it consists in simple laminectomy, opening the theca, and washing out the theca with a mercurial lotion. Here we enter at once on the general and interesting question of notable benefit attending the free opening of the so-called serous spaces and washing out with some antiseptic, because I suggest the parallel of this surgical treatment of spinal meningitis is the well-known surgical procedure of opening the abdomen to cure tuberculous peritonitis. I believe there is no risk in washing out the theca with strong solutions of mercury, even up to 1 in 500 strength, though I have only used that strength once or twice. Still, I should not have any hesitation in using it at any time where there was much exudation in the arachnoid, following it up with 1 in 2,000, and leaving in some of this strength when closing the wound.* The skin wound, I think, should be completely closed, not drained. I used to sew up the theca, my object being to arrest the escape of cerebro-spinal fluid into the wound. I have now given that practice up in almost all cases, because in the first place I found wounds healed as quickly, and there is as a rule no greater escape of cerebro-spinal fluid, so that that reason for suturing was not a very important one. Undoubtedly, too, there is less discomfort to the patient afterwards—namely, less tendency to headache and less tendency to the temporary pyrexia and tachycardia which laminectomy cases not infrequently show. But I have also come to believe that allowing the escape of the cerebro-spinal fluid into the wound cavity for a time, for a few days at any rate, secures a valuable new state of things, for it must get away. It does not necessarily get away through your suture opening, which remains as dry as when closed; therefore it must drain away through the lymphatics of the walls of the wound. If we can thus establish an artificial exit for the cerebro-spinal fluid by means of the lymphatics in and among the muscles surrounding the spine, then, of course, we have established a fistulous association for the carrying on of the circulation of the cerebro-spinal fluid exactly analogous to Senn's and Cushing's methods of treating hydrocephalus. Non-suturing of the theca in the operation, therefore, has a possible advantage. It is difficult to prove that this circulation exists to the degree one believes, but at any rate most of the fluid escapes in that way necessarily because it does not flow out between the stitches of the closely sutured wound. After the wound is completely healed, free mercurial inunction of the spine should be ordered, especially over the scar, on the idea that having arrested the disease an attempt should be made to secure active "absorption" and a complete restoration to health.

In concluding this sketch of an imperfectly understood chronic condition I would express the view that probably many cases of so-called acute myelitis are really meningeal in origin, and that a laminectomy and free drainage of the subdural space might arrest the whole process and the subsequent fatal injury which the cord sustains in such conditions.

REFERENCES.

¹ Spiller, Musser, and Martin, *University of Pennsylvania Medical Bulletin*, March, 1903, vol. xvi, p. 27. ² Krause, *Zur Kenntniss der Rückenmarks-Lähmungen: Verhandlungen der deutschen Gesellschaft für Chirurgie*, 1907, p. 598. ³ Schlesinger, *Beiträge zur Kenntniss der Rückenmarks und Wirbeltumoren*, 1898. ⁴ Oppenheim, *Beiträge zur Diagnostik und Therapie Geschwülste im Bereich des centralen Nervensystems*, 1907. ⁵ *American Journal of the Medical Sciences*, vol. cxxxvii, January, 1909, p. 95.

* As a matter of fact the circulation of cerebro-spinal fluid is so active that probably any drug introduced into the theca is very soon washed out into the wound and lymphatics.

THE sanitary staff in Cuba has recently been increased with the view of mastering the yellow fever, which has not been under complete control, and the addition has proved a fortunate step, for last October was a particularly wet month. The rain in Havana was continuous, rendering the mosquito campaign most difficult. It is, moreover, in October that *Stegomyia* is most abundant. The magnitude of the task may be judged from the fact that the number of houses visited and "petrolized" during the month was 51,381, and that there were 176 cases in which *Stegomyia* larvae were found. There were 15 cases of yellow fever in July, but these dropped to 2 in August and 1 in September, while in October no cases occurred. The work of the staff is, however, by no means confined to the war against mosquito larvae. The dairies are kept under very strict inspection, and during the month of October alone 2,416 analyses of milk were made, and only 38 samples were found to be unsatisfactory.

THE SCIENCE COMMITTEE

OF THE

British Medical Association.

REPORT CXII.

OBSERVATIONS ON THE PHYSIOLOGY OF
THE FEMALE GENITAL ORGANS.*

BY

W. BLAIR BELL, and PANTLAND HICK,
M.D., B.S.LOND., M.B., B.S.LOND.,ASSISTANT GYNAECOLOGICAL
SURGEON, ROYAL INFIRMARY,
LIVERPOOL.MEDICAL REGISTRAR,
ROYAL INFIRMARY,
LIVERPOOL.

I.—GENERAL CALCIUM METABOLISM.†

SINCE much of our work upon the physiology of the female genital organs has centred around the connexion existing between the calcium metabolism and the functions of these organs, it has been necessary for us to leave the bypath of our special investigation for the main road of general physiology, in order that we might, if possible, learn more than is usually known or understood concerning the rapid tissue changes which undoubtedly occur in the general calcium metabolism. We felt that unless we had some guide as to the ordinary (non-genital) influences at work we should be unable rightly to interpret or to assign proper importance to any observations we might make in connexion with the special functions under investigation.

