A CASE OF DWARFISM AND CALCINOSIS

associated with
WIDESPREAD ARTERIAL DEGENERATION

BY

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In 1931 there was admitted to Dr. Robert Hutchison's ward at The Hospital for Sick Children, Great Ormond Street, a dwarfed child of 2 years and 3 months. The colour of her skin was yellow like a faded leaf. The urine was albuminous and the blood pressure high. The peripheral arteries were hard and tortuous. Roentgenograms showed irregular, transverse bands of osteosclerosis and osteoporosis in the metaphyses of certain of the long bones, excessive calcification of the skull, and calcification of the larger peripheral arteries. At first it was thought that the case was unique, but medical literature showed it to be not without parallel. An autopsy provided an opportunity for histological study which, together with the clinical and post mortem findings, forms the basis of this report.

Widespread calcification in infancy and childhood is a rare but not unknown phenomenon. Bryant and Hale White¹ reported the case of a male infant, fatal at the age of 7 months, in whom the necropsy showed a calcifying endarteritis obliterans and calcification in the endocardium, associated with great congenital dilatation of the urinary tract. We must regard this association of congenital dilatation of the urinary tract and extreme arterial disease as unusual and probably fortuitous. Thus there is no mention of degeneration in the arteries in Holt's² account of his eight cases of congenital hydronephrosis with dilatation of the ureters, nor is there in those reported by Poynton and Sheldon³. And in an extensive experience of cases of congenital dilatation of the urinary tract studied at the Hospital for Sick Children, though the state of the arteries has not been made the subject of special study, no instance of arterial degeneration or thickening has been catalogued among them. Indeed, the systolic pressure was not very high in any, though it was raised as a rule in the older cases, especially when renal insufficiency had made its appearance. The findings in five of these cases are summarized in Table 1. Five children with congenital hydronephrosis, investigated by Neale⁴, Table 2, suggest also that the blood pressure rises with the onset of renal failure, and once again no evidence of arterial degeneration is recorded. From our own experience and from a study of the literature, it would seem reasonable to take the view that extreme arterial degeneration, and particularly calcification, are

not the end-results of the renal failure due to congenital dilatation of the renal tract. In the case of Bryant and Hale White the authors themselves did not think that the arterial calcification could be explained as the result of the renal abnormality.

TABLE 1.

CASES OF CONGENITAL DILATATION OF RENAL TRACT.

(The Hospital for Sick Children.)

Age.	Sex.	Anatomical defect.	Blood urea. Mgms. %	Blood pressure.
6	Male ...	Urethral obstruction ...	114	135 syst.
13	Female ...	Urethral obstruction ...	128	130 syst.
6½	Female ...	Dilatation of ureters ...	42	115 syst.
2	Male ...	Urethral obstruction ...	109	90-95 syst.
4	Female ...	Urethral obstruction ...	312-427	140 syst. 85 diast.

TABLE 2.

CASES OF CONGENITAL HYDRONEPHROSIS.

(Dr. A. V. Neale.)

Age.	Renal failure.	Blood urea. Mgms. %	Blood pressure.
7½	Absent	24.8	100/80
6½	Absent	30	110/90
14	Present	56	110/85
7½	Absent	39	110/90
8	Present	78	130/95

Arteriosclerosis, as seen in the adult, is known in children but usually occurs only at the end of childhood and many of the cases have been renal dwarfs. Thus of four cases of arteriosclerosis, described by Evans⁵, one was nine years old and three were fourteen. From his histological examinations he argued that the vascular lesion was identical with that found in the diffuse hyperplastic sclerosis of adults, and he considered it to be an active inflammatory lesion completing the link between arteriosclerosis and the endarteritis seen in the lesions of tuberculosis and syphilis. Calcification did not occur in his cases.

