3. The results are much better when glands are removed, recurrence being greatly delayed or altogether prevented in many cases.

4. Partial removals of the tongue were followed by *local* recurrence in 6 out of 29 cases.

REMARKS ON THE ESTIMATION OF THE CALCIUM METABOLISM.

WITH A DESCRIPTION OF A CLINICAL METHOD OF ESTIMATING THE AMOUNT OF CALCIUM IN THE URINE AND OTHER PHYSIOLOGICAL FLUIDS.*

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To gauge the condition of the general metabolism of the calcium salts, which are now admitted by all to be of so much importance both in health and disease, an accurate knowledge of the amount at the disposal of the tissues is necessary, and this knowledge has been difficult to obtain.

For instance, some workers have estimated—chiefly experimentally—the amount of calcium taken in with the food, and have compared this with the amount recovered from the faeces.

I have always held that this must be absolutely unreliable in the result. For, although we know the amount taken in by the mouth, we are unable to find how much of this quantity is absorbed, and how much passes through the alimentary canal without being absorbed.

An example will make this quite clear. Suppose that 10 grains are taken in by the mouth every twenty-four hours, and that 5 grains are recovered from the faeces, those 5 grains may represent 1 grain passed through and 4 grains excreted, or it may mean that 2 grains are passed through and 3 grains excreted, and so on. That is to say, a large proportion of what is being absorbed may be excreted, or only a small proportion—there is nothing to indicate which.

Recognizing this difficulty, in 1907 I published a method of estimating the quantity of ionizable calcium in the blood.¹ By this method one is able to determine at any given time the relative amount of ionizable calcium in the blood, and so to get a good indication of the amount at the disposal of the tissues. But, as I then and have since emphasized, this method requires careful interpretation. For instance, a low calcium content in the blood might mean, either that very little was being absorbed or that too much was being excreted. I devised the method for a specific experimental purpose in regard to menstruation, and it served that purpose; but when it is used for routine clinical work, unless careful consideration be given to the findings, wrong deductions—as I have just pointed out—may be drawn from them.

If, however, the blood estimation method be used in conjunction with a method which will indicate the amount excreted a perfectly reliable knowledge of the condition of the general metabolism in regard to the calcium salts may be obtained.

Since the excretions from the intestinal canal are, as I have just shown, useless for the purpose, we must fall back on the urine, in which it is safe to say that, provided the urinary apparatus be healthy, the calcium found should represent a true index of the excretory ratio. If the blood index be low and the amount excreted by the urine also be small, it is fair to assume that not enough calcium is being absorbed. If, on the other hand, the blood index be low and the urinary excretion high, then probably too much is being excreted; and conversely a high blood index and low excretory ratio might indicate that an excessive amount was being retained in the tissues.

I must here point out that, as with the blood estimation when considered alone, so also with the urinary excretion: no true interpretation can be formed of the calcium metabolism by an examination of the urine alone. Because a large amount of calcium was found in the urine it would be ridiculous to state on this evidence alone that the patient was suffering from a calcium surfeit, and to cut off all supplies of the salt. It might be that she was excreting

too much, as is the case in exophthalmic goitre, and was depleting her tissues. In such a case, far from cutting off the supply it should be supplemented. Or, again, in some cases in which very little was being excreted it might mean that the calcium was being stored in the tissues, and in such circumstances it would be the worst thing possible to assist in the process by administering more. To be scientific and accurate, when we have no definite clinical evidence or empirical knowledge to guide us, we must use all the means at our disposal to find out what is really happening with regard to the calcium metabolism; and we must not rely on one method alone without we can be quite sure of the interpretation to be put upon the result. In the future the whole subject will, of course, become more empirical, but at present it is far from being so, and I could give many instances of the value of accurate estimations and interpretations. It is, of course, not difficult with the requisite laboratory facilities to estimate chemically the amount of calcium in urine, since large quantities of the latter can regularly be obtained; but such a method of estimation is hardly possible for those engaged in clinical work, so that I think there is room for a reliable clinical method.

