an organic deposit containing a number of granular and hyaline casts, but no crystals of any kind. A second sample, examined two days later, showed no deposit, and no tube casts were found in this or any of the samples thereafter. During the second week of illness the urine became more highly coloured and muddy, and looked simply like a concentrated urine with a deposit of pale urates. Microscopical examination, however, revealed a very large number of crystals, as shown in Figs. 1 and 2. They had a beautifully clear and sharply defined appearance, consisting of a double contoured envelope and a finely striated structure centrally.

Fig. 3.

Dr. Middleton, Senior Visiting Physician to the Glasgow Royal Infirmary, who kindly examined the specimen, said he had never seen such a urinary deposit, but thought it most probably calcium carbonate, though the appearance of some crystals suggested leucin. Mr. Agnew, Lecturer in Chemistry, St. Mungo's College, examined some of the sediment, and reported that it consisted of calcium carbonate. Various books were consulted, and though some of the illustrations of lime crystals were a little like this specimen, none presented the picture shown in Fig. 1.

For some days this sediment continued to be present, and then was gradually replaced by one consisting chiefly of crystals as shown in Fig. 3. Among these, however, were always to be found a few circular ones, and also a few uric acid crystals. The very finely striated appearance in this second form was very clearly shown, and gave the impression that these crystals were simply the first form minus the double contour. They were clearly of the same chemical composition, possibly in a different phase of formation. Of this interesting and unusual deposit I offer no explanation.

The patient's diet latterly consisted of nothing but milk, and the only drugs he had during his illness were the alkalis, a few doses of erythrol-tetranitrite, and hypodermic injections of pilocarpine, and these latter I do not think offer an explanation.

A NEW CELL PROLIFERANT: ITS CLINICAL APPLICATION IN THE TREATMENT OF ULCERS.

By CHARLES J. MACALISTER, M.D., F.R.C.P.,

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THE inquiry of which the following is a short preliminary account originated in a somewhat accidental way when I was seeking for information concerning cell proliferants.

COMFREY.

My attention had been directed to the fact that from time immemorial the symphytum, or common comfrey, had been much recommended by the ancient writers in medicine as a vulnerary and as a dressing for sores and ulcers of various kinds. From the days of Saxon leechdom* (c. 1000) to the end of the seventeenth century there were few authors who did not refer to it, and it was sometimes spoken of as being the "chief vulnerary herbal." I can find no reference to comfrey in any books on materia medica or therapeutics of relatively recent date; Pereira, for instance, does not refer to it, and it was never an official remedy so far as I can discover. To this day, however, it has a traditional reputation among country folk, both in England and in Ireland, as a

domestic herbaceous "simple" for applying to sores, and I was much interested during the past summer, when visiting a farm at Tarvin in Cheshire, to find that its owner always keeps a bed of comfrey growing in order that he may provide the villagers with it when occasion arises.

I was a good deal impressed by the old accounts of this ancient remedy, and in particular with the description of one case, which led me to think that it might be quite worth while to investigate the qualities of comfrey and to discover whether it, or any of its constituent principles, had any influence upon cell growth; and as a result of researches carried out in collaboration with Dr. Titherley and Mr. Coppin, of the Chemical Department of the University of Liverpool, I shall presently show that it contains a body which may have some important clinical applications.

Through the kindness of Professor Harvey Gibson I was provided with a large quantity of the root, some of which was handed over to Dr. Titherley and Mr. Coppin, and while they were making a careful chemical analysis of it, which took a considerable time, I proceeded to dress the only ulcer which was then available to me with a strong infusion made from the powdered root. This case was an exceedingly unpromising one, because it was a "rodent" of about two years' duration, not a simple ulcer. It was a stroke of good fortune, however, that this case was the first to be experimented upon, because having resisted all kinds of previous treatment, the marked epithelial growth which took place upon it seemed more likely to be the result of a specific action of the application than would have been the case in an ordinary varicose ulcer for instance. It was a very large ulcer (measuring 4 in. by 3 in.), involving the skin and deeper structures over the upper thorax, and it was slowly spreading, more especially by its upper margin, which was high and undermined; the other margins were less raised. The base was irregular, and there was some sero-purulent discharge. After being dressed with the mucilaginous infusion for about a week the surface cleaned, and a distinct growth of epithelium could be seen taking place from some of the marginal points. Later on the upper margin flattened somewhat on its inner aspect, the undermining vanished, and after growing here and breaking down there for a time the epithelium became stronger and closed in to a considerable extent.

By this time Dr. Titherley reported to me that he had obtained a definite, so far unidentified, crystalline body from the root, and he was able to give me sufficient to experiment with. Since it was very sparingly soluble in water, quite a large amount of solution was made, which was now used as a dressing for the ulcer instead of the infusion. With this application the skinning-over process in the course of a month was all but completed.