We feel, at the same time, that it is expected of clinicians, when they leave their sphere of greatest activity, that they shall duly acknowledge and recognize the invidiousness of their position. We do this most assuredly, and most earnestly crave indulgence for the incompleteness and sketchiness of our work. In extenuation, it will be easily understood in the first place that we have been unable to devote continuous time to the work, which, consequently, has been carried on under difficulties; and, in the second place, that we have only endeavoured to get some insight into the general calcium metabolism in order to control our special observations. The real work on these general questions has yet to be done by others. We trust that some enterprising physiologists, to whom the work really belongs, will take it up—if, indeed, many of the matters to which we shall allude are not already under consideration.

In any investigation of the rôle of any product of, or factor in, metabolism, it is necessary first of all to be able to isolate that body from the tissues to which its activities are chiefly confined, and to be able to estimate any changes it may undergo quantitatively and qualitatively in different circumstances.

In order to be able to investigate the variations in the blood-calcium content, one of us (W. B. B.) devised a method for the quantitative estimation of the calcium salts. A preliminary communication was made in the *BRITISH MEDICAL JOURNAL*, April 20th, 1907, concerning this method and the reasons for which it was devised. Briefly, it consists in precipitating the calcium in the blood in the form of crystals of calcium oxalate, and, after certain dilutions and precautions against the formation of other crystals, counting those of calcium oxalate, which are very uniform in size, on a haemocytometer plate. Any slight inequality in size is corrected by the large

* The authors have been greatly indebted to the Science Committee of the British Medical Association for money grants. They also wish to express their indebtedness for assistance to Mr. George Barker, Mr. T. Williamson, and Mr. James Smith; also to Professors Benjamin Moore, Salvin-Moore, and Sherrington for laboratory facilities.

† This article is based on a paper read by W. Blair Bell, upon Some Observations on the Physiological Importance of the Calcium Salts, before the Liverpool Medical Institution, February 13th, 1908, and published in the *Liverpool Medico-Chirurgical Journal*, July, 1908.

number counted. An average of 1 crystal per square gives an index of 1 (see Fig. 1).

Since that date the method has been investigated by other observers—many of whom have been kind enough to communicate their views and results to the author of it—and the expression of opinion has been very favourable as regards its accuracy. In this respect the author has been greatly indebted to Professor Herbert Jackson, of King's College, for the deep and friendly interest he has taken in the matter, and for the comprehensive investigations made in his laboratory into the reliability of the method. His verdict is that it is an excellent clinical method.* We are ready to admit (in the present state of chemical knowledge) that this may not be a strictly accurate chemical method, for probably only the ionized calcium is precipitated and estimated; but this is of small importance so long as the method is, as we believe it to be, *relatively* accurate. At the same time we would point out to those chemists who have criticized the method on theoretical grounds that really they have no *locus standi* until they can define and demonstrate what amount of calcium is ionized in the blood and what is not.† We may here state that the only adverse criticisms that have come to our knowledge through the medical press or otherwise have been advanced by men who have never seen the method practised! It will, however, be observed that we are meeting criticisms that have arisen or may arise, even though they may not be worth serious consideration.¹

In further reference to the method—in augmentation or qualification of the original preliminary communication—we would like to say that we have quite recognized, as, indeed, was originally indicated, that no comparison can rightly be made between a watery solution and an albuminous solution, such as blood. In fact, strictly speaking, an index should be established for every fluid for itself. We hope eventually to indicate how this may best be done so as to bring all more or less into line, for we have always recognized that albuminous or colloidal solutions are the best adapted to this method of calcium estimation. Any actual estimation mentioned in these papers will only concern blood, unless it is specifically stated to the contrary. We have taken the normal maximum in human blood to be about 1 crystal per haemocytometer square. This is an index of 1, and is based on many observations. Whether it is strictly accurate or not is of little importance at the moment, for we have only required a relative measure.

From many communications received, and from observing the work of others not conversant with the method, we think that the main difficulties have arisen:

1. In bad technique with regard to the cleanliness of the flasks, pipettes, and plates, all of which must be scrupulously dry and clean when used.
2. In the illumination and magnification. As mentioned in the original paper, only a *dull artificial* light is of any use. An $\frac{1}{8}$ in. objective with a No. 2 eyepiece ($\times 420$ approximately) and an Abbe condenser give the best view. We cannot overrate the importance of getting the picture correctly, otherwise it is impossible to recognize the crystals for certain.

There is one more point also alluded to in the original

* Since this paper was written, a very careful experimental criticism has also appeared. See "The Effect of the Administration of Calcium Salts and of Citric Acid on the Calcium Content and Coagulation Time of the Blood," T. Addis, *Quarterly Journal of Medicine*, January, 1909.

