The danger of carrying infection to the child is demonstrated. After a mucus catheter has been blown through it should never be replaced in the baby's throat.

Mucus catheters of effective design can be cheaply made of glass and rubber, and several should be provided at every delivery.

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CHRONIC RENAL DISEASE WITH SECONDARY HYPERPARATHYROIDISM

BY

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It is now well established that a close relationship exists between renal disease and parathyroid hyperfunction. Thus many cases of primary hyperparathyroidism show evidence of disturbed renal function, and, pathologically, calcium deposits in the kidneys are a feature. These may be intratubular, peritubular, or interstitial, and be accompanied by cellular infiltration and fibrosis. The usual result is interference with tubular function, leading to urine of constant low specific gravity, polydipsia, and polyuria. The large amount of calcium excreted in the urine in this condition often results in renal calculus formation, and this may lead to obstruction or infection.

However, the functional relationship between the kidneys and the parathyroid glands is a reciprocal one. The subject is reviewed by Anderson (1939). Bergstrand (1921) noted the frequency with which parathyroid enlargement acompanied renal damage, and Gilmour and Martin (1937), in an extensive statistical study, found the parathyroid glands to be of a higher mean weight in renal disease than in other disease groups. They also noted that the glands had a higher percentage of parenchyma per unit of weight in renal disease than occurs normally. In rare instances of chronic renal disease this hyperplasia may be sufficiently well marked to give rise to clinical manifestations of hyperthyroidism. In still fewer instances bone lesions similar in every respect to the osteitis fibrosa of primary hyperparathyroidism have been present. Such cases have been reported by Hubbard and Wentworth (1920–1), Albright *et al.* (1937), and Herbert *et al.* (1941). The renal lesion has varied from case to case. Chronic nephritis, chronic pyelonephritis, and polycystic disease have been described, but in all cases the renal insufficiency has been long-standing and severe.

In children, as in adults, long-standing renal insufficiency may lead to parathyroid hyperplasia and hyperfunction. Langmead and Orr (1933) reported a case of renal rickets in which all four parathyroid glands were grossly enlarged and the histological changes in the bones presented a composite picture of classical osteitis fibrosa and of true rickets. Gilmour (1947) found similar histological changes in the bones of seven out of eight subjects aged 3 to 17 years with chronic renal disease. In five of these the parathyroid glands were definitely hypertrophied.

Metastatic calcification is an interesting phenomenon which has an undoubted association with both renal disease and hyperparathyroidism. In this condition calcium salts are deposited in previously normal tissues. In addition to the kidneys, the common sites of calcium deposition are the arterial walls, the heart, the mucous membrane of the stomach, and the skin and subcutaneous tissues (calcinosis). The condition may be produced experimentally in animals by overdosage with parathyroid extract or with vitamin D. In both instances deposition of calcium salts in the kidneys may lead to severe renal impairment. Essentially the same pathological picture has been produced in man by excessive administration of vitamin D. The association of metastatic calcification with renal disease has excited much interest since the original description of the condition by Virchow (1855). He observed five cases, in all of which there was more or less severe nephritis. Four of these were accompanied by destructive bone disease, but in one there were no demonstrable skeletal changes.

Barr (1932) stated that it was difficult to find cases of metastatic calcification in which a renal element could be excluded. Herbert *et al.* (1941) collected 19 cases of metastatic calcification from the literature, and 16 of these were associated with gross renal disease. In 11 of these 16 there was evidence of parathyroid hyperplasia, and in only one case was parathyroid hyperplasia definitely excluded. In three cases unassociated with gross renal disease the parathyroid glands were normal. Gilmour (1947) described three well-marked cases of metastatic calcification occurring in chronic renal disease. In each of these there was marked parathyroid hyperplasia and the bone changes of osteitis fibrosa.

In the case of chronic nephritis reported below, gross enlargement of the parathyroid glands was found in association with metastatic calcification and bone changes of osteitis fibrosa.

Case Report

The patient, a married woman aged 44, gave a history of scarlet fever in childhood. In 1927, at the age of 22, she developed swelling of the face and legs, and was treated in hospital for three months as a case of nephritis. She then remained well, and married in 1931. One year later a pregnancy was terminated because of persistent vomiting, and sterilization was performed by ligation and division of both Fallopian tubes.

She was first admitted to the Queen Elizabeth Hospital on January 23, 1949, for dental treatment. She had complained of lack of energy and poor appetite for the previous few months, and on admission presented a picture typical of advanced renal insufficiency.

Examination revealed a thin woman with a pale puffy face. Hypertension (blood pressure 200/110) and cardiac enlargement were present. A rough systolic murmur was heard all over the praecordium, with maximal intensity at the apex. The urine was of constant low specific gravity and contained albumin and granular casts.

The patient was discharged on February 15, only to be readmitted on September 16. She then complained of very severe pain in the toes of the right foot of three weeks' duration. Her general condition had deteriorated markedly in the seven months since her previous admission, and there was now persistent vomiting and low urinary output. All five toes of the right foot were cold, blue, and insensitive—the seat of a dry gangrene. Pulsations were absent from the popliteal, posterior tibial, and dorsalis pedis arteries of the right leg. The patient gave a history of intermittent claudication affecting both legs and growing steadily worse over the previous year. More recently similar pain produced by exertion—for example, by combing the hair—and relieved by rest had occurred in the forearms.

Gallop rhythm was audible over the praecordium, and the apical systolic murmur, heard first in January, 1949, was much rougher and was accompanied by a coarse thrill.

