AUTOGENOUS URINARY PROTEOSE IN ASTHMA AND OTHER ALLERGIC CONDITIONS*

BY

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In 1930 Oriel and Barber published an account of a substance, "proteose," which they stated is excreted in the urine of allergic patients during attacks and contains the specific antigen to which the patient is sensitive. This "proteose" can be extracted from the urine with ether, but its precise chemical nature is not as yet known. Oriel states that it contains amino-acids, histidine, arginine, etc., and will give a positive test for carbohydrates and for protein. Boyd (1931) suggests that it is a serum albumin contaminated with a mucoid. Oriel and Barber (1930) think that the "proteose" is produced by a damaged liver and excreted in the urine. "Proteose" has also been found in the urine of normal people and in that of allergic patients between their attacks, but Oriel claims that the amount is greater during allergic paroxysms. Murray Lyon, Percival, and Stewart (1932) and Tuft and Brodsky (1932-3) support this claim, but Burgess (1933) and Vaughan (1932-3) disagree. Oriel (1933) further states that there are chemical differences in the proteose excreted by normal and asthmatic persons. He found that the latter contains three fractions, which can be precipitated with acetic acid, trichloroacetic acid, and absolute alcohol, while proteose in normal subjects contains only the trichloroacetic acid fraction.

Review of the Literature

Oriel and Barber (1930) state that 0.025 c.cm. auto-genous proteose when injected intradermally will produce a positive reaction—that is, a wheal and erythema—in a sensitive patient. There has been much controversy as to the specificity of this proteose skin reaction. Oriel (1932) subsequently put forward the following claims: "(1) That the substance (proteose) isolated from the urine of an allergic patient during an attack would in a suitable dilution give a positive intradermal test in the patient's own skin. (2) That proteose from a normal person will not give positive tests on his skin under the same conditions. (3) That a distinction can be drawn between cases of asthma—that is, that the proteose substance from a patient with multiple sensitizations gives positive skin tests with asthmatics who have been demonstrated to have similar sensitization, and not with asthmatics who have not been so sensitized. (4) It is not claimed that urinary proteose is specific to the individual."

Conybeare (1931) and others have reported positive skin reactions with urinary proteose. Conybeare (1931) tested seventy asthmatic patients with (1) proteose from an active case of hay fever, and (2) proteose from an asthma patient not sensitive to pollen. His results showed that 69 per cent. of pollen-sensitive cases gave positive reactions to hay fever patients' proteose only and 17 per cent. gave positive reactions to both. In

non-sensitive cases 76 per cent. gave no positive reaction to either, 12 per cent. to hay fever proteose only, 8 per cent. to both, and 4 per cent. to proteose from the non-sensitive asthma patient. In non-allergic cases no reactions at all were obtained. Darley and Whitehead (1931) record positive skin reactions with proteose prepared from two asthmatics during an attack and negative reactions in three cases when the proteose was prepared during the asymptomatic period. They also found positive reactions in three out of five cases of acute arthritis and two out of three cases of serum sickness. Negative results were obtained in one case of generalized eczema, one case of urticaria, and one case of erythema multiforme. Yeoman, Sinclair Miller, Rutherford, and Wesley-Smith (1932) state that they have obtained positive intradermal reactions in 50 per cent. of cases of rheumatoid arthritis. Bruce Pearson (1933), working at Guy's Hospital, compared the skin reactions of fifty asthmatics with those of fifty normal people. He found that with a 1 in 1,000 dilution of proteose 54 per cent. of asthmatics reacted to their own proteose, in contrast to 6 per cent. of normal controls. He also found that 60 per cent. of asthmatics gave a positive reaction when tested with other asthmatic patients' proteose, in contrast to 40 per cent. positive reactions in controls tested with asthmatic proteose. He further showed that in protein-sensitive asthmatics 83 per cent. reacted to their own proteose and 60 per cent. reacted to normal proteose. In non-protein-sensitive asthmatics 15 per cent. reacted to their own proteose and none reacted to proteose from normal persons. Among his conclusions Bruce Pearson states that there is no evidence of individual specificity, that proteose is not entirely group specific, and that asthmatic proteose is relatively toxic as judged by skin reactions. Burgess (1933) found that 16 per cent. of normal people and 69 per cent. of allergic skin patients reacted to their own proteose. Eichenlaub (1933) found positive skin reactions in three allergic skin cases.