† In connexion with this question of "ionized" and the so-called "masked" calcium in the blood, we would point out that chemists are not all agreed. Many assert that the "masked" calcium—that is, the calcium in combination with proteins—cannot be split off and precipitated by oxalic acid. Others (see W. A. Osborne, *Journal of Physiology*, vol. xxvii, p. 400) think that oxalic acid precipitates all the calcium present.

paper. If there is a very large number of crystals with much unevenness in size, greater dilution must be made in the *initial* stage of the process, and allowed for in the final calculation. Conversely, we may add, if there are exceedingly few or no crystals (very rare) to be seen, the *final* dilution should be lessened—say, 250 c.mm. of water should be used instead of 500 c.mm.—and allowed for in the final calculation. It has been stated that in the dilutions used calcium oxalate is soluble; we can only say that if the method is properly carried out the solubility point of calcium oxalate is never reached.

Before describing the results of the observations made we should like to discuss what value can be attributed to an estimation of the lime salts in a blood examination. In the first place, we must state that we take it as an accepted fact that the other soluble salts are concerned in the part played by the calcium salts. Secondly, we would point out that in dealing with the blood one is dealing at all times with a very variable tissue; any chemical body it contains is like an elusive Will-o'-the-wisp, which leads us a merry dance before we can come to any conclusions at all. But, after all, how can we expect otherwise? If any one ever seriously anticipated that the calcium content of the blood could be finally and definitely expressed as being one in so many thousand, as is stated in the textbooks, he must, indeed, be inflicted with laboratory vision of the

worst type. These things cannot be settled by *in vitro* examination. Life, as we call it, with its never-ending changes, is a necessary adjunct to metabolism.

This statement, if carefully considered, should be sufficient answer to those who have written of the "curious use" of one of us (W. B. B.) has made of the word "index" in connexion with the calcium content. This word has passed into current medical use in connexion with many other varying metabolic factors; why not also in connexion with calcium? Far better had chemists qualify the statement to be found in textbooks that the blood contains so much calcium, estimated as CaO ! It may do so in regard to the special sample that was under investigation; but there the accuracy begins and ends. The use of the

word "index" makes the matter clear in regard to the method under discussion; no other word would do so.

The calcium content of the blood is, then, like that of any other food supply, a variable quantity. Apparently it corresponds to some extent with the coagulation-time variations which have been worked out by Coleman² and others. We would emphasize the fact very strongly, however—for it seems in danger of being overlooked—that the coagulation of blood depends on many factors, of which calcium is only one, and that acting within limits. We think, however, from our own observations and from a private communication we have received from T. Addis, that it will be shown that variations in the calcium content do not cause changes in the coagulation time to the extent usually believed.‡

In order to assure ourselves of the diurnal variations in the calcium content we each estimated the other's blood at frequent intervals throughout one day, during which we ate practically the same food and took the same amount of exercise and rest. The accompanying table shows the result.

It will be seen that, with the one exception, which may not have been quite accurate, our blood contents varied regularly and together. We have not followed the quest-

‡ Cf. action of "Antileukozytenserum" *in vitro* and in the circulation; it is diametrically opposite (Delezenne, *zit. nach. Jahresber. f. Tierchemie*, 1900, S. 141).

§ Since this paper was written, T. Addis's paper has appeared. See previous footnote.

Fig. 1.— $\times 420$. Normal blood, calcium content.

	W. B. B.	P. H.
Sunday, June 23rd, 1907:		
8.45 a.m.	Index, 0.7	Index, 1.2
10.0 a.m. Breakfast	—	—
11.30 a.m.	Index *	Index, 0.32
1.30 p.m. Luncheon	—	—
3.30 p.m.	Index, 0.45	Index, 0.5
3.45 to 5.15 p.m. Walking exercise	—	—
5.15 p.m.	Index, 0.65	Index, 0.56
8.0 p.m. Dinner	—	—
10.0 p.m.	Index, 0.6	Index, 0.43

* Error in technique spoilt this count; as far as could be seen index was about 1.0.

through the night. That is a small matter of research we leave open to others—not that we would shirk the task if we thought any knowledge of use to us could be gained by performing it.

This observation, which has been confirmed by other counts, was very instructive, and useful in helping one to form conclusions as to the value of indices under varying conditions, and showed the importance of taking the blood at the same time each day when making observations on a case, or performing experiments on animals. This diurnal variation gives confirmation also to the statement we have made that the blood is the agent of the tissues in respect of the calcium salts; and an index of the blood can, therefore, be construed into an index of the condition of the tissues.

In normal physiological conditions, if the tissues are needing calcium, one would expect to find a low calcium index—that is to say, the tissues will be taking up all the calcium they can get. There are, however, other sides to the question; for example, the calcium supply in the food may be low, or the absorptive functions in the bowel deficient; the tissues may want calcium, and the blood be unable to supply it in the form required; or, again, calcium may find its way into the blood in a reversed direction—from breaking down tissues—as sometimes occurs in pregnancy.

We refrain from mentioning further possibilities, for such a picture appears anything but easy of interpretation. It was, moreover, the complexity of these conditions which impelled us to seek out the regulating or controlling factors in the calcium metabolism, for we felt that upon some elucidation of this difficult problem depended the correct interpretation of many blood indices, and the probable deductions to be made eventually in questions of genital activity.

Let us state at once that much remains to be done in this direction, and one of us (P. H.) hopes in the near future to follow up the full relationship of the ductless glands to the general calcium metabolism, both in its normal and pathological aspects.