Hodgson⁶ in his 'Treatise on Diseases of the Arteries' (1815), says his friend Young 'possesses a temporal artery which he removed from an infant 18 months old, in which the coats of the vessel were covered with a complete tube of calcareous matter.' That severe arterial hyperplastic sclerosis may

be fatal in childhood is shown by a case of general systemic and pulmonary arteriosclerosis recorded by Hawkins⁷. Microscopically there was development of fibro-cellular tissue in the intima but no degeneration or calcification. Death resulted at 11 years from thrombosis of the renal arteries.

Primary arterial hypertension has been recorded in the young though it is rare. Cases have been described by Amberg⁸, Faerber⁹, Hutchison and Moncrieff¹⁰, Craig¹¹, and others. The state of the arteries in many of the cases has not been ascertained, there being no post mortem verification. In the case of Hutchison and Moncrieff¹⁰, the latter compared histological sections from their case with controls taken from a child of the same age and no trace of difference was found. Craig¹¹ verified that there was hypertrophy of the tunica media in the coronary, renal and coeliac arteries of his case, together with atheroma of the aorta, and ischæmic atrophies in the kidneys; but no calcification had occurred.

In our case, and in that of Bryant and Hale White, while the brunt of the changes fell on the arteries, pathological calcification occurred also in other tissues: in the endocardium in theirs and, as will be described later, in the kidney, lung, dura mater, endocardium and peritoneum in ours. In consequence there arises the possibility that the disorder is one in which calcium and phosphorus metabolism is disturbed. During the last few years much has been written on hypervitaminosis-D in which widespread calcareous deposits may occur.

By the administration of irradiated ergosterol to rats in excessive doses a condition described as hypervitaminosis has been produced. In general the results^{12, 13} in animals are anorexia, wasting, diarrhoea and death. There is hypercalcaemia, an increase in the inorganic blood phosphate, and an increased urinary excretion of calcium. Variations in calcium and phosphorus intake modify the effects. Post mortem, calcium salts are found deposited in the tissues especially in the kidneys, myocardium and walls of the large arteries. The thymus and spleen are atrophied and the bones may show hypercalcification or they may in time become demineralized¹⁴.

Moreover, it would appear from the details of the case recorded by Putschar¹⁵ that hypervitaminosis is a disease not only of laboratory animals. This was an infant who became weak soon after birth, with vomiting, a certain rigidity of the skin, and a sub-febrile temperature. Though there were no manifestations of rickets six drops of irradiated ergosterol (Vigantol) were given daily and continued for ninety-six days. After seventy days of this treatment leucocytes and albumin were found in the urine. Death occurred at 5½ months and at the autopsy Putschar found calcification in both cortex and medulla of the kidneys. We cannot accept without question that these changes were necessarily produced by the treatment, because our case and that of Bryant and Hale White did not receive any food or drug in the least likely to contain vitamin-D in more than physiological quantities. We cannot go further than to say that though Putschar's case was probably an instance of hypervitaminosis-D, it might possibly be of a nature similar

to the one we are describing, in which careful inquiry showed that no vitamin-D preparation had been given in excessive quantity.

Another clinical instance of hypervitaminosis-D, fatal at 18 months, has been described by Thatcher¹⁶. The symptoms were weakness and anorexia. Although there was no rickets the infant had received about twice the recommended dose of irradiated ergosterol, from the age of 13 months until a few days before death. Autopsy showed deposits of calcium throughout the renal medulla. The appearances suggested that the deposits were formed as casts within the tubules. Calcareous masses had obstructed and caused dilatation of some tubules. The blood vessels were healthy and no calcification had occurred apart from the kidney. Thus the changes were not so extensive as in Putschar's case and as in experimental hyper-vitaminosis-D.

Calcinosis has been recorded by Kennedy¹⁷ in a well nourished child of 6 years. Difficulty in walking was the earliest symptom of her complaint, and hysteria had been diagnosed until hard, bone-like masses appeared in the flexures. For three years she received a ketogenic diet and during this time the calcium deposits were gradually absorbed. No suggestions as to the cause of her disease were advanced.

