Only four of the cases (8 per cent.) were in women, and of these one was probably primary pleural, one a haemangio-endothelioma, one of the multiple bronchial type, and only one of the common type of bronchial carcinoma.

In no one case was the disease found in a patient of the Jewish race. As the City of London Chest Hospital is in the centre of a district in which the Jewish population is large this is somewhat striking.

The age incidence is as follows:

Years	Cases	Percentage	
21–30	5	10	
31–40	2	4	
41–50	16	32	74
51–60	21	42	
61–70	6	12	

At the Centenary Meeting of the B.M.A. last year some laryngologists expressed the opinion that bronchoscopy should be in the hands of the laryngologists. To us it appears that the bronchi are so obviously the field of the chest physician that though every chest physician should not be a bronchoscopist, the bronchoscopist may most advisedly be a chest physician.

We wish to acknowledge with gratitude the help of Dr. Roodhouse Gloyne and Dr. D. S. Page for the pathological examinations, which have entailed a large amount of work.

EXPERIENCES WITH PROTEOSE IN THE TREATMENT OF DISEASES OF THE SKIN

BY

NORMAN BURGESS, M.A., M.D.CAMB., M.R.C.P.

PHYSICIAN IN CHARGE OF THE SKIN AND LIGHT DEPARTMENTS, BRISTOL GENERAL HOSPITAL; CLINICAL LECTURER IN DISEASES OF THE SKIN, UNIVERSITY OF BRISTOL

It is somewhat surprising that although over four years have elapsed since Barber and Oriel produced their first paper[1] on the discovery of a urinary proteose, which in cases of allergy appears to be combined with an antigen, little has been published on this subject except by the original authors.[2 3 4] Beyond correspondence by Freeman[5] and myself,[6] and short papers by Lyon, Percival, and Stewart[7] and by Eichenlaub,[8] the work does not seem to have been followed up to any great extent by dermatologists, although many claims have been made for the results of treatment by proteose in cutaneous diseases. The present paper forms a part of a larger investigation carried out for the British Medical Association as their Research Scholar for 1931–2. Some of the results were communicated to the British Association of Dermatology and Syphilology at the annual meetings in 1932.

It will be remembered that Barber and Oriel make the following statements:

1. That a proteose may be extracted from the urine by ether, and precipitated from the ether extract by alcohol.
2. That although proteose is present in small quantities in health, it is very much increased in cases of allergy.
3. In cases of urticaria and asthma the proteose is found in large quantities in urine passed during the attack, while it is small in amount or absent between the attacks.
4. Solutions of the proteose obtained in cases of allergy, when injected intradermally, produce specific skin reactions in the patient from whom the proteose was obtained; sometimes they produce reactions in those suffering from the same condition, but not in normal persons.
5. This sensitivity may be transferred by the Prausnitz-Kustner method.
6. In cases of epidermal sensitization, positive reactions may be obtained by application of the proteose to the surface of the skin by means of a patch test.
7. Comparatively large doses of proteose injected intradermally cause an exacerbation of the symptoms, while minute doses over a long period lead to a cure of the condition.

Freeman has been unable to confirm these results, while Lyon, Percival, and Stewart found that twenty-one out of twenty-five proteoses which they prepared gave positive reactions not only in the patients from whom they were prepared, but also in normal persons and in those suffering from various skin diseases. They also found that proteose prepared from a patient suffering from the eczema-asthma syndrome gave a negative reaction in the patient from whom it was prepared, but positive reactions in other persons. A case of angioneurotic oedema failed to respond to its own proteose, but gave a positive reaction to a proteose prepared from a case of chronic urticaria. Two cases of asthma in which the proteose content of the urine was very high gave negative reactions to their own proteoses. They conclude that the peculiarity of proteose lies not in its specificity, but in its property of producing a local inflammation of great intensity in a proportion of individuals.

Eichenlaub treated eighteen patients suffering from skin diseases with proteose. All of the patients who gave definitely positive skin reactions—that is, ten of the eighteen patients—appeared to receive some benefit from the treatment. Only one of the other eight persons improved. Cases in which complete failure was observed gave no local or general reactions to their proteoses, but a case of psoriasis derived benefit from the treatment, although a positive skin reaction was not obtained. He came to the following conclusions as the result of his work:

1. It has been possible to confirm the specificity of the antigen by (*a*) securing negative reactions to foreign proteose in patients who definitely reacted to their own proteoses, and (*b*) obtaining a positive Prausnitz-Kustner reaction in a normal person.
2. Therapeutic results have been sufficiently encouraging to warrant further trial. They have not been definite enough to confirm entirely the value of this procedure.
3. The proteose is highly active in some persons. The patient's sensitivity to each of the dilutions should be carefully determined before treatment is started.

