normal. There was yellow gravel in the pelvis of the right kidney.

All the limb joints examined were affected, being distorted in varying degree by tophaceous deposit. When opened, they showed a thick white chalky coat covering all the joint surfaces, often distending the cavity. In the larger joints the ends of the bones looked as if they had been covered with a thick layer of glossy white paint.

In the upper cervical spine, a remarkable condition was found. A thick band of deposit lay between the base of the skull and the atlas, forming an almost complete collar between the two bones. The deposit had eroded the atlas, causing pathological fracture in one place, and had forced the anterior part of the atlas downward so that it lay opposite the disk between the axis and the 3rd cervical vertebra.

This subluxation resulted in the protrusion of the remains of the odontoid process upward into the foramen magnum, even though the process was reduced to about half its normal size by tophaceous destruction.

Several other deposits were present in the dura and between the posterior parts of the upper cervical vertebra; none of these deposits compressed the cord.

Histological Findings

Locomotor System

Bone and Articular Cartilage (lower end of humerus, tibia, and patella).

Humerus: articular cartilage almost completely destroyed by cellular fibrous tissue containing crystalline deposits. In these round deposits urate crystals lie in a hyaline matrix surrounded by a foreign body giant cell reaction. A similar loose connective tissue with urate deposits occupies the intertrabecular spaces of cancellous bone, urate deposits are present in trabeculae, often causing remarkable expansion. Small areas of lymphocyte infiltration are seen in more fibrous areas, but are not comparable in size or number with those seen in rheumatoid arthritis.

Patella and tibia: Similar changes to those in the humerus, but with less destruction of cartilage. Tophaceous deposits present in quadriceps tendon.

Synovial Membrane (knee and shoulder).—Largely composed of urate deposit in hyaline matrix with foreign body giant cells and loose stroma of cellular connective tissue. A few accumulations of lymphocytes seen in relation to vessels, as in osteo-arthritis. No Allison Ghormley foci seen. Lining cells present only in shoulder. (See Figs 13 and 14, pp. 300 and 301.)

Muscle (psoas, quadriceps, deltoid, sternomastoid, intercostal).—All except sternomastoid showed marked degenerative changes: fibres tortuous, atrophic, and vacuolated; striation lost; marked fibrosis. No amyloid change seen. Two paravascular perimysial lymphocytic foci in psoas resembling, though less compact than, the smaller foci found in muscle in rheumatoid arthritis.

Urogenital System

Kidneys.—Capsule thickened, patches of fibrosis and chronic inflammatory reaction in subcapsular region and throughout cortex; glomeruli show lobulation of tufts with hyaline change and atrophy, progressing in many to complete scarring and obliteration; red cells present in isolated glomerular spaces; patchy amyloid deposition. (See Figs 15a and 15b, p. 302.)

Tubules.—Patchy fatty degeneration and hyaline droplet degeneration in scattered tubules. Some amyloid deposits in basement membrane.

Vessels.—Medial thickening and duplicating of internal elastic lamina in interlobular arteries. Amyloid deposits in small arteries.

Tophi.—Many uratic deposits in deeper parts of cortex, consisting of radially arranged crystals in hyaline matrix with foreign body giant cells and degenerate leucocytes around; the tophi appeared to arise in interstitial tissues and not in tubules; around each was an area of compressed parenchyma, congestion, and lymphocytic infiltration.

Prostate.—Amyloid change in small arteries; no tophi.

Testis and Epididymis.—No amyloid change or tophi; spermatogenesis virtually absent.

Endocrine System

Thyroid and Pituitary.—No apparent abnormality.

Adrenals.—Slight disorganization of zona reticularis; lipid granules present in cortical cells, especially in middle zone of the zona fasciculata; extensive amyloid deposition in connective tissues and vessels of zona fasciculata; vessels congested, no haemorrhage; medulla normal.

Alimentary System

Stomach.—Toxic gastritis; small vessels show amyloid.

Small Gut.—Early amyloid deposition in small vessels.

Pancreas.—No abnormality except amyloid deposition.

Liver.—Generalized toxic changes and fatty degeneration of parenchyma; lobules appear smaller than normal; extensive patchy deposits of amyloid in vessels in the portal tracts and in connective tissues between sinus endothelium and parenchymal cells; no excess of iron and no urate deposits present.

Gall Bladder.—Very early amyloid deposition in submucous vessels.

