blood supply and ischaemic muscle pain in all four limbs for many months before death. Finally, arterial narrowing led to vascular occlusion in the right leg, and this led to gangrene of the toes of the right foot. Heavy deposits of calcium in the mitral valve brought about stiffening of the cusps, and was presumably the cause of a very rough systolic murmur and thrill.

In this patient, as in other patients with renal hyperparathyroidism, there were marked phosphorus retention and low plasma carbon dioxide combining power. The serum calcium was normal (10.9 mg. per 100 ml.) until two days before death, when it rose to 13.3 mg. According to Albright and Reifstein (1948) a tendency to low serum calcium occurs as an adjustment to phosphorus retention. Parathyroid hyperplasia takes place in response to the stimulus of this low calcium level. The increased production of parathyroid hormone leads to the mobilization of calcium from the bones and then the serum calcium is raised to normal or higher from the earlier low level. The serum phosphorus, however, remains high, as the usual action of parathyroid hormone in producing a phosphorus diuresis cannot occur because of the renal disease. The blood and tissues now become over-saturated with calcium phosphate, and this may lead to the precipitation of calcium salts in the tissues of the body.

Finally, it is interesting to note that in this case three out of the four enlarged parathyroid glands were found embedded in the thyroid gland. This raises the possibility of difficulty in the surgical treatment of primary hyperparathyroidism in which an adenoma or one or more hyperplastic glands may be hidden in the substance of the thyroid gland. However, this is not a common occurrence, and Norris (1947) records that out of 281 cases in which parathyroid adenomata were removed in the treatment of hyperparathyroidism the tumour was found within the thyroid gland in only nine instances.

Summary

The relationship between chronic renal disease and parathyroid hyperfunction is discussed and the literature is reviewed, with special reference to the occurrence of metastatic calcification and osteitis fibrosa.

A case is reported of chronic nephritis with parathyroid hyperplasia, showing widespread arterial calcification and the bone changes of osteitis fibrosa.

I wish to thank Professor W. Melville Arnott for permission to publish this case, Professor J. W. Orr for the pathological report, and both for their criticism and help.

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CRYOGLOBULINAEMIA IN MULTIPLE MYELOMATOSIS

BY

A. N. BLADES, M.B., B.S.

Assistant Pathologist, Royal Sussex County Hospital, Brighton

This article describes an unsuspected case of multiple myelomatosis in which the diagnosis was first suggested by the accidental finding of cryoglobulinaemia. This term, proposed by Lerner and Watson (1947), means literally "cold globulin in the blood," and implies the presence in the plasma of a globulin which precipitates or solidifies on cooling. In the recorded cases this usually took place at about 30° C., and it may produce partial or complete solidification of the blood. The phenomenon is reversible on warming to 37° C., and the changes may be repeated indefinitely, although they occur slowly.

I have been able to trace about a dozen cases in the literature. Rörvik (1950) gives a review of nine of these, with a tenth case report; Shapiro, Ross, and Moore (1943) reported a case which showed the essential features, although they did not use this name; and Hill, Dunlop, and Mulligan (1949) described a case. In most cases the primary disease is multiple myelomatosis, but there is evidence to show that such globulins are also found in endocarditis lenta (Lerner and Watson, 1947), in humans and dogs with kala-azar, in nephrosis (Wertheimer and Stein, 1944), and in infective arthritis (Rörvik, 1950).

Case Report

A retired gardener aged 64 was admitted to hospital on January 4, 1950, for a skin condition—phrynodema—which subsequently proved to be due to vitamin-A deficiency. He had had this complaint a year previously, and had been cured by the administration of vitamins; he admitted that he had had a very deficient diet, and his plasma showed a deficiency of vitamin A. At the time of admission, however, he felt well except for this complaint.