Cramer¹⁸, working with rats on synthetic diets in which the proportion of inorganic salts in the salt mixture was varied so as to produce mineral imbalance, has found that the omission of magnesium salts, the ions of which are biologically antagonistic to calcium ions, produced extensive degenerative lesions in the glomeruli and tubules of the kidneys. Sometimes but not always, these changes were accompanied by calcareous deposits. The significance of this observation lies in the fact that it appears possible to produce experimentally such changes by dietetic measures not involving the introduction of toxic substances. Cramer suggests that the mineral imbalance may have had a specific effect on the renal tubules and glomeruli. His experiments, which are not yet concluded, are giving somewhat different results from those of Kruse, Orent and McCallum¹⁹, who used diets carefully purified so as to contain about 40 times less magnesium than did those of Cramer, and produced much more general pathological lesions.

Case report.

HISTORY.—A female infant, aged 2 years 3 months, was admitted to the hospital because she had never grown properly. She had been seen twice by a specialist, congenital heart disease being suspected. Vomiting had occurred from time to time. At 5 months old she was in hospital on account of facial paralysis which appeared when she was teething. Except for an attack of diarrhoea there had been no other illnesses. At 15 months she was a tiny little creature, 17½ inches long, and weighing 12-13 lbs; there was a cardiac murmur loudest at the base. During the last 12 months she had gained no weight. There seemed to be difficulty in swallowing, and much flatulence causing pain and crying. Though she could move all her limbs she had never walked.

FEEDING.—For the first five weeks she was breast fed and then "Allenbury's" foods were used until she was 8 months old, when the attack of diarrhoea, to which allusion has been made, was treated by giving a mixture of equal parts of milk and lime water for six weeks. Subsequently the diet followed was not abnormal except

that one teaspoonful of lime water was given in each feed until she was one year old. Between 15 and 18 months half an eggspoonful of Scott's emulsion was given daily and for a short period of a fortnight before admission she was receiving Ostelin mii daily.

FIG. 1. There is osteosclerosis of the shafts and irregularity of the epiphyseal lines. In the metaphyses alternating zones of osteosclerosis and osteoporosis are to be seen. The femoral, popliteal and posterior tibial arteries are visible on account of the calcium deposited in their coats.

FAMILY HISTORY.—The parents were healthy and well-to-do, there was no consanguinity. No miscarriages had occurred and the mother had not taken cod-liver oil, ostelin, radiostol or any preparation of lime during her pregnancy. The

family tree was traced back for four generations on the father's side and three generations on the mother's. The paternal grand-mother had died at 56 of cerebral hæmorrhage, and the paternal great grand-father as an old man of renal disease. On the mother's side a grand aunt had died of nephritis at 29. Otherwise there was no family history of renal or vascular disease, or of any other condition bearing on the case.

EXAMINATION.—On examination she was found to be a dwarf with a biscuit-coloured skin. Her apparent age was 10-12 months and her mentality corresponded with this. Her nutrition was poor, she had a moderate knock-knee but no beading of the ribs. All the teeth had erupted but were carious. Heart: No enlargement was detected and there were no murmurs. The second sound over the base was accentuated. Systolic blood pressure 180 mm. Lungs: normal. Vessels: Radial

FIG. 2. There is much thickening of the vault of the skull with osteosclerotic changes at the base and in the maxillæ.

pulse hardly perceptible, but the radial artery could be felt as a hard and tortuous cord. The brachial and femoral arteries were hard and easily felt. All these arteries could be seen in the roentgenograms (Fig. 1). The retinal arteries were narrow and had a double contour. Central nervous system: A left external rectus and a right facial paresis were found. Abdomen: The liver, spleen and kidneys were not felt, and the bladder, though palpable, was not distended.

INVESTIGATIONS.—The urine was acid and contained a considerable amount of albumen, a few red and white corpuscles, and a few hyaline casts. The Wassermann reaction was negative. Blood urea 169 mgm. per 100 c.c. A urea concentration test was carried out, 3 grammes of urea being used: in the first hour the urea concentration in the urine was 1.45 per cent., in the second 1.50 per cent. These findings are

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indicative of renal insufficiency. Blood cholesterol 196 mgm. per 100 c.c. (normal 100-200). Serum calcium 11 mgm. per cent. (normal 9-11 mgm. per cent.). Blood phosphorus 6.68 mgm. per cent. (normal 4-5.5 mgm. per cent.).