I do not propose at this point to proceed with clinical results. Several other experiments were made, however, all of them confirming the suggestion that the symphytum root contained a principle which might be useful as a cell proliferant. It therefore behoved us to investigate its chemistry before studying its practical utility.

In his preliminary examination Dr. Titherley established the facts that the root contained:

1. Gums.
2. Sugars, including a reducing sugar.
3. Resins.
4. A protocathechuic derivative or derivatives.
5. A substance giving an intense yellow solution with sodium hydrate (not investigated further).
6. A crystalline solid, very rich in nitrogen and melting at 226° C.

Since from clinical observations this latter body appeared to be the physiologically active constituent of the root, Mr. Coppin was asked to devote his attention to its investigation. His methods of extracting it will be fully published at a later date; but Dr. Titherley and he found that the root contained about 0.8 per cent. of it, and by estimating its carbon, hydrogen, and nitrogen contents he showed that it possessed the same empirical formula as allantoin, which it greatly resembled in its chemical properties.

ALLANTOIN.

Some allantoin was now prepared from uric acid, and the product from the root was proved conclusively to be an identical substance by chemical methods. For example,

* Dr. Edward E. Nicholson (Neuilly) furnished references.

allantoic acid and other derivatives were prepared both from the chemically made allantoin and from that obtained from the root; their melting points were the same, and so forth.

Allantoin ($C_4H_6N_4O_3$) is a compound which is obtained by the alkaline oxidation of uric acid in the cold.

It is a pure white crystalline substance, melting at about 226° C., with decomposition. It is only slightly soluble in cold water (0.6 per cent.), but readily in hot water. It is rather more soluble in cold alcohol, but it is quite insoluble in ether. Dry allantoin is quite stable, but if boiled with water for a considerable time it undoubtedly undergoes decomposition to a slight extent. It is decomposed by alkali, giving a variety of products, the nature of which entirely depends upon the conditions under which the experiment is carried out. For instance, concentrated potassium hydrate in the cold gives allantoic acid, whereas boiling with dilute sodium hydrate for half an hour and then acidifying with nitric acid gives urea nitrate. Allantoin is to a certain extent an amphoteric substance—that is, it is capable of combining with both acids and bases.

A potassium salt of allantoin is $C_4H_5N_4O_3K$.
A salt of nitric acid is $C_4H_5N_4O_3HNO_3$.

Regarding the chemical physiology of allantoin or the part which it plays in human metabolism very little is known, but some interesting facts have been recorded which may throw light upon its action as a cell proliferant and may point to its having a function to perform in the bodily chemistry, apart from any possibility of its being a product of purin metabolism, in which light it has generally been regarded. It is present both in animals and plants. It was first discovered in the former, and received its name from the fact that it was found in the fetal allantoic fluid. Later on it was identified in the urine of pregnant women. Recently its presence has been demonstrated in very small amounts as a normal constituent of the urines of healthy people, but that it is not an end product of human metabolism, which means that it is probably not derived from the oxidation of uric acid to which it is closely allied, has been shown by a good many observers, as pointed out by Dr. Ackroyd in a paper published in the *Bio-Chemical Journal* for March, 1911. This is an important observation, and is based upon the works¹ of Schittenhelm, Wiener, Minkowski, Poduschka, and Wieschowski, who have shown that when allantoin is given to man it can be recovered to a considerable extent in the urine, and the author himself concludes "that the whole quantity of allantoin excreted by man on a milk and vegetable diet may be derived directly from that contained in the food." It will be noted that I am speaking of the relation of allantoin to human metabolism only. In the dog, cat, and rabbit, on the other hand, it appears to be a normal end product of metabolism.

If these facts are reliable the allantoin in human urine is mainly derived from vegetable foods, as pointed out by Dr. Ackroyd, and in the healthy individual it appears to pass practically unchanged through the economy, the amount eliminated representing about the amount which had been ingested.

Distribution of Allantoin in the Vegetable Kingdom.

Our knowledge of this is not very extensive, but it is a very suggestive and interesting fact that such analyses as have been made indicate that it is generally found in parts which are related to growth either active or potential. For instance, in 1881-82 Schultz and J. Barberi found it in the buds of certain plants and in the bark of branches of trees, and Ackroyd refers to its identification in the embryos of wheat separated in the process of milling, and in beet juice by Richardson and Crampton (1886); he has himself demonstrated its presence in bread, French beans, and green peas, whereas it is absent from bananas and rhubarb. Now this is a suggestive circumstance taken in conjunction with the fact that it is a characteristic component of the fetal allantoic secretion,

and related therefore to an important structure connected with the fetal circulation, a structure along which the vessels pass which convey the fetal blood to and from its intimate relationship with the maternal blood.