Freeman (1932) and others do not regard the skin reaction obtained with urinary proteose as specific, but consider it is due to the toxic action of the substance. Freeman compared the skin reactions produced by (1) pollen, (2) proteose from a hay fever patient (supplied by Oriel), and (3) control proteose from a normal case. Pollen gave typical skin reactions (wheal and erythema) in hay fever, but the hay fever proteose gave variable reactions in hay fever patients and in controls. He also prepared samples of proteose from five allergic patients and tested them on (1) the subjects from whom they were prepared, (2) other allergic patients, and (3) normal persons. The same type of toxic reaction was obtained in all cases. Freeman concludes that Oriel's proteose, no matter whence obtained or on whom tested, shows a fairly constant toxic reaction within a few minutes of injection into the skin and that there is no evidence of any specific skin reaction.

Murray Lyon, Percival, and Stewart (1932) prepared samples of urinary proteose from twenty-five allergic cases and found that twenty-one of these gave reactions both in normal persons, in the patients who supplied the proteose, and in other patients with various skin conditions. Four samples did not give any reaction at all. They conclude that the peculiarity of urinary proteose with regard to the skin seems to lie not in its specificity in certain conditions but in its property of producing a local inflammatory reaction. Steel (1932) found that eleven out of twenty-seven asthmatic patients reacted to their own proteose. He also found that asthmatics who did not react to their own proteose would quite often react to that from another asthmatic. Minchin (1932) pre-

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pared proteose in ten cases of epilepsy and did not obtain any positive skin reactions. Van Leeuwen (1932) tested the proteoses prepared from twenty-four cases and found that they sometimes produced positive reactions in asthmatics, but not necessarily in the asthmatics from whom the proteose was prepared. He concluded that the reaction was therefore non-specific. Aldred-Brown and Munro (1932) did not obtain any positive reaction with proteose prepared from fifty cases of acute rheumatoid arthritis. Cormia (1933), investigating allergic skin patients, found a positive skin reaction in both allergic and non-allergic patients, which he suggests is due to local skin irritation. Cornbleet and Kaplan (1934), in a chemical and biological study, obtained an erythematous skin reaction with proteose, but no reaction occurred when the proteose was first dialysed. They suggest that the skin reaction is produced by salts and other irritants.

Therapeutic Application of Proteose

Urinary "proteose" has been used in the treatment of a variety of allergic skin conditions (eczema, urticaria, etc.), asthma, hay fever, epilepsy, and rheumatoid arthritis.

ALLERGIC SKIN DISEASES

Oriel and Barber (1930) obtained a "cure" in sixteen out of nineteen cases of urticaria and in nine out of thirteen cases of simple prurigo. Benefit was noted in five out of fourteen cases of Besnier's prurigo. These authors also stated that proteose gives good results in dermatitis herpetiformis, but confess to disappointing results in psoriasis. Burgess (1933) reported that five out of eight cases of chronic eczema cleared up completely, three out of eight cases of chronic urticaria were "cured," and a further three cases were much improved. Temporary improvement was obtained in four cases of Besnier's prurigo, and of five cases of psoriasis one cleared up completely. One case of dermatitis herpetiformis cleared up, but subsequently relapsed. Burgess regards these results as satisfactory for eczema and urticaria.

Eichenlaub (1933) recorded marked improvement in four cases of eczema out of eleven. One of two cases of psoriasis was cured. He did not obtain any satisfactory results in neurodermia, dermatitis hepetiformis, or chronic urticaria. Eichenlaub (1934) subsequently stated that all the patients in whom he had reported favourable results had since relapsed and failed to respond to further treatment. Cormia (1933) had unsatisfactory results in eight cases of allergic skin conditions. Templeton (1933) also records poor results in fifteen cases of various allergic skin conditions. Cornbleet and Kaplan (1934) observed no therapeutic benefit after treating fourteen cases of eczema with proteose.

ASTHMA

Oriel (1933) treated seventy cases of asthma with proteose. In analysing his results he divided the cases into two groups: (1) protein-sensitive cases (forty-four patients), and (2) non-protein-sensitive cases (twenty-six patients). A summary of Oriel's results is shown in Table I.