After admission to hospital she was found to have slight irregular pyrexia and she vomited occasionally. A few days later the temperature rose to 102° and she died somewhat unexpectedly.

AUTOPSY.—The body was that of a stunted, marasmic infant with a yellowish skin.

The skull was considerably thickened throughout, and the tentorium cerebri heavily calcified; the dura mater, especially at the base, showed some irregular calcification (Fig. 2). The substance of the brain was normal but the cerebral arteries were somewhat prominent.

FIG. 3. The heart, and especially the ventricles are moderately enlarged, and the coronary arteries present a unique appearance of tortuosity and thickening.

The heart, and especially the ventricles, were moderately enlarged, and the coronary arteries presented a unique appearance of tortuosity and thickening (Fig. 3). On the outer surface of the auricular appendix, and in the endocardium of the auricles and ventricles, small patches of calcification were seen.

The state of the vessels was made the subject of careful study. Macroscopically nothing abnormal was noted in the veins, but under the microscope certain of them showed a slight thickening of the tunica adventitia. The capillaries showed no structural alterations. The arterial system was extensively diseased.

The aorta and the pulmonary artery, with their valves, were normal to the naked eye and even histologically the aorta showed no change. The largest of the arteries also appeared normal, but elsewhere, throughout the arterial system, there were proliferative and degenerative changes with the deposition of much calcium. Generally speaking, the medium-sized and small arteries were the most affected. Thus the pulmonary stem was normal but the pulmonary branches were atheromatous, the aorta showed no change until the iliac arteries were reached, and the arteries of the limbs were atheromatous. In the thorax it was seen that atheroma had affected the intercostal arteries but the subclavian vessels had escaped. In the neck the carotids appeared normal and the circle of Willis showed only minute histological changes, to be described later. The axillary arteries were normal but the brachials were atheromatous. The branches of the abdominal aorta showed degeneration seen well, for example, in the left colic branch of the inferior mesenteric vessel.

HISTOLOGY OF ARTERIES.—The exact nature of the changes found in these arteries raises points of considerable difficulty, but their main histological features can be

FIG. 4. A low power microphotograph (X 20) of the femoral artery. The sub-intima has proliferated and subsequently degenerated and slight calcification appears to have occurred in it. The media is partly destroyed and largely calcified (the calcium shows black). The adventitia is fibrosed. The vasa vasorum (top left and bottom right) show similar changes.

made clear with the aid of some representative microphotographs. A section of the femoral artery may be taken to illustrate the changes seen in a vessel of intermediate size. An enormous fibro-cellular and concentric proliferation, of what appears to be sub-intimal connective tissue, has taken place and degenerative changes have followed in it. A feature of this degeneration is the laying down of fine deposits of calcium. Furthermore, the internal elastic lamina has disappeared and the tunica media has undergone widespread destruction and massive calcification. The white fibrous tissue of the tunica adventitia shows some increase. Essentially similar changes are to be seen on a smaller scale in the vasa vasorum (Fig. 4). This sub-intimal proliferation would remind one of arteriosclerosis if it were less in amount and less concentrically distributed; the medial changes cannot fail to bring Mönckeberg's degeneration to mind. Figure 5 illustrates the changes seen in a

smaller vessels under a higher magnification. The microphotograph shows a small branch of the left coronary artery. The same sub-intimal proliferation is seen, the same disappearance of the internal elastic lamina, and the same calcification in the tunica media. Every branch of the coronary arteries showed similar or even greater change. The heart muscle shown in Figure 5 is normal but in other fields this also showed areas of degeneration and calcification, presumably a result of coronary occlusion. Thus it is highly probable that had this child been old enough to detail her symptoms, cardiac and possibly anginal pains would have been described, and it is interesting to speculate if the pain already mentioned in her history had any such significance.