A few days after admission the patient lapsed into coma and, with increasing nitrogen retention, died on September 25.

Laboratory Data.—A blood count on January 26 showed: red cells, 3,180,000 per c.mm.; haemoglobin, 58% (Haldane); colour index, 0.93; and on September 16: red cells, 2,230,000 per c.mm.; haemoglobin, 42% (Haldane); colour index 0.94. The blood urea was 158 mg. per 100 ml. on January 28, 195 mg. on February 19, and 365 mg. on September 23. The blood proteins on September 19 were albumin 4 g.%, globulin 1.4 g.%. The serum calcium was 10.9 mg. per 100 ml. on September 20 and 13.3 mg. on September 23. The serum phosphorus (as inorganic phosphate) was 8.7 mg. per 100 ml. on September 20 and 11.9 mg. on September 23. On September 20 the plasma carbon-dioxide combining power was 30 volumes % and the plasma *p*H 7.36.

Radiological Investigations.—A radiograph of the chest in January, 1949, showed cardiac enlargement and marked calcification in the aortic arch. In September, in addition to these findings, a radiograph of the chest showed marked calcification in the arteries of the thyroid axes and of the arteries in the lateral chest wall. There were also heavy calcium deposits in both lung fields, spreading out from the hila. A radiograph of the limbs on September 17 showed heavy calcification of the arterial tree, involving not only the main vessels but also the finer muscular branches. The branches of the common iliac arteries were similarly involved. A radiograph of the head showed calcification in the walls of the ophthalmic and meningeal arteries. There was diffuse mottling of the skull, giving an even "ground-glass" appearance characteristic of osteitis fibrosa. The skeleton elsewhere was radiographically normal.

Post-mortem Examination

This was carried out on September 26. The body was that of a middle-aged woman; weight 49.1 kg.

Heart.—This was moderately enlarged owing to left ventricular hypertrophy (weight 385 g.). The aortic valve showed slight calcification, which appeared to have originated in the sinuses of Valsalva. The pulmonary and tricuspid valves were normal. The mitral valve was heavily calcified and there was an irregular mass of calcified material 1.5 cm. in diameter at the junction of the cusps. The coronary vessels showed a fine nodular calcification.

Aorta.—Advanced atheroma with large calcified plaques was found immediately above the commissure and in the region of the great vessels. Atheroma was less marked in the descending thoracic portion, but in the terminal abdominal aorta calcification was very marked. The lumen was slightly reduced and the wall almost devoid of elasticity. Histologically advanced medial and intimal degeneration with heavy calcification was present.

Arteries.—There was moderate calcification of the proximal portion of the common iliacs. The external iliacs and proximal femorals were almost devoid of calcification. The subclavian arteries were calcified. Both popliteals were severely calcified. The right radial artery showed much calcification and recent thrombosis. Portions of the right femoral, left profunda femoris, left popliteal, digital, and basilar arteries were examined histologically. All showed advanced medial degeneration and fibrosis, and in many places degeneration of the intima also, with fibroblastic proliferation and atheromatous changes. In some of the arteries—for example, the radial—there was almost complete replacement of the vessel wall by calcified material. In general, the calcification seemed to follow degenerative changes in the arteries; and, broadly, was most intense where degeneration was most advanced.

Lungs.—There was partial collapse of the bases of lobular distribution. Mucous bronchiolitis was present, but no consolidation. The walls of the bronchi near the hilum were calcified. Histologically there was massive calcification of the bronchial cartilage, especially in the larger branches, but no vascular calcification. A few patches of calcareous material were found in the alveoli.

Kidneys.—Both were extremely small (total weight 125 g.). The subcapsular surfaces were finely granular. The cortex was reduced in width but the vessels were not unduly prominent. Histologically, the appearance conformed with "nephritis repens" type 2 (Russell, 1929). In the main the calcium deposits were limited to the vessel walls, though there were occasional deposits in the fibrinoid glomerular tufts and in the interstitium.

Parathyroids.—Four large glands were found. Three were embedded in the substance of the thyroid gland and measured 10 by 8 mm.; 8.5 by 6 mm., and 9 by 6 mm. (estimated weight 382 mg., 195 mg., and 221 mg. respectively). The superior left parathyroid was found in its normal position and weighed 419 mg. The histology corresponded with Gilmour's type 4. The structure was compact and lobular, water clear, and transitional cells predominated over dark principal cells. There were numerous foci of oxyphil cells and many areas of columnar-celled alveolar structure. Arterioles in the vicinity showed calcification.

Skeleton.—The skull, shaft of femur, sternum, and a portion of rib were examined. To the naked eye only the skull was abnormal. It was definitely thickened, and softer and easier to cut than normal. Microscopically all the bones showed lacunar resorption by osteoclasts, with fibrosis around the affected area—a picture typical of osteitis fibrosa. In many places the process could be clearly shown to have started in the Haversian canals, with progressive enlargement of these as the bone was eroded. Except in the skull, in which haemopoietic and adipose marrow was absent, the marrow proper was but little affected. There was only slight evidence of osteoplastic reaction, and the condition was evidently one of considerable activity and short duration. There was no evidence of rachitic changes.

Discussion

The essential features of this case of chronic nephritis were the gross enlargement of the parathyroid glands, the bone changes of osteitis fibrosa, and the extensive and widespread degeneration and calcification of the arterial tree. This latter feature resulted in diminished

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 Reifenstein (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.

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CRYOGLOBULINAEMIA IN MULTIPLE MYELOMATOSIS

BY

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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—phrynoderma—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