Some years ago Osborne and Mendel drew attention to the frequency of calculi in the urinary tract of rats on a vitamin A-deficient diet. In 857 autopsies they found calculi 81 times. "In every instance," they wrote, "where calculi developed, the animals were without an adequate source of the fat-soluble vitamin for some time." Mendel once more referred to this matter at a meeting of the Medical Society of the State of New York in March, 1920, in an address on the fat-soluble vitamin A. He said on that occasion, that Osborne and himself had observed additional cases and that the formation of phosphate calculi with vitamin A deficiency is still more frequent than would appear from their statistics.

"When it is recalled," thus Mendel states, "that phosphatic calculi deposited in a neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and the Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested."

McCollum has denied the existence of this connection. In a paper, "Our present knowledge of the vitamins," he says:

"Osborne and Mendel (1917) observed calculi of calcium phosphate in the urinary tract in ninety-one (read 81) animals among 857 necropsies. Forty-three per cent of these had not had a satisfactory supply of vitamin A. In McCollum and Simmonds' experience, calculi have occurred so fre-
quently in animals whose diets contained an abundance of this factor, but were faulty in other respects, that it would seem to be the result of general debility rather than lowered vitality brought about by specific cause."

Fujimaki, on the other hand, has been able to confirm Osborne and Mendel's conclusion. He found it easy to produce calculi in 40 days by means of a diet not containing any vitamin A, calcium, or phosphorus.

The contradiction in the observations of the experimenters led me to control the records of the rats in the laboratory of the Netherlands Institute of Nutrition. A considerable time ago I had examined many of these rats as to the presence of calculi in the kidneys, the urinary tract, and the bladder. They number 886, piebald and albino rats, of which 405 are males and 481 females. Among them are 241 rats (see Table I) which never suffered from vitamin A deficiency. Their diet consisted of whole meal bread, raw milk, butter or cod liver oil, raw carrots or cabbage, and now and then some cheese and spinach or lettuce. In none of these 241 rats (108 males and 133 females) were calculi found. Hence the conclusion does not seem unwarranted that, with healthy, adequately fed rats, calculi do not appear, or are at least rare.

Among the other 645 rats (297 males and 348 females) 197 cases of calculosis were found, namely in 130 males and 67 females. These rats had been fed on vitamin A-deficient rations. That these rats suffered from vitamin A deficiency was shown by clinical examination. The mortality among them was great; they grew but little. In a number of those I examined, the estrous cycle was disturbed, which, according to Evans, may be considered a sign of vitamin A deficiency. There were also many cases of xerophthalmia. That this eye disease did not occur more frequently must be attributed to the short lives of many rats.

The search for calculi in the urinary tracts was made with great care. Of many rats x-ray photographs were made (see Figs. 1 and 2). Of all, the renal pelvis, the ureters, and the bladder were carefully examined, and to make quite sure, the bladders apparently not containing calculi were also examined microscopically. It was several times possible, in this way, to find

concrements invisible to the naked eye (see Figs. 3 and 4). Rarely calculi were found in the ureters, rather often, however, in the pelvis of the kidneys. These were small as a rule; however, once I succeeded in photographing a calculus in the pelvis of one of the kidneys by means of x-rays (see Fig. 2). It proved to be a calculus 2 mm. long and 1 mm. thick. As regards the bladder, it is difficult to find calculi radiologically if they are less than 1 mm. in diameter, unless their position is favorable. If their shadow lies in the same place as that of the bone tissue, they may easily escape observation. Larger calculi, 2 mm. or more in diameter, are under all circumstances visible on the photographic plate.

<table>
<thead>
<tr>
<th>Diet,</th>
<th>No. of rats</th>
<th>Cases of calculus</th>
<th>Other lesions,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate diet with sufficient vitamin A</td>
<td>241</td>
<td>108♂ 133♀</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Vitamin A-deficient diet</td>
<td>645</td>
<td>297♂ 348♀</td>
<td>46 12 92</td>
</tr>
</tbody>
</table>

That calculi are more frequent in males than in females has its natural explanation, given by Hippocrates in "De aere, aquis et locis," namely that the urethra of females is short and wide.

It was not only phosphate calculi that I have found. Besides calcium and ammonia magnesium phosphate, I also frequently found calcium oxalate concrements, the latter occurring with McCollum's rickets-promoting diet; surely a proof that the nature of the food has an influence on the composition of the calculi. Far the greater part of the calculi consisted of calcium phosphate, mixed or not mixed with calcium oxalate.

A number of rats suffered from hematuria, which was evident from the blood-stained skin of the belly. However this hematuria did not occur so often as might have been expected, considering the frequency of the calculi. Though probably caused by the lack of vitamin A, it is yet of less frequent occurrence than cal-
Vitamin A and Urolithiasis

culosis and is not directly connected with it, for, in many cases of hematuria there were no calcui, while in many cases of calcui in the bladder, there was no blood in the urine.

Contrary to expectation, evident cystitis was rare. It would be natural to think that calcui would cause cystitis, but as a rule the urine was clear, and its reaction upon litmus was acid. I did occasionally find a trace of albumin, but this also occurs in the urine of normal rats. In most cases of calculosis, on microscopic examination, the mucous membrane of the bladder proved to be normal and the surface of the epithelium intact. I could rarely discover any bacteria. In one case, however, I found some very small concrements surrounded by bacteria on the mucous membrane.