Cardiovascular System

Heart.—Atrophy, cloudy swelling, and fatty change in myocardium with early amyloid deposits in connective tissue; no inflammatory reaction.

Arteries (mesenteric, coeliac, branches of brachial).—Normal except for early amyloid deposition in the small mesenteric vessels.

Respiratory System

Trachea.—No urate deposits.

Bronchi.—Purulent bronchitis.

Lungs.—R.L.L. extensive bronchopneumonia with hypostatic congestion and oedema. L.L.L., congestion and serous exudation; limited consolidation around affected bronchioles; no amyloid deposits.

Other Tissues

Skin over Shoulder.—Masses of acicular urate crystals enclosed in fibrous sacs in subcutaneous tissues. Foreign-body giant-cell reaction present, but no other inflammatory reaction except fibrosis.

Sciatic Nerve.—No abnormality.

Reticulo-Endothelial System

Spleen (removed three months before death).—Changes associated with general toxæmia; sinuses dilated, with endothelial swelling and proliferation; fibrous tissue increased; very early amyloid deposition in thickened small arteries and central vessels of malpighian bodies.

Splenunculus (autopsy).—Marked contrast with appearance of the spleen. Amyloid degeneration widespread and advanced in malpighian bodies and connective tissue.

Lymph Glands (axillary, lumbar, mesenteric, bronchial).—All were enlarged, showing fibrosis of capsule and trabeculae; follicles small, Flemming's centres small or absent; sinus catarrh; medulla infiltrated with chronic inflammatory cells; some focal lymphocyte proliferation.

Chemistry of Tophaceous Material.—Analysis of dried material gave these results:

Right Knee.

Uric acid, 48 per cent.
Protein, 35 per cent.
Cholesterol, 2.5 per cent.
Phosphate, a trace, less than 0.5 per cent.
Chloride, less than 0.2 per cent.
Sodium, 6.85 per cent.

Right Renal Pelvis.

Uric acid, 70 per cent.
Protein, 0.5 per cent.
Chloride, less than 0.2 per cent.
Sodium, 0.271 per cent.
Carbonate, phosphate, oxalate, cholesterol, and cystine absent.

Discussion

CLINICAL FEATURES

Though this is far from being the youngest case of gout recorded, for gout has been seen at the age of 6 (Garrod, 1876), and twice at the age of 8 (Scudamore, 1823; Talbott, 1943), it is the most rapidly progressing case we have seen. The onset was quite typical, yet the diagnosis of gout was not made till $3\frac{1}{2}$ years later, the condition having been treated as rheumatoid arthritis. When the patient was first seen his plasma uric acid was 16 mg. per 100 ml., and later 17.3 mg. per 100 ml., the highest values yet seen by us in any uncomplicated case with reasonable kidney function. He had the anaemia and loss of weight of the worst chronic cases, who have usually had the condition for 30 or more years. The sedimentation rate was persistently raised, not varying markedly as is usual in the earlier cases, and the blood cholesterol gradually dropped to the very low level of 42 mg. per 100 ml. The

spleen was enlarged when he was first seen, and did not alter markedly; he was always anaemic. His white-cell count gradually dropped to 2,500, with a definite lymphopenia (lymphocytes 225 per c.mm.).

Acute attacks of joint pain were largely warded off with colchicine, but his general condition rapidly deteriorated despite all treatment, which included cinchophen administration.

The most unusual feature clinically was, however, the sudden subluxation of the first cervical vertebra due to tophaceous softening—a condition so far undescribed.

In July, 1949, he first experienced some pain in the left side of his head and stiffness in the neck, but only mentioned this on careful questioning. On September 23 he complained of severe pain in the throat and the left side of the neck, and angulation to the left and rotation of the chin to the right were noted (Fig. 11). In view of the fact that a similar condition had been seen three times in rheumatoid arthritis, a diagnosis of subluxation was immediately made. This was confirmed by x-ray examination and traction was applied with relief of the pain. A plaster collar was made, and this was later replaced by a moulded leather collar, which proved most efficient.

Of the three rheumatoid cases who developed this disability, one died, one old woman continues to live in a bed-ridden condition, and in one, a young man in whom the generalized rheumatoid disease followed a gonococcal infection, excellent correction was obtained by traction; after this had been replaced by a collar for three months good recovery took place, the only remaining disability now being some stiffness of the neck. No case of spontaneous dislocation of the neck due to gout has to our knowledge previously been recorded and therefore prognosis in our case was impossible, but from September till the end of November, when the patient died, no material change occurred in the local condition.