RESULTS IN THE PRESENT SERIES

Twenty-six cases have been treated with intradermal injections of proteose. During the period of treatment local application was limited to the use of ichthyol-zinc cream, or 2 per cent. hyd. amm. and ac. salicyl. in zinc paste.

Five cases of *psoriasis* were treated, of which one cleared up completely, while two cleared up temporarily but later relapsed. Another patient was suffering from psoriasis and rheumatoid arthritis; a positive reaction was obtained on intradermal injection of 0.05 c.cm. of a 1 in 100,000 solution of proteose. After six weekly injections of 0.05 c.cm. of a 1 in 10,000,000 solution there was very considerable improvement, both in the psoriasis and in the arthritis. Following each injection there was some exacerbation of the joint pains within twenty-four hours; this patient is still under treatment. Another patient showed considerable improvement while undergoing the treatment, but although the eruption faded considerably it did not entirely clear up.

Eight cases of *chronic eczema* were treated. Of these, five cleared up completely and have not relapsed, one cleared up completely but relapsed in a few months, while two showed some improvement but did not completely clear up. One of the cases had a severe reaction twenty-four hours after an injection of a 1 in 10,000 solution of proteose. There was an exacerbation of the skin eruption and a considerable degree of general malaise.

On treatment with weekly injections of a 1 in 10,000,000 solution the condition began to improve and completely cleared up. There was, however, within twenty-four hours of each injection, a slight but definite increase in the skin eruption. Another patient gave a strongly positive local reaction to a 1 in 100,000 solution of proteose within twenty minutes, and twenty-four hours later there was a severe exacerbation of the eruption. This patient also cleared up after treatment with injections of a 1 in 10,000,000 solution.

Eight cases of *chronic urticaria* were treated, of whom three cleared up completely. Another patient who had suffered from daily attacks of urticaria for six years now only gets a very slight attack about once a month ; she is still under treatment. Another patient who is still under treatment had suffered from daily attacks of urticaria and angioneurotic oedema for three and a half years. He now suffers from a slight attack of urticaria about once a week. Another patient who was referred for treatment on account of chronic urticaria had had no attack for eleven days. An injection of 0.05 c.cm. of a 1 in 10,000 solution was followed within twenty-four hours by a generalized attack of urticaria, which persisted for twelve hours. No further attacks followed this, and seven days later he was given 0.05 c.cm. of a 1 in 10,000,000 solution, which produced a strongly positive local reaction but was not followed by an attack of urticaria. Similar doses were given at weekly intervals for six weeks, and there have been no further attacks. Intradermal injections of 0.05 c.cm. of a 1 in 1,000 solution of proteose were followed by a generalized attack of urticaria within ten minutes in three cases.

Four cases of *Besnier's prurigo* were treated with proteose, but although there was temporary improvement with diminution of irritation there was little permanent change in the appearance of the eruption.

A case of *dermatitis herpetiformis* cleared up after injections of a 1 in 10,000,000 solution of proteose ; a relapse occurred which cleared up with arsenic. When the patient was free from the eruption a similar dose was given, and was followed in twenty-four hours by another attack.

EXPERIMENTAL OBSERVATIONS

The investigations here recorded involved the preparation of proteose from the urine of normal persons and that of persons suffering from the diseases which I have already mentioned, and a comparison of the amount excreted and of the skin reactions obtained on intradermal injection. In some of the cases treated a proteose was prepared and tested prior to, and after, treatment, in order that the effect of the injections on the production of the proteose, and the skin reactions produced by it, might be ascertained.

The following method was devised in order to make comparative quantitative estimations of proteose:

Two hundred cubic centimetres of a twenty-four-hours specimen of known specific gravity are made acid to Congo red by the addition of 25 per cent. sulphuric acid. Forty cubic centimetres of ether are added, the mixture is shaken vigorously, and poured into a separating funnel. After standing for twenty minutes the urine is run off, and an equal quantity of absolute alcohol is added to the ether extract. After standing for five minutes this mixture is centrifuged, the supernatant fluid is poured off, and the deposit washed with distilled water. This is then placed in a graduated centrifuge tube, and centrifuged at a constant rate for five minutes. The volume of the precipitate is then read. The precipitate is dissolved in 1 to 2 c.cm. of N/10 sodium hydroxide and dilutions in saline made according to Oriel's technique. For testing purposes, in many cases 0.1 c.cm. of a 1 in 1,000 solution of proteose was injected intradermally into the skin of the flexor aspect of the forearm, the resulting wheal being observed immediately after the injection had been made and twenty minutes later. A positive response was indicated by an increase in size of the wheal and the presence of a surrounding flare. It was noted that some cases developed delayed positive reactions similar to those described by Lyon, Percival, and Stewart.

