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Author's compliments.

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Observations on the Action of Strontium Salts on the Coagulability of the Blood.

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THE following observations were made in the Pathological Laboratory of St. Mary's Hospital at intervals during the past year by the kind permission of Sir A. E. Wright, and were mainly carried out on a patient under his care whom I was allowed to examine with considerable frequency. They are intended to supplement a paper which appeared in the *Lancet* of October 14 last by Sir A. E. Wright and Dr. W. E. Paramore on the Therapeutics of Blood Coagulation, and another which appeared in the following number by Sir A. E. Wright and Dr. G. W. Ross on the action of Calcium and Magnesium Compounds in the Treatment of Physiological Albuminuria. The observations recorded were for the most part simultaneous in point of time with those of Dr. Paramore, he taking the action of calcium and magnesium and I that of strontium by agreement, so as not to interfere with one another.

The patient on whom I made these observations is a sufferer from hæmophilia, for whom it became desirable to find a drug as a substitute for calcium, as repeated observation by Sir A. E. Wright and myself established that in his case calcium salts were not absorbed when administered by the mouth. This is a detail which seemed to me worth working out in the interest of general therapeutics, as it is probable that there are other drugs with regard to which similar disabilities may exist and have to be overcome. I therefore took considerable pains to establish the fact in the present instance, and in this I think I have succeeded, the result of my observations being to prove

that the subject in question can absorb with facility, when they are given by the mouth, the soluble salts of strontium and magnesium while refractory to those of calcium.

The condition for which it was required to improve the coagulating power of this man's blood is a periodical oozing of blood from the alveoli of some of his teeth, with which it does not appear safe to deal surgically. Generally the time taken by his blood to coagulate in a Wright's capillary tube is two and three-quarter minutes or so at blood heat, the normal for that temperature being two minutes or rather less. At times he suffers from an attack of boils and then the extra amount of nucleo-proteid circulating in the blood has the effect of raising its coagulability to the normal or above, and the hæmorrhage is then suspended, to recur again on convalescence as the coagulating power falls. Sir A. E. Wright has tried to obtain a similar result artificially with such substances as peptone and thymus gland, but only with moderate success, and the desideratum therefore seemed to be to furnish the patient with a drug that would have a prompt effect when taken by the mouth whenever a hæmorrhage came on, without waiting for the time to visit the hospital. In this direction some advantage has been gained by means of the present research.

After it had been established that the patient could not absorb calcium salts by the mouth the idea occurred to me that a compound of greater molecular weight but otherwise possessed of the same properties would be indicated for trial, as presumably traversing a mucous membrane more easily; and my attention therefore turned in the first instance to strontium, of which the molecular weight is to calcium as 87 to 40; but inasmuch as subsequent observation showed that the patient absorbed equally well the salts of magnesium, of which the molecular weight is only 24, I fear that the hypothesis has no foundation. Nevertheless, as the starting point of the present investigation it requires to be mentioned; but I am not able at present to throw any further light on the cause of this curious and, I think, generally unrecognised condition that an individual should be able to absorb with facility two only out of three closely allied metals, when by the generality of persons all three are equally easily absorbed. As I have said, such a peculiarity may obtain in other cases, and, as a matter of fact, another instance of the same kind is

recorded in the paper of Wright and Paramore in the person of an individual, under the initials A. E. W., who can absorb the salts of magnesium but not those of calcium.

Among the salts of strontium the bromide, of course, has had considerable vogue in epilepsy, and other occasional uses of the metal are recorded in pharmacological literature; but no definite mode of action or the possession of any particular activity by strontium as a base seems as yet to be recognised by medical practitioners. Yet Arthus and Pagès in their classical work on the process of coagulation expressly state that strontium salts will replace those of calcium in restoring its coagulability to oxalated blood.[1] No one seems, as I say, to have ascribed to this palpable activity the medical benefits asserted to have been obtained by the use of strontium. The authors referred to, curiously enough, deny a similar property to magnesium, a statement which in the face of Wright and Paramore's results can only have a partial application. They say: "Les sels de strontium peuvent comme les sels de calcium produire la coagulation. Les sels de barium et de magnesium sont impuissants à faire coaguler le sang decalcifié." To Wright and Paramore, as far as I can see, belongs the merit of first demonstrating that an important effect of magnesium when absorbed into the system is that of increasing the coagulating power of the blood, the statement of Arthus and Pagès being either a slip of the pen or only applicable to the blood of animals with which they worked. In the case of milk[2] they say, on the other hand, "Les sels de barium et de magnesium par exemple se comportent comme les sels de calcium." By employing one of Wright's methods it is easy to demonstrate that if blood drawn from the finger be mixed with just enough of a solution of ammonium oxalate (in physiological salt solution) to prevent coagulation and then a little of this mixture be aspirated into a capillary tube with a fragment or two of a calcium or magnesium salt, coagulation will set in as rapidly with the magnesium as with the calcium. Strontium shows a similar but decidedly weaker action, often allowing a partial subsidence of red corpuscles before the clot forms, and barium I have not noticed to have any activity in this direction at all.