Calculi may soon form in case of vitamin A deficiency. I found a calculus in a rat which had been weaned when 4 weeks old and then had been fed for only 9 days on Osborne and Mendel's synthetic ration* and yeast. In another case a calculus had formed in 12 days in a rat fed on a xerophthalmia-promoting diet. I also found calculi after 17 and 19 days, while the formation of calculi in 3 weeks time proved to be very common.

As regards the kidneys, I found some cases of renal abscesses. These have the same cause as pneumonia and inflammation of the bowels, usual in case of vitamin A deficiency, and point to reduced resistance. This morbid condition of the kidneys is not always accompanied by urolithiasis and probably has nothing to do with it.

Several times I found formations in the urine, the shape of which reminded one of casts, but which were of a different nature; namely, straight or bent crystalline cylinders of calcium phosphate or calcium oxalate, evidently formed in the tubules of the kidneys (see Fig. 5). This discovery led me to examine the kidneys thereafter for calcium deposits in rats suffering from vitamin A deficiency. This examination showed me that in vitamin A deficiency, calcium deposits in the tubules are frequent, not to say constant. The simplest way to show these deposits is to expose the sections in a silver nitrate solution to sun or other strong light and then to wash them successively with distilled water, a diluted hyposulfite solution, and distilled water again.

The calcium deposit is then black and easy to discern in the uncolored tissue (see Fig. 6). These calcium deposits are found especially in the tubules, but never in the glomeruli. They take up the whole width of the tubule and vary in length. According to the shape of the tubules they are straight or bent.

Altogether I examined the kidneys of 254 rats, 54 of which had had normal food; five a synthetic ration, yeast, and good Newfoundland cod liver oil; six newly weaned; eleven on a rickets-promoting diet; and 178 suffering from vitamin A deficiency. Though the number is small it is yet remarkable that of the eleven rats on the rickets-promoting diet there was but a single one with calcium deposits in the kidneys. Among the six newly weaned rats and the five fed on good cod liver oil, there was none with calcium deposits. Of the 54 normally fed rats, nine had calcium deposits in their kidneys, but I must add at once that these deposits were exceedingly few in number, one or at most two to a section. Hence I believe that with healthy, well fed rats, calcium deposits of any importance in the kidneys may be said to be exceptional. On the other hand, calcium deposits were almost constant in animals suffering from vitamin A deficiency; in 178 rats 158 times, or 88 per cent compared with a bladder stone frequency of 35.4 per cent.

To check the influence of vitamin A deficiency on these calcium deposits in the kidneys, I first extirpated one of the kidneys of each of a number of rats on ordinary diet, then withheld vitamin A from their food, and those which had not died as a consequence of the operation or from other causes, I killed after some time, in order to examine the remaining kidney. In each of fourteen rats, which had died within 3 to 15 days after the operation, there were no calcium deposits in the extirpated kidney nor in the other one. In nine rats fed in the same way there were no calcium deposits in the extirpated kidney, but in seven cases, after more than 20 days of vitamin A deficiency, I found many in the other kidney. In six of these nine rats calculi (five calcium phosphate and one calcium oxalate) had also formed during 26 to 54 days. These calcium deposits too, form quickly in case of vitamin A deficiency. In one case they had been formed in 13 days. It is curious to notice how little inconvenience the animals experience from them; there have been animals living for 180 days on
insufficient vitamin A, in the kidneys of which I have found numerous deposits, that must have been there for a long time.

From what has been said above, it may be concluded that there is a connection between vitamin A deficiency and the formation of phosphate calculi; at least, that in rats vitamin A deficiency may be a cause of phosphate calculi in the urinary tracts. It is known that absence of the fat-soluble vitamin from the food causes typical changes in the epithelial cells of the mucous membranes, namely keratinization, as shown by the xerophthalmia and the lengthening of the duration of that stage of the estrous cycle characterized by the repulsion of the horny cells. Probably such a morbid change of the epithelial cells of the tubules, in the last instance, gives the impulse to the deposition of calcium casts, which, once liberated, by means of further deposition of salts from the urine, grow to greater concrements.

EXPLANATION OF PLATES.

PLATE 1.

Fig. 1. X-ray photograph of the pelvis of a rat, showing the shadow of the bladder filled with stones.

Fig. 2. X-ray photograph of a rat showing the shadow of a renal and a bladder calculus.

Fig. 3. Microscopic concrements of calcium phosphate found in the bladder of a rat on a vitamin A-deficient diet.

Fig. 4. Microscopic concrements of calcium oxalate found in the bladder of a rat on a rickets-promoting diet.

PLATE 2.

Fig. 5. Microscopic concrements found in the urine of a rat on a vitamin A-deficient diet.

Fig. 6. Photomicrograph of a section of the kidney of a rat suffering from vitamin A deficiency. Calcium deposits in the tubules stained with silver nitrate.
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VITAMIN A DEFICIENCY AND UROLITHIASIS
E. C. van Leersum


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