That the lime salts play a very prominent part in the metabolic processes of all living tissues there can be no doubt, and it is therefore somewhat strange that until recently so little interest has been displayed in the matter. The part played in bone formation, and in the coagulation of blood and milk (comparatively recent discoveries), and the so-called "tonic" influence on cardiac muscle, founded on the splendid work of Sidney Ringer, have been the only matters to attract attention, and even these have never been followed out properly.

Lately, however, a calcium "wave" seems to have come over medical science, and admirable work has been done in different departments by Sir A. E. Wright, Sir James Barr, MacCullum, and many others; even at the present time, however, the conclusions arrived at are very imperfect, and this we venture to think is largely due to the absence of a broad and comprehensive view of the subject, which alone can correlate all the issues.

We have, therefore, kept ever before us the importance of taking a wide outlook on all the work that has been done, and have attempted to harmonize our own observations of a general nature with those of the special functions we set out to study, for those functions are not local in origin or effect, but general.

Broadly speaking, then, we have come to the conclusion that the lime salts are not only necessary for the construction of the body and its growth, but also for keeping it healthy and in repair, and for the reproduction of the species.

These salts only become apparently pathological—as far as we can discover—when, like that beneficent process known as inflammation, they endeavour to rescue diseased structures and to repair them. As long as the disease—arteritis, for example—continues, so long will the reparative attempts, which include a determination of calcium salts to the part, be carried on. This reparative function of the calcium salts naturally follows on the original constructive rôle. You can cause no definite lesion, medical or surgical, in an animal, nor find one in the human subject, without there being a determination of calcium salts to the injured region, as indicated, if the lesion is severe enough, by a fall of the calcium salts in the blood until convalescence sets in—that is to say, until the demand has been met or the regulators of the calcium metabolism have established an equilibrium in the altered circumstances.

This selective and retentive power of the cell for calcium salts is probably in part under the influence of the calcium-regulating factors to be discussed presently. At the same time there is every reason to believe that individual cells exhibit a self-regulating selective and retentive power in regard to all chemical compounds with which they are brought into contact.

Had we not been able to make these observations experimentally the fact has always been there for the observing. Who has not seen the calcareous deposits at the site of many an old chronically inflamed area? It is an everyday observation in the case of tuberculous disease, but has the full significance ever been realized?

We believe that there is no such thing as calcareous degeneration. What does happen is that there is a calcification—the result of a reparative process—in diseased structures.* We would refer, in this connexion, to an extremely interesting paper by O. T. Williams,³ in which he claimed that the calcium soaps, which he demonstrated to be deposited in diseased appendices, were the cause of the condition known as appendicitis. Is it not possible, however, that these calcium compounds are there as the result rather than the cause of the inflammation? We would also point out that ordinary fibrous tissue, especially scar tissue, is relatively exceedingly rich in calcium salts, for the benefit of those who are at all sceptical of the deductions drawn concerning the deposition of calcium compounds.

These views, as already stated, have been entirely supported by hundreds of blood examinations, particulars of which would be superfluous here; and these observations, like those on the diurnal variations, have been of great importance in assisting us to understand the blood index.

In addition to constructive and reparative processes in which the calcium salts are retained or fixed, there are other processes no less important—indeed, it was the mystery surrounding them that led us to look for the regulating factors in the calcium economy.

Even while circulating in the blood the calcium salts play a large part in the health of the individual. We say "even while circulating," whereas, of course, we mean to speak of them in the same way as one does of the oxygen in the form of oxyhaemoglobin, or of the opsonins in the blood—in the potentialities each possesses.

It is to the metabolism associated with the rapid tissue changes rather than that associated with the retention of lime salts, already alluded to, that we now wish to call attention. Suppose that the individual is structurally and physiologically perfect for the time being, what are the processes in which the calcium salts take part? We do not pretend to know all, nor perhaps even the larger number, but we will mention briefly those which we think are most worthy of attention, and of which we have some knowledge.

In regard to these rapid tissue changes, in the first place there can be no doubt, we think, that the lime salts are largely concerned in the contraction of the involuntary muscle throughout the whole body. If we were able to abstract the lime salts from the blood, or prevent them gaining

* The deposition of calcium soaps is an intermediate stage leading to calcification.

admittance, the heart would fail and involuntary movement generally would cease. Sidney Ringer's brilliant work in this direction established these facts. In a later paper, when dealing with uterine contractions, we shall illustrate the effect of calcium salts upon the heart. We do not for one moment say that involuntary muscles cannot be affected by other chemical and physical agents, but there is very strong evidence to show that the calcium salts play a large part in the production of the normal stimulus, and—to speculate—probably of the primary stimulus in the embryo. In subsequent papers we shall deal with the question of uterine contractions, and also with the processes with which calcium salts are concerned in menstruation, pregnancy, and lactation.

We have made, also, some observations in regard to the calcium content of the blood and its coagulability, and while we have not made any serious study of the question—for T. Addis, of Edinburgh, has informed one of us in a private communication that he has this matter in hand*—we would like to make a few remarks upon the subject here.