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[1] "Archives de Physiologie Normale et Pathologique," 1890, p. 742.
[2] *Ibid.*, p. 339.

An important practical application of the strontium salts in medicine was made in the year after the publication of Arthus and Pagès' research, but without apparently any attribution of the results obtained to the properties which they had demonstrated. In 1891 Dujardin-Beaumetz and others in Paris gave an exhaustive trial to the action of lactate of strontium in cases of albuminuria, instigated thereto by Laborde, who had shown the harmlessness of strontium salts on dogs. In vol. xiv. of the *Progrès Médical* (1891, pp. 313, 409) will be found abstracts of communications made to the Société de Thérapeutique with regard to this point, from which it appears that lactate of strontium given in doses up to six grammes per diem will produce a great diminution in the amount of albumin excreted in cases of "parenchymatous and desquamative nephritis, but not in the interstitial form." This treatment seems to have been subsequently abandoned, and certainly has never come into general use, perhaps from proving only palliative, and still more, I imagine, because no intelligible mode of action was assigned to the drug by the experimenters. On this point they all express themselves very vaguely. Later still, Reid is quoted in the *Lancet* of October 27, 1894, from the *Centralblatt für Gesammte Therapie*, as having found that "lactate of strontium, which is certainly an excellent diuretic, is beneficial in a large proportion of cases of Bright's disease, at all events when no sclerosis of the kidney has taken place," but he, too, only vaguely conjectures its mode of action. Yet, as confirming the more advanced results of Wright and Ross with regard to physiological albuminuria, these bygone empirical observations have their value and ought to stimulate fresh workers to the elucidation of an important problem.

I must now pass on to the record of my own experiments with the lactate of strontium which, beginning in the early part of last year, have been continued up to the present as opportunity offered.

February 8, 1905.—The patient at this date was suffering from daily oozing of blood from his gums. After the coagulation time of his blood had been found to be 2 minutes 16 seconds, he took a dose of 4 grammes of calcium lactate, an amount sufficient to produce a decided effect on most persons, but after 40 minutes, when the coagulation time was estimated again, no change could be

detected. On February 10 the coagulation time was 2 minutes 30 seconds, and therefore no effect remained from the previous dose (compare this with the figures of Wright and Paramore, *loc. cit.*). The strength of oxalate solution required in equal quantity to inhibit coagulation according to Wright's standard was $\frac{1}{1200}$, so that there was no actual deficiency of lime in the blood, but the object in view was to force it above the normal. Another line of treatment was adopted for the time being as the patient continued to bleed. On February 17 the patient was found to be no better and his coagulation time had receded to 2 minutes 50 seconds. Four grammes of calcium lactate were again given, and again 45 minutes later no improvement could be detected in the coagulating power. On February 24 the coagulating time was still longer—namely, 3 minutes. At 6.15 p.m. an injection of half a gramme of calcium lactate in salt solution was made into the flank. The coagulation time was then taken every 5 minutes so as to ascertain the rate of absorption ; 30 minutes after the injection it began to shorten, at 7 p.m. reaching 2 minutes 15 seconds, and at 7.15, 2 minutes precisely. At this figure it remained to the end of the observation, the rapid improvement minute by minute being very interesting to watch. On March 15 the patient was somewhat better as regards the oozing of blood. Two grains only of calcium lactate were injected hypodermically, an intermediate injection of 10 grains having apparently got into dense fascia and produced local coagulative effects, ending in great pain and collapse. Most certainly this risk attends all hypodermic injection of coagulative salts. The small quantity given on the present occasion without any injury was sufficient to reduce the coagulation time in the course of one hour from 2 minutes 35 seconds to 2 minutes 5 seconds, and thus it became clear that the obstacle to the entry of lime salts into this man's blood resided in his alimentary canal. It was at this point that the idea was conceived of looking for an alternative drug, and for the time being Sir A. E. Wright put the patient on thymus gland, which had previously been found useful. By July 21, having become acquainted with the pharmacological literature of strontium, I obtained a supply of the lactate and began experimenting on myself. On this date, my blood coagulating in 2 minutes 5 seconds, I took 1 gramme at 4.15 p.m. By 5.15 the time of coagulation was reduced to 1 minute 30