TABLE I.—Showing Oriel's Results in Seventy Cases of Asthma Treated with Urinary Proteose

Type	No.	"Free"	Much Improved	Improved	Unchanged
Protein-sensitive asthmatics	44	10 (23%)	20 (46%)	10 (23%)	4 (8%)
Non-protein-sensitive asthmatics	26	2 (8%)	5 (19%)	5 (19%)	14 (54%)

His criteria of improvement are as follows: (1) "Free"—symptoms practically absent for six months. (2) Much improved—attacks 75 per cent. less. (3) Improved—attacks 50 per cent. less. (4) Unimproved. Oriel states that 70 per cent. of protein-sensitive asthmatics have a chance of "marked amelioration" compared with 27 per cent. of the non-protein-sensitive asthmatics. It should be noted that of the seventy cases twelve (that is, 17 per cent.) became "free" for six months. Darley and Whitehead (1931) reported improvement in six out of nine cases of asthma. Trasoff and Meranze (1932-3) state that they had unsatisfactory results in eight cases of asthma.

HAY FEVER

Darley and Whitehead (1932) found that six out of twelve cases of hay fever obtained complete relief. Watson (1933) reported improvement in seven cases of hay fever.

RHEUMATOID ARTHRITIS

Barber and Oriel, in one of their original communications, stated that when proteose was given to patients with psoriasis associated with rheumatoid arthritis, although the psoriasis did not improve, the joint condition was ameliorated. Aldred-Brown and Munro (1932) treated fifty cases of rheumatoid arthritis with proteose, and recorded apparent success in one case only. Yeoman, Sinclair Miller, Rutherford, and Wesley-Smith (1932), in a letter to the *Lancet* following Aldred-Brown's paper, stated that they had obtained satisfactory results using proteose in the treatment of rheumatoid arthritis.

EPILEPSY

Haviland Minchin (1932) treated seven cases of epilepsy with autogenous proteose. Four cases showed no change, one was slightly better for three weeks and then relapsed, one case formerly having four to five fits a month became free for two months and subsequently relapsed, one case having major fits began having minor fits.

Results in Present Series

In our investigation it was decided primarily to assess the therapeutic effects of proteose. It was realized that even if proteose was not specific in its action, as claimed by Oriel, some therapeutic benefit might be obtained as often happens with non-specific injections. Proteose was administered to a series of fifty-eight patients, composed of forty-eight cases of asthma and ten cases of various allergic skin conditions. Autogenous proteose was prepared from the urine in every case.

Oriel and Barber suggested minute doses. In their original paper they stated that injections of 0.025 c.cm. will often cause a severe reaction. Subsequently Oriel suggested an initial dose of 0.1 c.cm. of a dilution ten times weaker than the lowest dilution of autogenous urinary proteose which gives a specific skin test, the injection to increase by 0.1 c.cm. at a time, until there is a reaction (increase of symptoms or malaise), or until the condition shows definite signs of improvement. We were never able to confirm the presence of a specific skin reaction, the only skin reaction produced being a small erythematous zone such as might be produced by the intracutaneous injection of any toxic substance. We thus had to formulate our own method of dosage. The routine doses given in our series were as follows:

Weekly intramuscular injections of 1/2 c.cm. followed by 1 c.cm. of 1 in 1,000,000, 1 in 100,000, 1 in 10,000, and 1 in 1,000 dilutions. These were followed by two further injections of 1.5 c.cm. and 2 c.cm. of the 1 in 1,000 dilution. The patients thus received ten weekly injections. In only

two cases did the initial dose of 1/2 c.cm. of 1 in 1,000,000 dilution produce any general reaction (precipitation of severe asthmatic attacks the night following the injections), and in these cases smaller doses were subsequently given which, however, also produced reactions, but of a milder character. It was further found that no general or local reaction was produced by the injection of large doses of proteose, the majority of our patients having received 2 c.cm. of 1 in 1,000 proteose without any ill effects.

The assessing of the results of treatment in asthma is notoriously very difficult. Full consideration must be given to the fact that asthmatics often improve with any type of treatment for a varying interval, possibly due to psychological causes. Thus, for example, Conybeare and Witts (1935), using injections of normal saline (in addition to ephedrine and specific allergen avoidance) report: "At the end of two months' treatment 15 per cent. of the whole group are 'much improved,' 31 per cent. are 'slightly improved,' and 54 per cent. are 'not improved.' In other words, approximately half the patients have improved."