It has been mentioned that the largest vessels (aorta, pulmonary, subclavian, axillary, carotid and renal arteries) were normal and it was a matter of interest to look for the exact point where the earliest changes would make their appearance.

FIG. 5. A high power microphotograph (X 200) of a branch of a coronary artery. The sub-intimal layer has proliferated and degenerated, the media is calcified (calcium shows black). Many other coronary branches show an even greater degree of endarterial obliteration than is seen here.

By good fortune a microscopical section of a portion of the circle of Willis provided this opportunity. Here the whole extent of the internal elastic lamina was seen to be thickened and at one point it was split to enclose a patch of proliferating fibroblasts (Fig. 6). Strongly suggesting an origin primarily vascular, this localized proliferation must be taken as highly significant. No changes were to be seen in the medial or adventitial coats of this vessel and no calcification. In the middle cerebral artery there was thickening of the internal elastic lamina but no degeneration, and the tunica adventitia showed slight increase.

There were patches of calcification in the trachea. The branches of the pulmonary artery were so thick and rigid that they stood out from the lung. There was a terminal, confluent bronchopneumonia and oedema of the lower lobes. Histologically the parenchyma of the lung showed much degeneration and scattered calcification. In the parietal pleura covering each rib posteriorly, there was

thickening and deposition of calcium. There were patches of thickening, apparently with the deposition of calcium, in the peritoneum covering the stomach. There were slight fatty changes in the liver, and the spleen showed in moderate degree the changes associated with a terminal septicemic condition.

The kidneys were small, tough and pale. The capsule was adherent, and the cortex narrow, with loss of differentiation between it and the medulla. The arteries were thickened and gaping, and in the region of the hilum they were seen to be calcified. The main renal arteries appeared normal except for the presence of an accessory left renal artery going to the lower pole: a not uncommon finding which had resulted in no disturbance.

Fibroplastic proliferation
splitting the internal elastic
lamina.

FIG. 6. A low power microphotograph (X 75) of a portion of the circle of Willis which illustrates the earliest apparent arterial change. Cellular proliferation is seen under the intima at 6 o'clock. An elastic tissue stain shows that this proliferation has split the internal elastic lamina. Note the thickening of the internal elastic lamina elsewhere.

HISTOLOGY OF KIDNEYS.—The histological appearances in the kidneys are difficult to describe and difficult to interpret. Of all the small arteries examined the renal arterioles most nearly approached the normal, and degenerative changes were conspicuous by their absence. In most of them some hypertrophy of the muscular coat was present, though this point required to be established by comparisons with control material. The vessel pictured in Figure 7 shows a little fibrosis of its tunica adventitia and a moderate medial hypertrophy; the intima is normal, and the internal elastic lamina can be recognized by appropriate staining. The renal parenchyma showed a remarkable degree of interstitial fibrosis (Fig. 8). A majority of the glomeruli were pathological: either fibrosis of the tuft, or of Bowman's capsule, or of both. Sometimes this fibrosis was slight, sometimes the

changes had proceeded to hyalinization. Many of the glomerular tufts showed a small deposit of calcium eccentrically placed (Fig. 9), a few were solid with calcium, and sometimes a fibrosed Bowman's capsule contained a calcium deposit. The renal tubules also showed a great variety of pathological change: some normal, some dilated and some fibrosed. Both secreting and collecting tubules were the frequent site of calcium deposition. An exhaustive study of hundreds of tubules left little room for doubting that the calcium had usually precipitated as a cast within the tubule. Sometimes the calcium cast contained the remnants of dead cells and sometimes the tubular epithelium itself was encrusted with a thin layer of the mineral. Often calcification within a tubule had proceeded to widespread tissue destruction in its vicinity, thus giving rise to large deposits. The dilatation of tubules might be explained either as a result of the fibrosis, or blockage by these deposits. Visible calcium was fairly evenly distributed between the cortex and the medulla. The renal capsule was thickened.