Whenever we find any substances constantly in certain parts of plants or animals it is quite reasonable to suppose that they may be in some way related to and necessary for the particular tissues which have selected them, and although the allantoin in the human embryo might be regarded as a fetal waste product, I think we may feel justified in assuming that, in the economics of Nature, it has a function to perform, perhaps in relation to cell multiplication, especially as it is not at once eliminated through the maternal circulation. The same suggestion is raised by the fact that it is also present in milk, the food of the rapidly growing young organism, and in the parts of some plants in which active cell multiplication takes place. We are making some investigations concerning these matters, and later on this preliminary communication will, I hope, be augmented by a description of the results of that work.

Having thus referred to the history of events which led up to this inquiry concerning comfrey root and the discovery of its comparative richness in allantoin, I must proceed to say a few words concerning its effects upon the cases which have been treated with it.

Clinical Observations with Allantoin.

In making clinical experiments great care has to be exercised in the selection of cases, in order to make certain that other conditions which would ordinarily promote healing are not alone operating and bringing about or starting the cell proliferation. On this account I have tried to safeguard my observations in the first place by treating those ulcers which have refused to heal under ordinary forms of rest and cleanliness and under ordinary forms of treatment, and in the second place I have provided a good many medical men with solutions of allantoin to treat their cases with, in order that my own results might be confirmed or tempered by theirs. One is rather apt, when experimenting with a substance in this way, to allow optimism to exaggerate the resultant benefits, and it is an advantage to get others to form independent judgments concerning them from their own observation.

I shall begin by shortly relating a few of the numerous cases where, under my own care, several long-standing ulcerations were the subject of investigation. One of the most striking cases was the following:

A woman, aged 48, who was transferred to me by Mr. Douglas Crawford on July 20th, 1911. There was a large ulcer on the dorsum of the foot and another, practically continuous with it, over the lower third of the leg. The bases were in places sloughy and even gangrenous looking, and there was a purulent discharge. She was sent to Mr. Crawford, I understand, for his opinion as to whether the leg should be amputated. The ulcer measured 5 in. by 4 in., and had been in existence for five years. Allantoin dressings were commenced on July 25th; a week later the surface had cleaned and presented healthy granulations, and a rapid growth of epithelium was taking place from all the margins. On August 12th it was manifestly healing, and on August 17th, that is, in thirty-three days, this huge ulcer was reduced to the size of a pin's head. The scar was healthy and sound. She was kept in bed for a fortnight, and since her discharge has remained sound and well.

Another class of ulcer which has quickly responded to allantoin includes those which are apt to occur in paralytic cases.

We had an example of this in a girl aged 11 years, who had a large ulcer on the dorsum of her left foot. The skin had broken down rapidly, leaving a large, deep, circular ulcer about the size of a penny. Since it showed no signs of healing at the end of five weeks, Mr. Robert Jones invited me to dress it with allantoin. This treatment was commenced on March 10th. The epithelium rapidly grew in, and in four weeks it was entirely healed.

Another case analogous to this was that of a young woman, also a patient of Mr. Jones, who had circular paralytic ulcers on each leg. They were examples of what used to be called weak ulcers in my student days, and they had remained practically unchanged, one of them for five months and the other for eight months, in spite of the fact that the patient had been recumbent for several weeks. On May 2nd they were dressed with allantoin, and on May 17th the ulcer on the right leg was skinned over. The one on the left leg took longer, but it was healed on June 8th. The epithelial coverings in this case were thin and the cicatrices soft and flat. She was one of those patients with flail legs, the surface cold and the muscles atonic, and one was not surprised to hear that one of the ulcers subsequently recurred.

I might quote many cases of various kinds which have been treated under my own observation, such as chronic varicose ulcers, burns, etc., all of which have exhibited increased growth of epithelium and hastened healing processes, but there are others to which I attach almost more importance because they have not been under my own immediate care.

Dr. Arthur Wallace records a case of an abdominal hysterectomy for fibroids; during the course of the operation gall stones were discovered, which were removed, and the gall bladder was drained. A fistula persisted for a month without any indications of closing. A light gauze wick saturated with allantoin solution was introduced twice daily into the fistula. From that time the track steadily narrowed, and ten days after the first application bile ceased to escape and the sinus healed up steadily.

Dr. Wallace also reports a case of abdominal hysterectomy for carcinoma of the cervix uteri, with pelvic dissection. On the day following operation an irregular area of skin on the right buttock was noted to be hyperaemic. The margins were sharply defined. On pressing against it sensation was found to be diminished, and the pressure was followed by temporary local anaemia. Such areas have been previously noted after this operation. Usually they disappear in a few days, but in a few cases necrosis of the skin has occurred, and this happened in this case. Experience of such ulcers in other cases has shown that they are long in healing, many weeks being required for the process.