On January 12 blood was taken into a Wintrobe oxalate bottle for a blood count. This showed an anaemia (60%), with a normal colour index, a normal white cell count and distribution, and a corrected sedimentation rate of 22 mm./hour (haematocrit 28%). The haematologist stated: "The red cells show a marked tendency to auto-agglutination, with a very rapid sedimentation rate. There is also an unusual phenomenon, spontaneous clotting in an oxalate bottle after one to two hours on the bench." The protein constitution of the blood was queried on this account. On the following day I went to the ward to obtain venous blood to investigate the plasma proteins, using a syringe sterilized in the laboratory, and therefore cold. The veins were prominent, but only a few drops of blood were obtained before the flow ceased. A large needle boiled up in the ward was substituted and 30 ml. of blood was readily obtained. The significance of the temperature difference between the two needles was not appreciated at the time. The blood was placed in the incubator (37° C.), and the serum separated off in the usual way. By Harrison's (1949) method, using 27.79% ammonium sulphate for the precipitation of globulin, and biuret estimation, the serum proteins were: albumin, 3.8 g.%; globulin, 8.2 g.%; total, 12 g.%.

It was then observed that the serum had solidified on the bench. This suggested that the clotting referred to by the haematologist and the blocking of the first needle were in fact processes of solidification due to cooling. Investigation showed that the serum set slowly into a soft solid white opaque mass at 22° C., and melted into a normal clear

pale-yellow serum at 30° C. This change could be repeated indefinitely. When a drop was allowed to cool on a slide a mass of small burr-like crystalline deposits separated, the individual mass being composed of fine needle-like crystals arranged radially. These disappeared again on warming.

Since such high globulin figures are found in only a few conditions—commonly sarcoidosis, kala-azar, and myeloma—and there was nothing to indicate the first two, investigations were put in hand to confirm the third. Radiographs of the skeleton showed a generalized osteoporosis without any localized defects. Bence-Jones protein was not found in the urine at this or any other time, though a slight albuminuria was constant. The serum calcium was 11.2 mg. and the uric acid 2.9 mg. per 100 ml. It is of interest to note that the thymol turbidity test of MacLagan (1947) gave a result of 1 unit, since the gamma globulin was afterwards shown to be high. Sternal puncture was next performed; this decided the diagnosis, showing a great preponderance of plasma-type myeloma cells. The patient died on February 28.

Necropsy.—The bones showed the expected changes; the clots in the vessels were particularly opaque and tenacious, a feature on which von Bonsdorff *et al.* (1938) remark. Sections of the bone-marrow showed the most extensive deposits of plasmacytoma, and sections of blood clot the same crystalline masses as those referred to above. Death was due to bronchopneumonia.

The original serum was now further investigated. Because of the white colour of the solid serum, the total ether-extractable matter was estimated. It proved to be 1.1 g.% against 1.5 g.% in pooled normal serum, suggesting that there was no excess of fat. Next the proteins were fractionated (see Table), using the method of Kibrick and Blonstein

	Patient's Serum (g. %)	Average of 6 Normal Persons (g. %)
Total protein	12.0	7.2
Albumin	1.9	4.3
Globulin	10.1	2.9
Alpha	1.9	1.0
Beta	1.2	0.9
Gamma	7.0	1.0

(1948), which gives results close to those obtained by electrophoresis. The estimation was completed by the method of Gornall, Bardawill, and David (1949). The normal figures were obtained from six normal people, and showed close agreement among themselves.

Discussion

The case described did not present any of the clinical features that have been directly attributed to cryoglobulinaemia. The case of Rörvik (1950) showed bleeding and ulceration of the ears and limbs, particularly following exposure to cold; that of Hanson and Faber (1947) had Raynaud's syndrome; that of Wintrobe and Buell (1933) had retinal thrombosis and Raynaud's syndrome; one of Lerner and Watson's cases (1947) had purpura; and in this connexion it is interesting to note that Waldenström (1944) collected seven cases of "purpura hyperglobulinemica," two of which, while they did not have cold precipitable globulins, had uveoparotitis, a feature of sarcoidosis.

Von Bonsdorff *et al.* (1938), who described one of the earliest cases of cryoglobulinaemia, made the following observations on the serum in their case: (1) clumps formed spontaneously in Hayem's solution; (2) the serum agglutinated both its own and other red cells; (3) clot retraction was incomplete and slow; (4) the serum separated into two layers, the lower third being turbid and containing needle-like crystals; (5) the total protein was 9–10 g., with a raised globulin; (6) the molecular weight of the crystalline protein was about

200,000; and (7) the Takata-Ara and formol-gel tests were positive. In my case very rapid sedimentation with clumping of the red blood cells took place. Clot retraction was poor on the bench, but normal in the 37° C. incubator, a feature which Rörvik also noticed.