We have often been asked if there is not a certain element of danger in the free administration of calcium salts. From many observations and experiments we feel quite justified in saying No. One cannot force up the calcium index in the blood much beyond the usual maximum, in normal circumstances, either by oral administration or subcutaneous injection, and even if this were possible—to have a lawyer's alternative—clotting in the vessels, *if they were healthy*, would not occur. We have killed animals with intravenous injections of calcium salts without producing intravascular clotting, *except where the vessels had been previously damaged*. There is therefore, we think, an optimum amount with a quickest normal clotting time, and the latter excess of calcium salts cannot increase. Given, of course, an inflamed or damaged vessel—for example, phlebitis after typhoid fever or arteritis—and one may get a deposit of lime salts in the damaged walls (*vide supra*), and possibly clotting in the damaged vessel, which will be most likely to occur if the calcium optimum index for clotting exists.

One more point in this connexion. Sir A. E. Wright showed that the oral administration of an excess of calcium—which we presume he thought got into the blood—delayed clotting; but apparently, from observations we have made, this is not due, as he thought, to an excess, but to a deficiency, in the blood. It is probable that after excessive dosage the body becomes immune or resistant to the absorption of calcium salts, or excessively active in their excretion, effected probably by the thyroid secretion. This point might with advantage be studied in infant feeding and rickets.

Of the many other points that have interested us in taking a general survey of the calcium metabolism we may single out two which have brought into our minds matters of some importance.

If we are right in our main belief that the calcium metabolism is largely concerned in the physiological processes of women, may not the alteration in the calcium economy at the menopause be to some extent accountable for the deposition of fat? This does not of course coincide with the general ideas concerning obesity and the allied metabolic processes to which that condition is usually attributed; but in view of the close connexion between certain fatty acids and calcium metabolism we feel that there may be some association which future investigation will lay bare. Excellent work on the relationship of these fatty acids to one another in regard to the absorption and deposition of fats, and on the formation of calcium soaps has already been carried out by O. T. Williams (*loc. cit.*).

The other suggestion we would make is this: May not the deficient excretion of calcium soaps by the bowel in physiologically active women be the cause of chronic constipation—an ever-present evil with the female sex? We think these points are well worthy of bio-chemical investigation.

Before discussing the regulating factors it may be well to include here an observation which has given rise to some controversy. While looking for a suitable organic compound of calcium for hypodermic injection it occurred to us to try gelatine, which, as is well known, contains a large amount of calcium; indeed, it has been suggested

that the power of gelatine, when used therapeutically in cases of aneurysm to influence the coagulability of blood, is due to the contained calcium.⁴

We were consequently led to investigate this animal product, and found that by the method already described it was possible to estimate the calcium. Though, of course, not strictly comparable with blood, we may state that, although the commercial samples vary, we found the average index to be about 20. It will be readily understood how this quantity might influence the blood of the individual into whom it was injected. As yet no direct experiments have been done in this direction, but we found that intravenous injection of 4 per cent. gelatine solution did not cause intravascular clotting. Gelatine corresponds, therefore, with other calcium compounds in this respect, and by this behaviour tends to confirm the suggestions that its calcium content is responsible for the raised coagulability, if this does occur, rather than any nucleo-proteid-like substance.

The following protocol illustrates the action of a 2 per cent. solution of gelatine subcutaneously injected upon the systemic blood calcium content.

White Buck Rabbit.		
November 1st, 1907:		
9.45 a.m.	Index 0.67	10 c.cm. 2 per cent. gelatine-solution subcutaneously injected.
11.45 a.m.	.. 0.67	
12.45 p.m.	.. 0.7	
3.45 p.m.	.. 0.7	
5.40 p.m.	—	10 c.cm. 2 per cent. gelatine-solution subcutaneously injected.
5.55 p.m.	Index 0.76	

If, therefore, the gelatine does raise the calcium content of the blood a 2 per cent. solution does not appear to be strong enough. It is only fair to state that Boggs⁵ found the period of increased coagulability to be at a maximum as long as twelve hours after the injection. The diverse results obtained in the experiments of Boggs and the conflicting opinions of Dastre and Floresco⁶ on the one hand, and those of Brat⁷ and Sackur⁸ on the other, regarding the influence of gelatine upon the coagulability of the blood may be explained on the theory of immunization we have already alluded to, or—and this is more likely—on the ground that the methods employed by them for estimating the coagulability were inaccurate.

It was in connexion with the coagulation, or "setting," of gelatine that we made some observations which have given rise to controversy. The results of our experiments led us to ask if it was not possible that the presence of calcium was necessary for the occurrence of this process. In October and November, 1907, we carried out a series of experiments in which we tried the effect upon the coagulation of gelatine of solutions of the following substances: oxalic acid, acetic acid, ammonium oxalate and sodium citrate.† We do not think it necessary to give the protocols in detail, but will briefly summarize our results.

We found that we obtained a heavy white precipitate of calcium oxalate with ammonium oxalate and oxalic acid, and that the salts above mentioned caused marked retardation of the coagulation time. Further, that the acids (if the gelatine was in weak solution) also retarded the coagulation under ordinary circumstances; but that if the solutions were kept at a temperature which would prevent gelatinization for about forty-eight hours, that process did not occur at all. Further, we found that the *prolonged action of ammonium oxalate, but not of other salts, prevented coagulation*.