The nature of the tophaceous deposits found at autopsy make it seem unlikely that healing could have occurred naturally.

COLCHICINE THERAPY

This case illustrates the value of long continued colchicine therapy in gout. One of us (G.D.K.) has now had a patient with gout on colchicine gr. $\frac{1}{120}$ twice daily for 5 years, with complete relief from attacks, which were previously

FIG. 11.—Patient showing emaciation, position of head with spasm of right sterno-mastoid due to subluxation of atlas vertebra, tophi (including ears), and condition of joints (September, 1949).

frequent, and with no toxic symptoms. In the present case, the patient was taking colchicine for three years, in a dosage of gr. $\frac{1\frac{1}{2}}{120}$ 3 times a day, with only brief intervals; during these intervals he immediately developed fulminant attacks of gout, which on one occasion caused him to become dangerously ill. The acuteness of the attack with high fever immediately colchicine was withdrawn, and its therapeutic superiority over cinchophen was very striking. Very rarely an idiosyncrasy to colchicine may occur and the toxic effects may then even be fatal (Macleod and Phillips, 1947), but, properly controlled, the risk is considered to be negligible (Talbot and Lockie, 1949). Some of the gastro-intestinal symptoms are probably due to local irritation as they are less liable to occur when the drug is given intravenously (Wolfson, 1949). The dosage used intravenously is similar to that used orally; intravenous administration may be of value in acute gout with gastric intolerance and during surgery. It was used at the time of splenectomy in the case under consideration. Colchicine is a nuclear poison and has been used in large doses as such and also in the production of an alarm reaction in experimental adrenal work (Yoffey, 1946; Selye, 1949).

In this patient there was considerable anaemia, resulting from hypoplasia of the red-cell series, and also some leucopenia. But the patient was extremely ill and there is no reason to incriminate colchicine as the cause of his blood condition.

X-RAY THERAPY

Radiotherapy has been but little used in gout and, as there are usually fairly complete remissions between attacks, and the joints affected as a rule vary from one attack to another, its therapeutic value is obviously much limited. One of us (G.D.K.) has, however, used x-ray treatment in two other cases of gout, where there has been permanent change in a joint with long-continued persistent pain. The effect has been similar to that produced in this patient, namely an acute exacerbation followed later by some improvement. It is only when all other therapy has failed to relieve chronic pain in a gouty joint that x-ray therapy appears justified.

SPLENOMEGALY AND SPLENECTOMY

Some six cases of gout associated with anaemia and splenomegaly, treated by splenectomy, have been reported. The majority have probably been cases of acholuric jaundice with gout and, in at least three, the gouty condition has appeared to benefit (Lambie, 1940; Deitrick, 1940; Owen and Roberts, 1937; Davis, 1949).

Report of Former Case.—Lambie (1940), in a paper almost amounting to a monograph, describes the case of a boy of 18 who had had his first attack of gout four years earlier. He was said to have been anaemic from birth and had been noted to have slight splenomegaly and hepatomegaly since the age of eleven. He had also had recurrent attacks of jaundice. There was no family history either of this condition or of gout. This patient had an orthochromic anaemia with haemoglobin varying from 50 to 60 per cent., but normal red-cell fragility and reticulocytes 5 per cent. The white cells were normal in numbers or slightly increased, and occasionally there was slight eosinophilia. The blood uric acid was raised to 11.4 mg. per 100 ml. and the plasma cholesterol decreased to 75 mg. per 100 ml. A splenectomy was performed, the organ weighing 320 g., and the morbid

histologists reported that the malpighian bodies showed little abnormality, though some had pale lymphoblastic centres, and in others there was some epitheloid or hyaline change. The arteries had a layer of hyaline material external to the intima. The splenic sinuses were moderately dilated. The pulp cords appeared dense, and contained cells with vesicular nuclei, there were only faint traces of collagen, their diagnosis was hepato-lienal fibrosis. In the marrow there was an increased proportion of both red and white primitive cells.

In the days immediately following splenectomy there was leucocytosis and slight fever. The tophi became slightly more painful and then later softened and decreased in size. There was some improvement in the anaemia, and slight decrease in the blood uric acid with a marked increase in the ultra-filtrable fraction, but the plasma cholesterol remained unchanged.