In thirty-five estimations made in thirty-three normal persons the average amount of proteose excreted was 0.12 c.cm. Of the twenty-five cases in which skin tests were made 16 per cent. only were positive to proteose. In the seventy estimations made in sixty-eight untreated skin cases the average amount excreted—0.15—was slightly higher than in the normal controls, while 67 per cent. of patients were positive to their own proteoses. The majority of the cases were controlled by injections of 1 in 1,000 peptone solution. Of eighteen normal persons four gave positive reactions to proteose and peptone, three were positive to peptone only, and none were positive to proteose only. Of fifty untreated skin cases none were positive to peptone only, nine were positive to proteose only, and twenty-two gave positive reactions to both. Six cases were tested after treatment and cure: one of these remained positive to peptone, but none were positive to proteose.

A case of angioneurotic oedema excreted more proteose during an attack than in a quiescent interval, and only that passed during the attack gave a positive skin reaction. This agrees with the work of Barber and Oriel. It was found, however, that the skin reaction obtained does not always correspond with the amount of proteose excreted. In the cases of untreated psoriasis the majority of the acute cases gave positive reactions, while the majority of the subacute and chronic cases gave negative reactions. More proteose was excreted in cases of acute than in cases of subacute or chronic psoriasis. There was a reduction in the average amount of proteose excreted prior to and after treatment in cases of psoriasis, but in cases of eczema this reduction was very slight. Of the latter cases, before treatment, 66 per cent. gave positive skin reactions to their own proteoses, while after treatment and relief none of the cases gave positive reactions. The highest average excretion of proteose was obtained in cases of Besnier's prurigo, but the highness of this figure was due to one case in which the excretion was 0.75. The other cases fell within normal limits. In a case of chronic urticaria, treated and cured by proteose, the excretion of proteose diminished and the skin reactions to proteose and peptone became negative. In the cases of psoriasis which were relieved as a result of treatment by this method, the skin reaction to proteose prior to treatment was positive in all cases, while reactions after treatment were negative. In the cases of eczema similar results were obtained. A case of Besnier's prurigo gave positive reactions before and negative reactions after treatment with proteose, while exactly opposite results were obtained in another case. In this latter case 0.75 was excreted before treatment, and only 0.03 after treatment.

DISCUSSION

The clinical results of treatment are definitely encouraging, especially in cases of chronic urticaria and eczema, good results having been obtained in cases which had defied treatment by other measures. In chronic cases, in which the cause is obscure, proteose treatment is worthy of trial. In psoriasis the results were not so striking, but in any case it is difficult to assess the value of any therapeutic measure in this disease. The results in Besnier's prurigo were disappointing, but it is possible that difficulty in estimation of the dose may have been partly responsible for the failures. One would, of course, expect that a long course of treatment would be necessary in this disease. It is clear, in view of the occurrence of exacerbations following the injection of proteose, that

the optimum dose must be minute. I originally used a 1 in 1,000 solution for testing purposes, but I now use a 1 in 100,000, or even 1 in 1,000,000, for the preliminary test. Cases treated recently have given better results than the earlier ones, and I attribute this to the reduction of the therapeutic dose. The results of skin tests in normal persons and patients suffering from the skin diseases under discussion show very striking differences, for while only 16 per cent. of normal persons gave positive reactions to their own proteoses, 67 per cent. of the skin cases responded in this way.

With regard to the statements of Barber and Oriel, my results tend to show that the amount of proteose excreted is not of very great significance, for the difference between that excreted in health and in various skin diseases was not great. More, however, was excreted from patients suffering from skin diseases, and in one case of angio-neurotic oedema more was excreted during an attack than in a quiescent interval. I have also confirmed the statement that exacerbations of the skin condition may follow *relatively* large doses of proteose. My clinical findings agree very closely with those of Eichenlaub, and I agree with his conclusion that the method should be more widely used in order that its full value may be determined.

SUMMARY

1. Treatment with proteose prepared from the patient's urine has given satisfactory results in cases of chronic eczema and urticaria. Less striking results were obtained in cases of psoriasis and Besnier's prurigo, but benefit seemed to be derived from the treatment in some cases.

2. Sixteen per cent. of normal persons and 67 per cent. of patients suffering from various skin diseases gave positive reactions to their own proteoses. Slightly more proteose was excreted by the latter than by the former.

3. All the cases relieved by this treatment gave positive skin reactions to their own proteoses before treatment, while, after treatment and cure, all those tested gave negative skin reactions.