seconds, but by 6.45 it had again increased to 1 minute 50 seconds, and at 7 p.m. had reached the original figure of 2 minutes 5 seconds, thus showing that the effect of strontium, though typical and decisive, has a certain fugitive character, not so marked in calcium and magnesium. Possibly this is due to the fact that strontium is not a normal ingredient of the blood, but this fugitiveness is not always to be noted, as will be seen hereafter, nor can I exactly specify the conditions under which it appears. On July 24 I took a smaller dose—two-thirds of a gramme of strontium lactate. At 6 p.m. my coagulation time was 1 minute 45 seconds, by 6.40 this had been reduced to 1 minute 10 seconds, and an hour later, at 7.40, had begun to recede again, being 1 minute 20 seconds. The observation was here stopped for dinner; and I may say that observations of this detailed character have to be limited to the time between meals or changes of occupation if they are to have any value. On August 14, my time was rather longer than usual—namely, 2 minutes 20 seconds. At 6 p.m. half a gramme only of the lactate was taken and at 6.50 the time had become reduced to 1 minute 45 seconds, extending again by 7.20 p.m. to 2 minutes exactly. For practical purposes it was deduced from these experiments that a proper dose would be from 1 to 2 grammes. On August 23 the first opportunity occurred for testing Sir A. E. Wright's patient with the lactate of strontium. He had now for some months been taking 35 grains of thymus extract daily, and was consequently in much better condition, though not altogether exempt from hæmorrhage. At 4.30 p.m., when his coagulation time had been found to be 2 minutes 35 seconds, he received 1 gramme of strontium lactate and at 5.30 the coagulation time had become reduced to 1 minute 55 seconds, at which it remained to the end of the observation. An improvement of 30 per cent. in coagulating power at the first trial was a welcome contrast to the experiences with calcium. A considerable interval here elapsed owing to my holidays. On November 8 the patient's blood was found to coagulate in 2 minutes 50 seconds, and at 4.10 p.m. he had a dose of 2 grammes of the lactate. By 4.50 the time was reduced to 2 minutes 5 seconds and at 5.20 to 1 minute 50 seconds, when the observation terminated. Again an improvement of 30 per cent. recorded. November 15.—The joint paper of Wright and Paramore

having now appeared and their results therefore available, I thought I would try a comparative test with magnesium, choosing the lactate as preferable for a rapid effect in the place of the more insoluble carbonate. On this occasion the patient's blood coagulated in 3 minutes exactly. At 4.15, 2 grammes of the lactate of magnesium were given and by 4.50 the coagulation time was reduced to 2 minutes 25 seconds, and further by 5.20 to 2 minutes 10 seconds. It appeared, then, that magnesium acted as well on this patient as strontium, producing also an improvement of nearly 30 per cent. December 13.—As the result of occasional doses of magnesium carbonate prescribed by Sir A. E. Wright the patient had improved perceptibly. An oxalate test showed a strength of $\frac{1}{1050}$ as required to inhibit coagulation. The lactate of strontium was again tried on this occasion, a dose of 1 gramme being given at 3.50 p.m.; the coagulation time was then 2 minutes 50 seconds. By 5.20 the time had been reduced to 2 minutes and at 6 p.m. to 1 minute only. This excellent result of an improvement of 60 per cent. for the time being in the coagulating power was apparently due to the longer continuance of the present observation and might possibly have been before recorded if the times available had allowed. No fugitiveness in the effect was to be noted on this occasion; I cannot say why. On December 20 and January 3 and 5 of the present year fresh trials were made to reaffirm the inability of this patient to assimilate calcium; the results were exactly as before, at the most on the third occasion an improvement of 15 seconds being noted after the lapse of 3 hours, after a dose of 2 grammes of calcium lactate. The treatment of hæmophilia not being the special object of this paper, I need not detail the further observations made on this man, except to say that he has of late been supplied with powders of strontium or magnesium lactate for self-administration in emergencies, and as a result he has been able to report to me on more than one occasion that hæmorrhages have ceased within 12 hours instead of going on for days. Perfect success, however, is not always obtained, as might be expected with such a difficult pathological condition to contend with, but it may be affirmed that something has been accomplished for his comfort so far.

Conclusion.—From these experiments I think it is clearly established that the lactates of both strontium and mag-

nesium in doses of from 1 to 2 grammes are serviceable substitutes for the salts of calcium when the latter are not absorbed from the alimentary canal, thus enabling us to dispense with the dangerous practice of hypodermic injection, which my experience does not show to have any advantage in speediness of action.

These observations also, I think, enforce the old lesson of the complexity of vital action with which the physician has to contend and show how the recognition of minute differences and the mastery of minute details must not be avoided if one wishes to triumph in a difficult art like medicine. I hope to see someone else with the requisite opportunities taking up the question of albuminuria and its treatment with these coagulative salts, when probably other differences in their action will be demonstrated.