Gout has been noted as occurring in erythraemia and in acholuric jaundice and, both in the latter condition and in pernicious anaemia, an increased uric acid excretion has been found to parallel reticulocytosis. It would therefore seem reasonable to expect a worsening of any tendency to gout in a condition where there was an increased production of the red cells, as this would cause an increase in endogenous purine formation from break-down of nuclear material during red-cell maturation. Apart from this, it is possible that the spleen may play some more fundamental part in metabolism, as suggested by the rapid improvement in certain rheumatoid cases following splenectomy (Bach, 1940). One such case, not yet published, in which the result was particularly startling, has been observed by one of us (G.D.K.).

Lambie discusses in some detail the relation between blood uric acid levels and uric acid excretion. This can be explained only on the hypothesis of a high renal threshold in gout, or that there is a change in state of part of the blood uric acid, a very old theory. He states that, at the *pH* of blood, a uric acid level above 6.4 mg. per 100 ml. must denote super-saturation, or that part in a colloidal form. He therefore attempted to throw new light on this problem by means of ultra-filtration. In normal individuals he found that the ultra-filtrate contained as much or more uric acid as the blood. In his case of gout, with a blood uric acid of 13 mg. per 100 ml., the ultra-filtrate amounted to 28 per cent. of this, yet a case of leukaemia with blood uric acid of 26 mg. per 100 ml. had an ultra-filtrate fraction of 51 per cent. He found that with a rise in the blood uric acid from any cause the percentage that was ultra-filtrable decreased, but that in gout the decrease was more marked than in other conditions. In Lambie's case, after splenectomy, the ultra-filtrable fraction increased to 100 per cent., though the blood uric acid only fell by 3 mg. to i.e. 10 mg. per 100 ml. He believed that the fall would have been greater had there not been an absorption into the blood from tophaceous deposits, which were softening.

It is difficult to draw conclusions as to the result of splenectomy in our case. Clinically the patient stood the operation well, considering his serious condition. The operation provoked no attack of gout in the joints, but it must be remembered that colchicine was never discontinued even for a day. All the blood and urinary examinations (detailed in Figs 6-10) must be scrutinized with care before conclusions

can be drawn, as the patient was a very sick man, and at times some degree of dehydration and haemo-concentration may have affected the figures. The diffusible fraction of uric acid was not estimated. The blood uric acid, however, fell to 8 mg. per 100 ml. at the end of three weeks after splenectomy, to rise again to 12 mg. per 100 ml. after another three weeks. 24-hour specimens of urine were sent to Fishponds Mental Hospital Research Laboratories for steroid, creatinine, and uric acid estimations. Total ketosteroid estimations were carried out by the method of Callow, Callow, and Emmens (1938), and the ketonic fraction according to Callow and Callow (1938). Cortin was estimated by the method of Heard, Sobel, and Venning (1946) modified by Hemphill and Reiss (1947).

It must be realized that, with every care, steroid investigations are still far from satisfactory, both with regard to technical methods and to interpretation. In the case under discussion it was found that there was a marked rise in total crude and ketonic 17-ketosteroids, from 11 to 22.7 mg. per 100 ml. in the former and from 7.5 to 15.9 mg. per 100 ml. in the latter, on the fourth day following splenectomy, and that after this there was a gradual fall. The uric acid/creatinine ratio actually fell a little, on account of the slight decrease in uric acid excretion. No conclusions could be drawn as to the effects of splenectomy on cortin or on the α and β fractions of the ketonic ketosteroids. The rise in the total and ketonic ketosteroids may well have been the result of an alarm reaction working through the hypophysis, causing temporary stimulation of the adrenal cortex by endogenous ACTH.

ACTH ADMINISTRATION

On October 17 the administration of 5 mg. ACTH 6-hourly was begun and this was continued for six days (21 doses, i.e. 105 mg.). Urinary uric acid/creatinine ratios, urinary steroids, and complete differential blood counts were estimated daily (see Figs 6-10). Clinically the outstanding effect was on the appetite, which from being negligible became ravenous. The patient's mental outlook also improved and he slept better, but some improvement of this kind had been observed with previous control injections, and these results may have been partly psychological. Two days after discontinuing these injections the patient appeared decidedly worse; there was some twitching of the muscles and he was very restless and sweated a great deal.