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CALCIUM THIOSULPHATE IN THE TREATMENT OF THE COMPLICATIONS OF "914" AND BISMUTH ADMINISTRATION IN SYPHILIS

PRELIMINARY COMMUNICATION

BY

A. E. W. McLACHLAN, M.B.

SURGEON TO OUT-PATIENTS, ST. PAUL'S HOSPITAL

Schamberg and Brown (1930) introduced calcium thiosulphate into the therapy of the post-arsenobenzol complications, and in 1932 Schamberg and Wright quote Cannon as having employed the preparation in a series of cases of arsphenamine dermatitis with excellent results. It was particularly effective in drying up surface exudation. The dose recommended was 5 c.cm. of a 10 per cent. solution daily for three days, and subsequently two or three times a week. Schoch (1931) commented: "A new drug brought out for the treatment of arsphenamine dermatitis is calcium thiosulphate. The highly rational combination of calcium with the detoxifying action of the thiosulphate radical may prove to be an excellent prophylaxis for treatment reactions from arsphenamines other than arsphenamine dermatitis." The value of the sodium salt of thiosulphate, introduced by Râvaut (1920) for the treatment of arsenical dermatitis, has been shown by McBride and Dennie (1923, 1924) and by many subsequent observers, while the value of calcium chloride in the prevention of certain cutaneous inflammations has been shown by Wright (1896), Chiari and Januschke (1911), and Blum (1921). On theoretical grounds, therefore, the combination of calcium and thiosulphate should be advantageous, especially in that group of cases which fails to react to sodium thiosulphate or which fails to clear up completely under its administration.

CASE RECORDS

Recently the following series of cases of intolerance to "914" or bismuth has been treated with calcium thiosulphate.

1. *Early Arsenical Dermatitis.*—Male, aged 31. Sero-negative primary syphilis. Developed arsenical erythematous dermatitis three weeks after completion of first course of "914" and bismuth. Calcium thiosulphate, 0.6 gram intravenously, daily for three days, then at three-day intervals. Skin lesions completely clear on the thirteenth day.

2. *Post-arsenical Dermatitis.*—Male, aged 50. Persistent sero-positive syphilis. Developed exfoliative dermatitis, which was treated over a period of several months with sodium thiosulphate. Condition became stationary, with scattered areas of scaly, fissured, infiltrated skin over flexures of arms, legs, and trunk. After twenty-two injections of calcium thiosulphate, at three-day intervals, the skin was completely clear.

3. *Jaundice.*—Male, aged 49. Persistent sero-positive syphilis. Had post-arsenical jaundice in April, 1932, which yielded after one month's treatment with sodium thiosulphate. Four months later administration of "914" was recommenced. Developed jaundice December, 1932, while under dual therapy. Calcium thiosulphate, 0.6 gram intravenously, the first two doses on successive days, then at two-day intervals. Icterus completely clear after the fifth dose.

4. *Immediate Reaction (Vomiting) after "914."*—Male, aged 40. Persistent sero-positive syphilis. Vomited after each injection of "914." No other signs of intolerance over a long period of treatment. Vomiting controlled by admixture of sodium thiosulphate; equally well controlled by calcium thiosulphate. Other factors—bulk of injection, rate of administration, etc.—were kept as far as possible unchanged.

5. *Bismuth Dermatitis.*—Male, aged 49. Persistent sero-positive syphilis. Developed arsenical erythema while under dual therapy. This yielded rapidly to sodium thiosulphate. Bismuth administration recommenced two months later. After a course of 3 grams metallic bismuth in ten weeks he reported with a scattered papulo-squamous erythematous rash on the trunk, with moist, fissured, eczematous lesions of scrotum. The skin lesions partly cleared under the administration of sodium thiosulphate, but those of the scrotum remained unaltered after bi-weekly treatment for one month. Calcium thiosulphate was then commenced, 0.6 gram bi-weekly; the scrotal lesions and the residua on the skin cleared up completely after five injections. That bismuth was an aetiological factor in the production of this dermatitis, in a skin previously damaged by an arsenical erythema, was proved by the recurrence of a similar rash on the re-exhibition of bismuth.

6. *Dermatitis, probably due to Bismuth.*—Male, aged 27. Sero-negative syphilis. Treated originally with "914" and mercury, then with "914" and bismuth. No "914" for three and a half months, during the last ten weeks of which he received 3 grams metallic bismuth. In the eighth week of the bismuth therapy he reported a papulo-squamous erythematous dermatitis, which was aggravated by the subsequent injections. There had been no intolerance while under dual therapy, a total of 13.35 grams "914" and 8.7 grams bismuth having been administered. The dermatitis was considered to be due to bismuth, and treatment with calcium thiosulphate was instituted. After the seventh injection (0.6 gram bi-weekly) the skin had completely cleared.

In one case of bismuth stomatitis the pain and discomfort were relieved by the administration of calcium thiosulphate, although clinically there was no improvement in the condition of the mouth. One case of seborrhoeic dermatitis, which showed a tendency to flare up during the administration of bismuth, was markedly improved.