Now, in regard to the criticisms raised with reference to the suggestion that it might be worth while for chemists to discover if calcium was really an integral part of gelatine, and whether gelatine existed as such without calcium—in the first place, let us state that in all the papers quoted to disprove our suggestion (it has never been more than a suggestion) there is no mention of calcium-free gelatine having been obtained. Morner⁹ and

* See previous note.

† Compare these experiments with the statements made by H. E. Roaf (Reference).

many others have done their best to obtain calcium-free gelatine, but as far as we know no one has succeeded. It seems to us, therefore, that, whether our suggestion is right or wrong, it is hardly logical to argue that because a certain percentage has been removed without interfering with the coagulability, calcium has therefore nothing to do with the process. In regard to this point, Addis's work on blood coagulation is of much interest.

Nor does it appear reasonable to assume, as has been done,¹ that because in certain experiments delayed coagulation only was obtained, therefore the calcium cannot be concerned. We have secured prevention of coagulation, but to that we do not wish to attach undue importance, although such positive evidence is certainly of more value than the negative evidence just alluded to.

It has also been suggested that the hydrogen ions in the oxalic acid are responsible for the result. This seems to be quite as indefinite a statement, and one which requires some proof. However, until calcium-free gelatine has been obtained which will gelatinize, and so prove our suggestion to be wrong, we would commend to unbiased observers the following points which seem to us to be worth consideration in any attempt to settle the question:

If calcium is a factor in the coagulation of blood—and we believe that this is usually accepted—and oxalic acid and ammonium oxalate prevent that coagulation by precipitating the calcium, is it not possible that the same result obtained in the case of gelatine is due to the same cause? Again, most salts retard the coagulation of blood, just as the "setting" of gelatine is delayed by them. C. J. Martin¹⁰ attributes the result obtained by citric acid and citrates in the case of the blood to an alteration in the ionization of calcium; and this is, we believe, universally accepted. Is it not possible to apply the same idea to the action of these and similar compounds upon gelatine? This is a small matter, perhaps, and we have no wish to discuss it at greater length, as it in no way concerns our work; but, having made a promise to deal with any criticisms raised,¹ we have therefore attempted to fulfil it.

In our investigations we have so far touched but slightly upon the importance of the ductless glands in the regulation of the calcium metabolism. Time has not allowed that complete inquiry which will, as already mentioned, be pursued later by one of us. There are several points, however, to which we desire to draw attention, for they seem to have some relation to genital activity.

First, in regard to the thyroid gland. Clinically, we had observed that in most cases of exophthalmic goitre, where the thyroid secretion was in excess, the blood calcium index was low, an observation which caused us to suggest to Sir James Barr that calcium salts might possibly have some therapeutic, or at least symptomatic, advantage in this disease. Sir James Barr very kindly gave these salts a trial, with undoubted advantage in many cases, the pulse-rate being markedly lowered.

Following this up, we excised the thyroid, and as far as possible the parathyroid glands of four cats. Two were quite young, and two full grown. Two died in a few days—one young and one adult—the former with tetanic convulsions on the fourth day, and the adult a few days later with slight spasms and great muscular weakness.

The other young cat died at the end of fourteen days, much emaciated, and with great muscular weakness. The last—a large black tom-cat—was becoming lethargic and myxoedematous, so we castrated him. From that time he steadily improved, and is at present quite lively and particularly intelligent. His coat is perhaps a trifle dull and dusty-looking, otherwise there is nothing at all indicative of myxoedema.* This effect of castration, if one can claim so much in a solitary instance, requires further investigation. We have been told that Stanley Kent obtained the same result, but never published an account of his experiments.

With regard to the observations made on the blood of these cats, in each of the young cats the calcium index ran up to a remarkable extent, while the older cats were not affected in the same way. All the animals lost weight.

The following are the protocols of these experiments:

I. *Large Tortoise-shell Tom-cat.*

November 25th, 1907. Index 0.78. Weight 3,350 grams. Complete thyroidectomy.

* Recently an improvement in the condition of his coat has been brought about by the administration of thyroid gland extract.

November 28th, 1907. Not well; lying very quiet. Slight muscular twitchings.

November 29th, 1907. Very quiet. Spasms when touched. Some muscular weakness. Index 0.74. Given 5 c.cm. thyralcol solution and 5 c.cm. 20 per cent. gelatine solution.

November 30th, 1907. Better. Still weak. No spasms. Index 1.3.

December 1st, 1907. Died during night. Weight 2,800 grams.

II. *Young Tortoise-shell She-cat.*

November 25th, 1907. Index 0.48. Weight 1,550 grams. Complete thyroidectomy.

November 28th, 1907. Very restless; quite strong.

November 29th, 1907. In continual tetanic convulsions; cannot stand. Index 5.5. 5 c.cm. thyralcol solution hypodermically and 5 c.cm. gelatine solution 20 per cent.

November 30th, 1907. Convulsions more intermittent. Still violent. Index 9.0. 10 c.cm. thyralcol solution given hypodermically.

December 1st, 1907. Better. One slight convulsion. Very weak. Index 3.0.