FIG. 7. A high power microphotograph (X 200) of the kidney showing an arteriole with changes fairly characteristic of those seen in the smaller renal branches, namely, hypertrophy of the medial and slight fibrosis of the adventitial coat, without calcification. The appearance of endarteritis is false, and due to partial thrombosis. See also the dilated tubules on the left of the microphotograph.

The suprarenal arteries were grossly diseased but the histology of the suprarenal capsules was not otherwise disturbed. There was arterial degeneration and deposit of calcium in the thyroid and lymphatic glands. One of the parathyroid glands was dissected out; it measured 2.3 mm. in diameter and was histologically normal. There was no evidence of any parathyroid tumour in the neck.

All the long bones showed changes. These were studied in the tibiae, the description of which will serve for all. There was no bending or other deformity, and no epiphyseal enlargement. The lower epiphyseal line was slightly broadened and irregular. Lying above it was a wide irregular zone of dense calcification, and then alternating bands of osteoporosis and osteosclerosis. Roentgenograms of the long bones taken during life had already given a very clear idea of these changes (Fig. 1).

HISTOLOGY OF TIBIA.—Before describing the histology of this bone a brief outline of the results to be expected from the staining of decalcified bone with hæmatoxylin and eosin will make what follows clearer.

An actively growing and normal metaphysis, decalcified in acids and stained with hæmatoxylin and eosin, is seen to have a narrow epiphyseal line consisting of regular columns of some 10-15 cartilage cells. The older cells in these columns lie towards the diaphysis, and stain blue with hæmatoxylin in association with the calcium recently deposited in their neighbourhood (preliminary calcification). Disturbances in calcium and phosphorus concentration may delay preliminary calcification and provided growth continues, this results in the formation of longer columns, which tend to more or less linear irregularity and stain badly with hæmatoxylin.

Properly formed bony trabeculæ usually stain pink with eosin. It has been suggested that hæmatoxylin does not specifically stain calcium salts but it often

FIG. 8. A lower power microphotograph of the kidney (X 75) showing great interstitial fibrosis, a dilated tubule (at bottom left) and to its right a small deposit of calcium in the cells of a tubule.

identifies areas in which changes favourably to the deposition of calcium are taking place, particularly if iron and mordants, such as aluminium, chromium, etc., are present. The staining reaction, which occurs even after decalcification, probably depends on the special nature of the ground substance in which calcium is deposited, and on the presence of small quantities of other heavy metals²⁰. The younger the deposits the more intense the hæmatoxylin stain. This rule also applies to alizarin, a specific calcium stain.

A section of the lower end of the tibia, decalcified in acid and stained with hæmatoxylin and eosin, showed a slightly broad epiphyseal line, containing some 25-40 cells in the cartilage columns. The columns were somewhat irregular and the older cells (those towards the diaphysis) did not take up hæmatoxylin, indicating deficient calcification. Immediately above these cells, and towards the diaphysis,

there was a zone of osteoid tissue, and then a zone of normally trabeculated and well-formed bone in which a very unusual feature was observed, for the trabeculae were encrusted with a thick layer of calcium (stained blue) clearly outlining the pink structure of each spicule of bone. In addition a few small areas of calcium were to be seen pathologically deposited in the marrow spaces.

Thus strikingly were the radiological, pathological and histological appearances in these bones correlated. But to what purpose? With excessive and pathological deposits, how could it come about that there was insufficient calcium and/or phosphorus to permit of normal preliminary calcification taking place in growing cartilage? To this question we will return later.

FIG. 9. A high power microphotograph of the kidney (X 300) showing various stages of glomerular fibrosis. Calcium is seen deposited in two of these glomeruli.

Discussion.

This case of stunting with widespread calcification in the tissues and arterial disease, might be provisionally classified as a case of renal dwarfism in so far as there was retarded growth and renal disease. But this takes us no nearer to an explanation of the pathology of the condition, for renal dwarfs are seldom the subjects of extreme arterial disease and seldom, if ever, of calcinosis. We may be forced to leave it an open question whether there was primarily renal or primarily arterial disease in this case, but it is clear that we have to deal with abnormal tissue calcification. If we wish to enquire into the possible causes for the excessive deposition of calcium in a case such as this we must consider the following possibilities.