The method of estimating the calcium in the urine which I shall now describe owes its origin to Sir James Barr, who for some time has been in the habit of making a rough calculation of the amount excreted by adding to the urine freshly passed the solutions I originally suggested for the estimation of the blood calcium content—that is to say, oxalic acid and acetic acid—and gauging roughly the quantity of the precipitate obtained. On learning from him of this practice I undertook to have the accuracy of his findings investigated chemically. This was done by my assistants working in the biochemical laboratory at the university, with the following results:

1. The sediment sent by Sir James Barr, which was collected from many specimens of urine, was found to consist of pure calcium oxalate. It may be noted here that practically all the calcium present in urine is in an inorganic form, consequently it is precipitated. When the proper measures, to be described directly, were adopted, no phosphates were found in the many precipitates examined.

2. Of the urines submitted by Sir James Barr for chemical investigation of the accuracy of his conclusions the specimen supposed to contain the least amount of calcium was found on analysis to contain 0.008 per cent. of Ca; that supposed to contain a medium quantity was found to contain 0.007 per cent. of Ca; the specimen supposed to contain the largest amount of calcium gave on analysis 0.045 per cent. of Ca.

It is evident, therefore, that the method employed by Sir James Barr is accurate in so far as it is possible to recognize a very large deposit from a small one, and to recognize that a patient is excreting a good deal more than the normal quantity, or possibly, though this is much more doubtful, that he is excreting considerably less. The most obvious difficulty in regard to Sir James Barr's method arose in connexion with the estimation of medium and small quantities, which predominated in the specimens examined, for it was not possible to say whether these were above or below the average quantity. Nor would it be possible with the method employed by Sir James Barr to detect and recognize whether there were an improvement or the reverse during treatment, unless the changes happened to be very marked.

It was, of course, clear that one had to obtain some method of estimating accurately the amount of the precipitate, which we had proved to consist of pure calcium oxalate; and, as I have stated elsewhere, my method of blood estimation cannot be applied in its present form to urine. Consequently our experiments consisted in centrifuging and measuring the deposit in specially calibrated tubes.

Our first difficulty was to prevent the deposit sticking to the sides of the tube, and to get it to lie fairly evenly in the calibrated portion. After trying many things, we finally overcame what threatened seriously to interfere with the perfection of our method by adding alcohol or methylated spirit to the urine and reagent. Next, we found, as we anticipated, that with different rates of revolution of the centrifuge, and with different times spent in the operation, we obtained different results—that is to say, urines and solutions containing the same quantity of calcium gave deposits which stood at different levels according to the circumstances mentioned.

* Read before the Liverpool Medical Institution, March 14th, 1912.

We eventually got over this difficulty by centrifuging a standard solution of an artificial urine, containing a known quantity of calcium in one tube, and the urine to be examined in the opposite one. In this way we were able always to get an absolutely accurate relationship between the two deposits, whatever the rate of revolution or the time employed. So that if the urine showed a deposit of calcium oxalate standing at half the height of the precipitate in the tube containing the standard solution, that urine was found on chemical analysis to contain a quantity of calcium just half in amount of the known quantity in the standard solution. All our results were, of course, verified chemically.

Description of the Method.

A sample from a twenty-four hours specimen of urine is made faintly acid with hydrochloric acid to dissolve any insoluble phosphates present. It is then made faintly alkaline with ammonia, and filtered. Next, 5 c.cm. of the filtrate are placed with a pipette in the special centrifuge tube, which is of the usual size and shape in the upper portion, but tapers at the lower end into a cylindrical extremity of even bore (1.25 mm.), and calibrated into 1 mm. divisions (Fig. 1). A line, with "urine" marked

Fig. 2.

Fig. 1.

below it, encircles the upper part of the tube at the 5 c.cm. level. Any air bubbles which may collect in the calibrated portion are got rid of with a fine wire or strand of silkworm gut.