December 2nd, 1907. Died during the night. Weight 1,240 grams.

III. *Young Black Tom-cat.*

November 27th, 1907. Index 0.67. Weight 1,750 grams. Complete thyroidectomy.

November 29th, 1907. Apparently quite well.

December 1st, 1907. Index 2.7.

December 5th, 1907. Index 14.0. Cat getting weak.

December 6th, 1907. Index 15.0. Cat much weaker.

December 7th, 1907. Index 11.0. Cat still very weak, but seems a little brighter.

December 8th, 1907. Index 12.0. Cannot use hind legs. Injection of 5 c.cm. thyralcol.

December 9th, 1907. About the same condition. Weight 1,210 grams.

December 10th, 1907. Index 7.0. Cat seems much better. Injection of 5 c.cm. thyralcol.

December 11th, 1907. Index 18.0. Cat seems not nearly so well to-day.

December 12th, 1907. Died during the night.

IV. *Large Black Tom-cat.*

November 27th, 1907. Index 0.3. Weight 3,250 grams. Complete thyroidectomy.

November 29th, 1907. Apparently well.

December 1st, 1907. Index 0.7. Apparently well.

December 5th, 1907. Index 0.5. Very quiet.

December 6th, 1907. Index 0.4. Rather weak.

December 7th, 1907. Index 0.8. Seems better than he was yesterday.

December 8th, 1907. Index 0.4. Seems strong but very lethargic.

December 9th, 1907. Index 0.4. So dull and apathetic that he is apparently developing myxoedema. Weight 2,890 grams. Castrated.

December 10th, 1907. Index 0.8.

December 11th, 1907. Index 0.6.

December 12th, 1907. Index 1.0. Quite active and bright. Stole some fish.

December 23rd, 1907. Index 1.0. Apparently normal.

We likewise operated upon three rabbits, but in none of these did we get the results obtained with cats. Beyond some temporary loss of weight they showed hardly any symptoms at all; nor did the calcium indices show marked increases. It will be noted, however, that the only one at all ill was the young one. The primary drop in the calcium content which follows all operations occurred, and was followed by a gradual restitution to the normal. This is seen from the following protocols:

I. *Grey and White Buck.*

November 23rd, 1907. Index 0.8. Weight 2,700 grams.

November 24th, 1907. Complete thyroidectomy.

November 25th, 1907. Index 0.57.

November 26th, 1907. Index 0.45.

November 27th, 1907. Index 0.3.

November 28th, 1907. Index 0.4. Weight 2,550 grams.

November 29th, 1907. Index 0.7.

November 30th, 1907. Index 1.0.

December 2nd, 1907. Index 1.1. Weight 2,410 grams.

December 4th, 1907. Index 0.72. Weight 2,340 grams.

December 11th, 1907. Index 1.0. Weight 2,420 grams.

December 18th, 1907. Index 0.8. Weight 2,640 grams.

II. *Brown Buck.*

November 23rd, 1907. Index 0.8. Weight 2,140 grams.

November 24th, 1907. Complete thyroidectomy.

November 25th, 1907. Index 0.54.

November 26th, 1907. Index 0.57.

November 27th, 1907. Index 1.2.

November 28th, 1907. Index 1.0. Weight 2,140 grams.

November 29th, 1907. Index 1.1.

December 9th, 1907. Index 0.62. Weight 2,120 grams.

December 16th, 1907. Index 1.7. Weight 2,260 grams.

December 20th, 1907. Animal seems ill.

December 21st, 1907. Died. *Post-mortem* examination showed intestinal obstruction. Intestines much matted together and distended. This was evidently the cause of death.

III. Black and White Doe (not full grown).

November 23rd, 1907. Index 2.0. Weight 1,510 grams.
November 24th, 1907. Complete thyroidectomy.
November 25th, 1907. Index 1.4.
November 26th, 1907. Index 0.7.
November 27th, 1907. Index 0.4.
November 28th, 1907. Index 0.2. Weight 1,400 grams.
November 29th, 1907. Index 0.56. Rabbit seems ill.
½ c.cm. thyralol given hypodermically.
November 30th, 1907. Index 0.74. ¼ c.cm. thyralol given hypodermically.
December 2nd, 1907. Index 1.2. Weight 1,410 grams. Rabbit better.
December 4th, 1907. Index 0.9.
December 7th, 1907. Index 0.9. Weight 1,320 grams.
December 11th, 1907. Index 1.8. Weight 1,310 grams.
November 18th, 1907. Index 0.87. Weight 1,340 grams.

It is, however, well known that rabbits and herbivorous animals generally do not exhibit the effects of complete thyroidectomy and parathyroidectomy (if the latter is effected, which is somewhat doubtful) to the same extent as carnivorous animals. This probably explains the results of our experiments on rabbits.

There can be little doubt, we think, that the thyroid secretion plays some part in the calcium metabolism along, perhaps, with other functions, and the evidence all seems to point to an excretory effect.