Chemically there are two factors controlling the precipitation of calcium phosphate, these are the Ca/P multiple and the H ion concentration. An increase in the first or a decrease in the second should bring about an increased deposition of calcium.

Clinically alkalosis does not appear to be of great importance in increasing calcification although an acidosis is undoubtedly of importance in the reverse effect. Variations in the calcium and phosphorus concentration appear to be more important.

The levels of both calcium and phosphorus in the blood can be temporarily increased by suitable feeding methods (e.g. calcium gluconate) but this would not appear to be of long enough duration to produce effects. Both vitamin-D and parathormone are capable of increasing the calcium and phosphorus concentration, and both bring about deposition of calcium in the tissues when given over long periods in excess. This result, however, is dependent on an adequate supply of calcium and phosphorus being obtainable in the diet. On diets deficient in calcium and phosphorus large quantities of parathormone or vitamin-D raise the values for calcium and phosphorus in the plasma, the mineral being obtained by a process of mobilization from the bones. Deposition of calcium in the tissues under these circumstances consists in a transference from bone to tissue.

There is no evidence in this case to determine whether any of the above causes contributed to the condition. On general grounds one would suspect an increased activity of the parathyroids, but not of such degree as would bring about the now well-recognized bony changes. Of this the evidence is entirely negative. In this connection it should be recalled that parathormone has a biphasic effect. Small doses increase the rate of removal of calcium from the blood and therefore increase calcification, while with large doses the stimulus to mobilize calcium is greater than that to deposit and the serum calcium increases. The possibility that this case can be explained on the basis of an excessive intake of vitamin-D seems to have been excluded by repeated questioning of the parents and their medical advisers. At this juncture it may be recalled that lime water began to be administered (a common enough practice) at the age of 8 months. Might a small, but long-continued, excess intake of lime have conducted to high calcium levels in the blood? We think that on account of the amount, duration and date of lime water administration this factor cannot have been more than a contributory one.

It has already been asked how a rachitic state (demonstrated histologically in the growing cartilage) could have arisen in the presence of a more than adequate supply of calcium in the tissues. It is tempting to try to explain this anomaly by assuming a relatively deficient supply of phosphorus. But the single quantitative estimation carried out in hospital showed a somewhat high phosphorus value in the blood (6.68 mgm.) and a diminished Ca/P ratio. The alternating zones of osteoporosis and osteosclerosis described in the tibia suggest some phasic disorder of calcium and

phosphorus metabolism in this case and demand extra caution in the interpretation of the calcium and phosphorus values. It seems that only on these lines is any sort of biochemical explanation forthcoming.

Summary and Conclusions.

The clinical and pathological observations in a case of calcinosis with widespread arterial degeneration, fatal at the age of 2 years and 3 months, are recorded. The ætiology of the arterial disease in this case is quite unknown, nor is its relation to the disordered calcium and phosphorus metabolism understood. An extreme obliterative endarteritis predisposed to local tissue degenerations, and a slightly excessive intake of lime, in the virtual absence of normal bone growth, may have been a factor in the deposition of calcium in the damaged arteries, degenerating tissues, and in the bones. These secondary changes may have been dependent on phasic disturbances in the Ca/P ratio, sufficient to produce pathological calcifications, disordered growth of bone, and latent rickets.

The calcinosis in this case was not due to excessive intake of vitamin-D. Other cases found in the literature, such as those of Bryant and Hale White (1901), Hodgson (1815), and possibly Kennedy (1932), make it clear that there are conditions in childhood, other than hypervitaminosis-D, which can give rise to pathological calcification, and that some of these cases are associated with extreme arterial degeneration. For this rare group the descriptive clinical title of 'calcinosis with arterial degeneration' is suggested.

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