Separation into layers is a point which several authors have remarked upon. It varies in degree, sometimes the whole volume becoming solid and depositing crystals, as in my case and in Rörvik's, and sometimes only a layer being deposited, as in the cases of Wintrobe and Buell, von Bonsdorff *et al.*, and Hill *et al.* The small quantities of cryoglobulin to be expected in the infectious diseases may be discovered only after prolonged observation in the icebox.

Nature of the Abnormal Protein

The method of choice in separating and classifying proteins at present is electrophoresis. By this method Adams *et al.* (1949) have examined the sera of 41 cases of myelomatosis; they found sometimes an excess of gamma globulin, sometimes of beta globulin, sometimes of an intermediate fraction, and sometimes no abnormality. Kekwick (1940), in five cases, found three with an excess of gamma globulin and one with excess of beta globulin. Lüdin (1947) reports two cases with a rise in the alpha fraction. Gutman *et al.* (1941), using Howe's method, found all combinations of level of euglobulin and the pseudoglobulins in myelomatosis, but assert that in all the other diseases in which hyperglobulinaemia occurs the excess protein is solely euglobulin. In my case, by the method of Kibrick and Blonstein (1948), the excess protein fell in the gamma fraction, and in four cases of cryoglobulinaemia which have been examined by electrophoresis (Rörvik) the protein was in each instance a euglobulin falling into the gamma fraction.

The crystals in the present case were needle-shaped, as in all the other recorded instances except that of von Bonsdorff, in which some were boat-shaped. Needle-like crystals have been found in the plasma cells in a case of myeloma (Steinmann, 1949) and also flat plates (Neumann, 1949). Sikl (1949) found flat plates in the kidneys. None of these was observed in the present case.

Summary

A case of multiple myelomatosis is reported in which the diagnosis was suggested by the finding of cryoglobulinaemia. The nature of the abnormal protein in this condition is discussed.

My thanks are due to Dr. E. Colin Jones for permission to report this case and to Dr. L. R. Janes for laboratory facilities.

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because the child remained so well during his 10-day illness despite the fact that part of the intestine had become strangulated and had actually sloughed, producing a faecal fistula.

FRANCIS E. STOCK, F.R.C.S.,
Professor of Surgery, University of
Hong Kong.

Medical Memoranda

Faecal Fistula and Bilateral Strangulated Hernia in an Infant

Strangulated inguinal hernia in an infant does not occur very often. The following case report presents unusual features and is worthy of record.

CASE REPORT

A Portuguese male child, aged 7 weeks and weighing 6 lb. (2.7 kg.), was brought to hospital with the following history. He was born prematurely after seven months' gestation, weighing 3½ lb. (1.6 kg.). Shortly after birth an umbilical hernia and an absent testis on the left side were noticed. Ten days before admission to hospital a tender red swelling, which was considered to be cellulitis of unknown origin, developed in the left groin. It was treated with systemic penicillin and hot compresses and appeared to settle down, but after a week it became more obvious. The day before admission a small white bleb appeared on the scrotum. This burst and discharged faeces but no pus. Throughout these 10 days the child had been reasonably well, with no vomiting, and the bowels had opened regularly.

On examination the patient was fairly well and had no evidence of dehydration. A large red swelling was present in the left groin extending down into the left scrotum. At the lowest point in the scrotum a small opening discharged yellow semi-solid faeces. The abdomen was not distended. There was an umbilical hernia about 1½ in. (3.8 cm.) in diameter. A diagnosis was made of a strangulated hernia of the Littré or Richter type.

Operation.—Under ethyl chloride and open ether anaesthesia, an incision was made over the upper part of the swelling. All tissues were very oedematous and the layers could not be defined. The hernial sac was identified and opened. An attempt was made to withdraw the contents from the sac. These were found to consist of caecum and the appendix. The distal end of the caecum was adherent and part of the wall had sloughed. The appendix was not strangulated. The contents were separated from the sac, the caecal wall was repaired in two layers, the hernial sac closed, the abdominal wall repaired with nylon mattress sutures, and the scrotum drained. The child stood the operation well.