Scordo and Franchini (Grocco's Clinic)¹¹ have recently arrived at the same conclusion from a careful examination of the calcium excretion in the urine of patients suffering from exophthalmic goitre. On the other hand, MacCallum and Voegtlin,¹² in their work on the parathyroids and calcium metabolism, arrive at a different conclusion. There must be, however, some connexion between the secretion of the thyroid gland and the calcium metabolism, even if only an intermediary one, and we shall allude to this in a later paper in regard to thyroid activity during menstruation and pregnancy.

Next, the pituitary gland has engaged our attention. It is hardly necessary to say that the gland has frequently been found to be diseased in connexion with bony overgrowths, such as one finds in acromegaly; consequently it is natural to imagine that the secretion of the gland is normally concerned in the limitation of bony deposition, or calcium retention. But, further, it is found that the extract made from the infundibular portion of the gland (Fig. 2, i)—strangely enough the non-glandular portion—has an enormously powerful influence upon involuntary muscle fibre. This effect is most marked upon the uterus, as we hope to show in a later paper. The glandular portion of the gland (Fig. 2, h) is inactive in this respect. Mr. H. H. Dale, of the Wellcome Laboratories, who has kindly furnished us with the extract, has done much good work on this subject. Professor Schäfer, however, was the first to remove the pituitary gland from the lumber room of "embryonic relics."

We have reason to believe that further investigation will show that an intimate connexion exists between the pituitary extract and the calcium metabolism. Our experiments have been limited in number, but seem to show that under the influence of pituitary extract there is an

increase of calcium in the blood, whether it is a normal or permanent effect we are not at the present moment prepared to say.

Again, adrenal extract, as every one knows, has not only a marked influence on involuntary muscle, but also causes calcium retention in the tissues. Acting upon this knowledge, Bossi¹³ of Genoa has found that osteomalacia can be much improved by the administration of this product, and experimentally it has been shown that calcareous retention in the blood vessels is brought about by its influence.¹⁴ This, however, may be a natural process consequent upon an arteritis.

Lastly, the ovaries (and testes possibly also) influence calcium metabolism, as is shown in many ways: osteomalacia has been cured by oöphorectomy, and we know that calcium retention occurs after the menopause. It is possible, also, that the part played by the internal secretion of the ovary in menstruation and pregnancy has reference to the calcium metabolism concerned in these processes.

This syndrome of facts leads one to many speculations—speculations which must be checked by careful experimentation. It seems, however, more than probable that the ductless glands preserve a balance in the calcium metabolism—as they do in many other metabolic processes—one acting anabolically, another katabolically.

It is sufficient for our present purpose to know that there is some important relationship, but we hope in the subsequent papers to indicate and illustrate more fully the connexion that exists between these glands and the functions of the female genital apparatus.

Fig. 2.—Pituitary gland ($\times 250$). Note sharp line of demarcation between hypophysis and infundibulum

REFERENCES:

- ¹ See Correspondence, BRITISH MEDICAL JOURNAL, March 14th, and 21st and April 4th, 1908.
- ² *The Biochemical Journal*, vol. ii, No. 4, p. 387, 1907
- [The methods used by Coleman, Wright, Brodie and Russell, and others, have been seriously questioned.—W. B. B., P. H.]
- ³ O. T. Williams, *The Etiology of Appendicitis*, *Liverpool Med.-Chir. Journal*, July, 1908.
- ⁴ Zibel, *Munch. med. Woch.*, 1901, S. 1643; Gley and Richard, *Comptes Rendus Soc. de Biol.*, 1903, Bd. 55, S. 464.
- ⁵ T. Boggs, *Deut. Archiv. f. klin. Med.*, 1904, 79, xxix, S. 539 [The methods used by him have also been questioned.—W. B. B., P. H.]
- ⁶ Dastre and Floresco, *Archiv. de Physiol.*, 1895, S. 402.
- ⁷ Brat, *Berl. klin. Woch.*, 1902, S. 1146 and 1170.
- ⁸ Sackur, *Grenzgebiete*, 8, S. 188.
- ⁹ Morner, *Zeit. f. Physiol. Chem.*, 1899, Bd. xxviii, p. 471.
- ¹⁰ C. J. Martin, *A Communication to the Physiol. Soc., Lister Institute*, 1904.
- ¹¹ Scordo and Franchini, *Il Policlinico*, 1907, xvi, p. 285.
- ¹² MacCallum and Voegtlin, *Johns Hopkins Bulletin*, March, 1908.
- ¹³ Bossi, *Zentralbl. f. Gynäk.*, Nos. 3 and 6, 1907.
- ¹⁴ Wells, *Chemical Pathology*, p. 545, various references.

ON SLEEP AND WANT OF SLEEP.

BY

THE RIGHT HON. ROBERT FARQUHARSON, M.D.

"A BLESSING on him that invented sleep. It wraps us up like a garment," and "Sleep that does weigh our eyelids down, and steep our senses in forgetfulness." These hackneyed quotations sum up the case in favour of Nature's sweet restorer, and we all sympathize with the poor monarch who in vain sought the nightly refuge from the trials and worries of the world so freely granted to the meanest of his subjects.

I am not going to attempt to be instructive in this paper. My ambitions do not point so high, and I should like to imitate the man who, if not witty himself, was the cause of wit in others, by inducing more especially general practitioners of large practical experience to help in clearing up some still obscure points in connexion with sleeping;