September 21st. Ulcer measured 2½ in. by 1 in. Dressing with allantoin solution was begun.

September 28th. A rapid growth of epithelium has occurred during the week, and the ulcer is two-thirds of its former size.

October 2nd (that is, four days later). The ulcer measures 1½ in. by ½ in. It is surrounded by a zone of thick epithelial growth of whitish colour, softened by the solution.

The patient was then dismissed with a dry dressing. The remainder of the ulcer required a fortnight for healing.

Dr. Wallace writes that he has used the solution in several cases in which a drainage tube track has been slow in closing.

An example occurred in an obese woman whose healing powers were of a poor kind. Healing by first intention occurred, but the cicatrix was thin and weak, and broke down superficially without apparent cause. An immediate change took place when allantoin solution was employed as a dressing, the epithelial margin thickened and quickly spread in towards the centre, permanent healing being secured by the end of five or six days.

Dr. Kidston records an excellent result in a chronic myxodematous ulcer which was making very slow progress under other dressings, but with the use of allantoin the progress was steady, and a ring of young epithelium could be seen growing in from the margins. He reported that the scar left was much more healthy than had been the case with previous ulcers in this patient (she had suffered from them before), and that the scar was strong and healthy.

Allantoin in Gastric Ulcer.

The following case suggests that allantoin may have a useful application in gastric and other internal ulcerations:

On February 17th, 1911, a woman aged 47 was admitted into my ward in an extremely debilitated condition in consequence of a very severe attack of haematemesis. For many weeks previously she had suffered from pain after food, and had vomited persistently for a fortnight prior to her admission. Even water caused pain and was immediately rejected. There had been melaena for some time prior to the attack of haematemesis for which she was immediately admitted. For twelve months she had been conscious of pain on pressure over the abdomen, and had noticed a lump in the epigastrium, extending into the hypochondrium. This woman was so feeble that the ward sister said that it was a pity that a patient so ill and advanced in disease should be sent into hospital. I felt disposed to agree with this opinion, because on examining her abdomen I found a tumour just underneath the ribs on the right side. It was rounded, irregular, and intensely painful, and my impression at the time was that she had a carcinoma of the stomach, an opinion which was strengthened by the fact that she had an undoubted cancer of the breast. When the irritability of the stomach subsided, she was given the mucilaginous infusion of comfrey root reinforced with some of the saturated solution of allantoin. In addition to the improvement which took place in her stomach symptoms, in the course of a month the abdominal tumour disappeared, an area remaining, however, which was extremely painful on pressure; but in time this also disappeared, and what I had taken to be a malignant growth had vanished.

I have treated other cases of gastric and duodenal ulcers in the same way, and have reason to think that it is a helpful measure for them. My experiences with allantoin have led me to believe that it may prove to be of considerable practical utility, not only in the types of ulcers to which I have referred, but perhaps also in

tuberculous cases and even in corneal ulcerations, and I would suggest to my surgical brethren the possibility of its being serviceable as a dressing when skin grafting has been performed. It is easy of application and, so far as I have seen, non-irritating. Although allantoin itself is somewhat expensive, the solutions for application only require to contain from 0.3 to 0.4 per cent. of the crystals.

In conclusion I desire to thank all those medical men who have assisted me by sending cases or by making independent observations, and I am especially indebted to Sir William Hartley (who provides funds for this research), and to Dr. Titherley and Professor Harvey Gibson and other scientific friends at the university who have done so much to assist and encourage me in the work which I have undertaken.

REFERENCE.

¹ Schittenhelm and Seisser, *Zeit. Exp. Path. Ther.*, 1909, vii, 116-133. Hirokawa, *Biochem. Zeit.*, 1910, xxvi, 441-457. Wiczkowski, *ibid.*, 1910, xxv, 431-459.

THE NEW CELL PROLIFERANT:

A NOTE ON THE SYMPHYTUM OFFICINALE OR COMMON COMFREY.

BY

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An interesting question was raised at a recent meeting of the Liverpool Medical Institution, when Dr. Macalister introduced the subject of a long-forgotten remedy—the *Symphytum officinale*, or common comfrey—which once held a prominent place in the medical armament of the older writers. Dr. Macalister has wisely had this singularly efficacious remedy analysed, and Dr. Titherley and Mr. Coppin (of the chemical department of the Liverpool University) have discovered that the root is rich in allantoin, which they found to be a "potent cell proliferant."

I have on more than one occasion cured old ulcers which have resisted other treatment, by the simple extract from the root applied on lint to saturation. After a few hours this dressing, in favourable cases, sets quite hard, and can only be removed by the lengthy application of water, which is often more tedious and painful than the average patient, who has been in the habit of applying some simple dressing, cares to endure. This hard setting acts, in some measure, like strapping, drawing the edges of the ulcer towards one another, but probably much more