The immediate effect of ACTH on typical gout should be the same as that of cortisone, i.e. the production of a remission of any acute attack, an increase in the excretion of uric acid and corticoids and in the uric acid/creatinine ratio, and a drop in the eosinophils and lymphocytes in the circulating blood. In addition the urine should show an increase in ketosteroids due to stimulation of the adrenals to androgen production. About the fourth day after discontinuing treatment a relapse reverse phase, which should not occur with cortisone therapy, might be expected. This follows a lowering of adrenal activity on cessation of stimulation by the pituitary hormone, and this phase is more pronounced in gouty than in normal individuals (Wolfson, 1949; Thorn, 1949).

In the present case, as previously stated, care must be taken in interpretation

of the figures because of the sickness of the patient, haemo-concentration, and starvation factors, and in addition the dosage used was very small, both because of shortage of the drug and because of the risk of flooding the circulation with uric acid in so ill a patient. Further work on less critically ill cases of gout, using larger doses of ACTH, is proceeding. In spite of these complicating factors the following changes in blood and urine may be noted:

(i) The plasma uric acid dropped to 7 mg. per 100 ml. during ACTH administration, and rose to 13.7 mg. per 100 ml. on the fifth day after cessation.

(ii) The cholesterol rose from 50 to 58 mg. per 100 ml. in two days, and then dropped to 42, the lowest figure recorded in this case.

(iii) A fall in plasma cholesterol occurs in normal persons during ACTH administration, because of depletion of the adrenal cortex (Mason and others, 1948) and during an acute episode of gout (Wolfson and others, 1949).

(iv) Total eosinophil counts had not by this time been started and there were insufficient eosinophil cells for the percentage count to be of any value. The total white-cell count had started to drop before ACTH was commenced. It continued to fall rapidly, but the lymphocytes fell in a corresponding manner to the granular cells. Some target cells and normoblasts were regularly seen.

(v) The total plasma proteins showed no change, but the albumin and fibrinogen fell a little, and the globulin rose on both occasions when ACTH was given. During the first period the albumin/globulin ratio dropped from 3.6:1 to 1.6:1 and on the second occasion from 4:1 to 2.5:1.

(vi) On urinary examination both the crude and ketonic ketosteroid content of the urine increased, but no significant change was seen in the urinary cortin.

(vii) The urinary creatinine dropped markedly on the first day of ACTH administration, and it is thought that this may have been due to the patient suddenly beginning to eat for the first time for several weeks.

(viii) The uric acid/creatinine ratio rose a little, but the significance of these figures is very doubtful in view of the complicating factors of starvation and the general condition of the patient.

AUTOPSY AND HISTOLOGICAL FINDINGS

The cervical spine furnished a remarkable appearance at autopsy (Fig. 12). The base of the skull could be freely moved upon the cervical spine. When the head was flexed, a considerable bulge appeared in the anterior wall of the spinal canal

FIG. 12.—Sagittal section through the upper cervical vertebrae, showing uratic deposits in the odontoid process of the axis (A); dura mater (B); subluxation of atlas vertebra (C); tophaceous material enclosed in fibrous sac (D).

FIG. 13.—Post-mortem appearances of left knee joint opened showing the cavity filled with white tophaceous material.

just below the foramen magnum; this bulge consisted of the peg of the axis, thrust into prominence by the downward displacement of the anterior arch of the atlas which was fractured by massive tophaceous destruction. From the point of view of the cervical spine, it appears that, had life continued for long, two results might have ensued: compression of the cervical cord by the increasing size of the two dural deposits, or sudden death from infringement of the odontoid process upon the medulla during flexion of the head.

All major joints showed gross distortion by tophaceous deposits (Fig. 13). Articular cartilage was in varying degree destroyed by a pannus of fibrous tissue containing urate deposits, and the joint cavities were filled with chalky material. The adjacent bone was frequently disorganized by tophaceous deposits, which eroded and distended trabeculae, and gave rise to giant-cell reactions and fibrosis. There was also massive deposition in the synovial membranes (Fig. 14, opposite).

The muscles examined showed marked degeneration with fibrosis. The

FIG. 14.—Capsule of shoulder joint. Massive urate deposits stained black, in capsule and adjacent muscle. (Holmes and Van Gieson $\times 50$).

typical cell reaction found in rheumatoid arthritis was not seen, but it is interesting to note that two lymphocytic foci, with considerable resemblance to rheumatoid foci, were present in the piece of psoas examined.