Then 1 c.cm. of the reagent, consisting of a saturated solution of oxalic acid in a 5 per cent. solution of acetic acid, is added. The correct quantity of reagent (1 c.cm.) is also indicated by the line round the tube which is marked "reagent." Finally 2 c.cm. of alcohol or methylated spirit are added, as indicated by the line marked "alcohol," and the contents of the tube are thoroughly mixed by shaking. The second tube is then taken, and 5 c.cm. of the standard solution* is run into it with a pipette up to the line marked "solution" (Fig. 2), and any air bubbles removed as before. Next the reagent and alcohol are added, as in the case of the first tube, and the whole is thoroughly shaken. Both tubes, with their calibrated ends packed in wool, are then carefully placed in the opposite

buckets of a centrifuge, and are centrifuged for about a quarter of an hour.

On removing the tubes the precipitate will be found to stand at a certain height—say 10 mm. in the "standard solution" tube, while it may stand at 7 mm. in the other, which contains the urine to be examined. As a rule, there is a slight slant on the surface of the deposit. This can be obviated by stopping the machine at the end of one or two minutes and turning the tubes through half a circle. The middle of the meniscus or slant is read off in each tube, and comparison made between them. In the above instance the deposit in the tube containing standard solution was stated to stand at 10 mm., and that in the tube containing the urine at 7 mm.; consequently the urine contains seven-tenths, or 0.7 of the quantity in the standard solution, which is known to be 0.2 per cent., so that the urine contains $0.02 \times 0.7 = 0.014$ per cent. of calcium.

This gives a general equation $\frac{U}{S} \times \frac{1}{50} = \text{percentage of}$

Ca in the urine examined, in which U = height in millimeters of precipitate in the urine examined and S = height in millimeters of precipitate in the standard solution. If the urine be found to contain an unusually large amount of calcium, so that the precipitate more than fills the calibrated portion of the tube, the urine should first be diluted with an equal quantity of distilled water, and the final result obtained in regard to the calcium content doubled.

In our experiments to test the accuracy of the method, we found that the difference between the total amount of calcium obtained in this way and that obtained by chemical analysis never amounted to more than 1 per cent. of the quantity present.

I have already indicated how much this research owes to Sir James Barr's initiative and assistance; but I must also express my indebtedness to Professor Benjamin Moore for laboratory facilities.

The expenses of the investigation were defrayed out of the fund for research which Mr. Arthur Smith has generously placed at my disposal.

REFERENCE.

¹ BRITISH MEDICAL JOURNAL, April 20th, 1907.

A CASE OF OSTEITIS DEFORMANS

IN WHICH FRACTURE OF A FEMUR TOOK PLACE
AS THE RESULT OF STOOPING.

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Cases of osteitis deformans are always interesting. It is only some thirty years ago that Sir James Paget first described this disease, and since then cases have been recorded from time to time, though the disease is undeniably a rare one. Osler tells us that of eight traced to the end, five died from cancer or sarcoma. The following case is of more than ordinary interest, as special opportunities were afforded for witnessing the entire course of this disease, from its earliest apparent onset till its fatal termination, which was accelerated by an accident occasioned by the effects of the disease itself. The whole period covered a space of $4\frac{1}{2}$ years.

The patient was a lady 63 years of age, and the mother of eight children, all living but one, who died in infancy. Her father died quite suddenly at a railway station, when in apparently good health, at the age of 81. Her mother died at the age of 82. There were eight in this family also, three girls and five boys. The eldest son was killed on the hunting field, a daughter died at the age of ten, and another son died last year in New Zealand of "heart and kidneys," at the age of 56. This leaves us with three brothers and a sister, all of whom are still living. A curious feature is that the only living sister, now 61 years of age, is also afflicted with osteitis deformans. The three brothers are aged respectively 53, 50, and 45, and are all in good health.

The patient had an attack of appendicitis in May, 1906. On November 10th, 1906, she had a second attack, and the nurse was then unable to notice anything abnormal about her limbs. On January 12th, 1907, appendectomy was performed by Mr. Mower White. The case, as far as the operation was concerned, made an uninterrupted recovery. When she got up she complained of pain and stiffness in her lower extremities (she had

* Standard Solution.—0.05 gram of calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) is dissolved in a little hydrochloric acid. This is made alkaline with ammonia, and finally acid with acetic acid. Finally 2 grams of urea are added to the solution, and the whole is diluted up to 100 c.cm. with distilled water. The specific gravity of this solution is about 1.015.