Feeding was resumed as soon as possible, 1 oz. (28 ml.) of half-strength milk being given every two hours, alternating with glucose water two-hourly. "Aureomycin," 125 mg., was given four-hourly in a teaspoonful of condensed milk. The child made an uninterrupted recovery. The stitches were removed on the tenth day, by which time the scrotal wound was healed, and he was discharged from hospital 14 days after admission. Three weeks later the patient was readmitted with a strangulated right inguinal hernia, which was successfully treated immediately. The umbilical hernia was repaired at the same time to prevent a third crisis.

This case is of interest, for it presents an example of intestinal malrotation, with the caecum and appendix appearing in a left-sided hernial sac. It is also of interest

Unusually High Blood Sugar in a Boy

Noteworthy features in the following case were an unusually high blood glucose concentration, eventual stabilization on 5 units of insulin daily, and maintenance of good progress for more than three years.

CASE REPORT

The patient, a boy aged 8, an only child whose birth was normal of normal parents, was underdeveloped, weighing only 36 lb. (16.3 kg.). He had seemed tired and listless for two or three months, and recently frequency of micturition and some thirst but no polyuria had occurred. There had been no apparent loss of weight, and the chief trouble had been "colds" and septic teeth, for which sulphathiazole (4 g.) had been given on the day before admission.

He was admitted to hospital on January 15, 1947, in profound diabetic coma of 42 hours' duration. Dehydration was pronounced, acetone was detectable in the breath, his blood pressure (by palpation) was extremely low, temperature 94° F. (34.4° C.), respirations 28, and pulse 132. Urine, by catheter, gave strongly positive reactions for glucose and acetone. The blood glucose concentration was 1,076 mg. per 100 ml. by Folin-Wu micro-technique using unclaked blood—Herbert and Bourne's method (Harrison, 1937a); carbon-dioxide-combining power was 10 ml. of CO₂ per 100 ml. plasma by Van Slyke's volumetric technique (Harrison, 1937b).

Treatment was begun with 20 units of soluble insulin half-hourly, continuous intravenous 5% glucose in saline, and 10 g. glucose, with 5 g. sodium bicarbonate given hourly by stomach tube. In the first 20 hours the patient received 820 units insulin, 380 g. glucose, 100 g. sodium bicarbonate, and 3,600 ml. intravenous saline, but the blood glucose concentration persisted at a level well over 1,200 mg. per 100 ml. and reached the value of 2,100 mg. per 100 ml. at the 16th hour.

Despite persistence of gross hyperglycaemia, similar treatment was continued to the 23rd hour, when it was changed to 20 units insulin three-hourly; later it was varied to 10 units two-hourly. Glucose, 10 g., was continued hourly by mouth, and intravenous glucose in saline was continued up to the 30th hour, when the child regained consciousness at a blood glucose concentration of 226 mg. per 100 ml. and carbon-dioxide-combining power of 100 ml. CO₂ per 100 ml. plasma. In all, from the 20th to the 44th hour, he received 240 units insulin and 340 g. glucose; during that period the blood glucose concentration diminished rapidly, reaching 70 mg. per 100 ml. at the 36th hour.

In the next six days, while 20 units insulin twice daily was continued and glucose feeding was gradually replaced by a 1,200-calorie diet, blood glucose concentrations varied between 91 and 188 mg. per 100 ml. A sudden rise of blood glucose to 500 mg. per 100 ml. was met by increasing the insulin to 26 units twice daily. Contrary to expectations at this time, the patient showed marked sensitivity to insulin, and two days later developed hypoglycaemic coma, with blood glucose 31 mg. per 100 ml. The dose of insulin was promptly reduced to 15 units, then to 5 units twice daily, and this last dosage was maintained for 25 days while the diet was built up to 2,000 calories. The patient then appeared to be well stabilized and a glucose tolerance test (25 g. oral) showed: fasting, 138 mg. per 100 ml. blood