The occurrence of chronic nephritis with urate deposition in the kidneys is well recognized in chronic gout. The kidneys of our case showed gross changes in many ways reminiscent of 'arteriosclerotic kidney'—widespread, patchy obliteration of glomeruli by hyaline change and fibrosis, with areas of parenchymal hypertrophy and interstitial inflammatory reaction. The changes in the vessels, however, did not appear adequate to explain the severe lesions. There were widespread tophaceous deposits, in the deeper parts of the cortex, and it is possible that these, by their size and by the fibrosis which they produced, may have contributed to the cortical ischaemia (Figs 15*a* and 15*b*, overleaf).

The endocrine glands showed no distinctive abnormality; the adrenals, in common with many organs, showed some amyloid deposition in vessel walls and connective tissues.

The large blood vessels showed a conspicuous lack of atheroma; the only abnormalities were microscopic, namely, widespread slight amyloidosis of small arteries, and hypertrophy of the intima renal vessels.

FIG. 15(a).—Right kidney. Capsule of glomerulus fibrosed and tuft shrunken. Adjacent area of round-cell infiltration. Hyaline casts in some tubules. (Mallory $\times 200$.)

FIG. 15(b).—Left kidney. Large tophus, showing masses of urate surrounded by degenerate leucocytes and fibrosis. Inflammatory reaction in adjacent parenchyma. H. and E. $\times 100$.

The reticulo-endothelial system showed the changes of long continued toxæmia. When the spleen, removed 3 months before death, and a splenunculus, found at autopsy, were compared, a considerable increase of amyloidosis was seen to have occurred in the last three months of life.

CHEMISTRY OF TOPHACEOUS MATERIAL

The high protein content (35 per cent.) of the material from the right knee is worthy of note, and also the sodium content which is almost exactly that required to account for the estimated 'uric acid' being in the form of sodium biurate. In the more acid medium of the urine the tophaceous material contained much less sodium and was presumably in fact composed of uric acid with very little urate.

Summary

The clinical history, pathological findings, and post-mortem examination of a case of severe gout associated with splenomegaly are outlined. Striking features are the high plasma uric acid level and low cholesterol, the enlarged spleen with at one stage leucopenia, the rapid deterioration of the patient's condition in spite of treatment, and the tophaceous softening and subluxation of the first cervical vertebra.

The morbid histology of the lesions and the chemical composition of tophaceous material are described.

Treatment by means of continuous colchicine therapy for approximately three years, intravenous colchicine, radiotherapy, splenectomy, and finally ACTH, is discussed.

We should like to thank Dr. Max Reiss and the staff of the Bristol Mental Hospital Laboratories for the steroid estimations, Messrs. Organon Laboratories for the provision of the ACTH, and Dr. Hubert Gibson and Mr. Richardson for assistance with the morbid histology.

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Goutte:

Cas Peu Commun, avec Ramollissement et Subluxation de la Première Vertèbre Cervicale et avec Splénomégalie. Résultats d'Administration de l'ACTH et Découvertes à l'Autopsie

RÉSUMÉ

On rapporte l'histoire clinique, les résultats pathologiques, et les découvertes à l'autopsie d'un cas de goutte grave, associée à la splénomégalie. Un taux élevé d'acide urique dans le plasma et un taux bas de cholestérol, la rate augmentée de volume, la leucopénie au cours d'un stade, la détérioration rapide de l'état général du malade malgré le traitement ainsi que le ramollissement graveleux, et la subluxation de la première vertèbre cervicale, en constituaient les traits saillants.

On décrit l'histo-pathologie des lésions et la composition chimique du matériel graveleux.

On discute le traitement par la colchicine (continu pendant à peu près trois ans), par la colchicine intraveineuse, par les rayons X, par la splenectomie, et finalement par l'ACTH.

Gota:

Caso Poco Común, con Reblandecimiento y Subluxación de la Primera Vértebra Cervical y con Esplenomegalia. Resultado de Administración de ACTH y Hallazgos de Autopsia

RESUMEN

Se esboza la historia clínica, los resultados patológicos, y los hallazgos de autopsia en un caso de gota grave, asociada a la esplenomegalia. Entre los rasgos notables de este caso hay que mencionar las cifras altas del ácido úrico y las cifras bajas del colesterol, el bazo aumentado de volumen, leucopenia durante un cierto período, la deterioración del estado general del enfermo a pesar del tratamiento, así como el reblandecimiento pedregoso, y la subluxación de la primera vértebra cervical.

Se describe la histo-patología de las lesiones y la composición química del material pedregoso.

Se discute el tratamiento por la colchicina durante cerca de tres años, por colchicina intravenosa, por radioterapia, por esplenectomia, y, finalmente, por ACTH.