In the presentation of these results the cases have been divided into four groups: (a) Much improved—those showing benefit for twelve months or over; (b) improved—benefit for three to twelve months; (c) slightly improved—benefit up to three months; (d) the remainder. The length of history, together with the severity and frequency of attacks, before and after treatment, were carefully considered in each case before placing it in one or other of these groups. The results are shown in Table II, from which it will be seen that 23 per cent. of the cases were markedly improved for twelve months or more.

TABLE II.—*Showing Results of Proteose Therapy in Present Series*

No. of Cases of Asthma	Marked Improvement	Improvement	Slight Improvement	Unchanged
48	11 (23 %)	14 (29 %)	9 (19 %)	14 (29 %)

An attempt was made to ascertain if there were any special factors in the successful cases which would account for their marked response to the proteose treatment. The eleven cases in the first group were therefore compared with the fourteen cases in which no improvement occurred. Age, sex, family history of allergy, history of previous chest disease, duration, special precipitating factors, sputum, eosinophilia, presence or absence of nose and throat disease, were compared in the two groups. It was found that the incidence of all these factors was of the same order in both groups. No evidence was found to suggest that the cases with marked improvement contained a greater number of protein-sensitive cases than did the group with no improvement. It should also be noted that the cases which did well did not give any specific skin reactions. We previously mentioned that two cases gave marked general reactions following the initial injections of proteose. After receiving smaller doses of proteose these patients showed considerable improvement, remaining free from attacks for over twelve months. These two cases were the most dramatic "cures" of our series, but we feel that in any series of asthmatics this may occasionally occur.

The dosage of proteose employed in allergic skin conditions was similar to that given in the asthma series. Six cases of urticaria were treated. One case became free from attacks, one case became free for six months, two were free for three months, and the remaining two showed no benefit. One of two cases of chronic eczema improved for three months, the other case did not

improve. One case of dermatitis herpetiformis showed marked improvement, and one case of plant dermatitis improved for six months, but subsequently relapsed.

Proteose Compared with Peptone

Desensitization by intramuscular injections of peptone is another line of treatment which has been used in this clinic. The peptone course consisted of a series of graded doses of 7½ per cent. peptone (Martindale), starting with 0.3 c.cm. and increasing by increments of 0.2 c.cm. to 1.3 c.cm. Four doses of 1.5 c.cm. were then given. A continuation course of three doses of 2 c.cm. and three of 2.5 c.cm. was subsequently administered. The injections were given at weekly intervals. We have analysed a series of cases in which peptone had been administered, and contrasted the results of this treatment with those obtained in other cases on proteose medication. The results have been set out in three groups, as shown in Table III.

TABLE III.—*Comparing Results of Proteose and Peptone Therapy in the Present Series of Asthma Cases*

	Treatment	Marked Improvement	Improved	Slight Improvement	Unchanged
Group A, 26 Cases	(1) Proteose (2) Peptone	2 8	11 4	4 9	9 5
Group B, 55 Cases	Peptone only	9 (16 %)	11 (20 %)	15 (27 %)	20 (37 %)
Group C, 81 Cases	All cases receiving peptone	17 (21 %)	15 (18 %)	24 (30 %)	25 (31 %)

Group A consists of twenty-six patients who had previously received proteose with no improvement, or who had relapsed after some initial benefit, and were subsequently given a course of peptone. This group contains a number of patients who did better on peptone than on proteose. Of the nine patients in this group who received no benefit at all from proteose three received benefit up to three months with peptone and two were markedly improved for over twelve months. Group B cases consist of fifty-five asthmatics who received peptone alone, and Group C contains all the eighty-one patients receiving peptone. Of Group C (Table III) cases 21 per cent. were markedly improved after peptone, as compared with 23 per cent. in the series of proteose patients (Table II). Statistically, if one can use statistics in assessing the cure of asthma, these results would indicate that proteose and peptone have both about the same influence in the treatment of asthma, and that the results of treatment with autogenous proteose appear to be no better than those obtained with a non-specific agent. The former method, too, has the following drawbacks:

1. Treatment cannot be begun until the patient has had a further attack of asthma, the urine has been collected, and the proteose prepared.
2. The preparation of proteose, because of its individual nature, is rather expensive and laborious.

Treatment by non-specific means—for example, peptone—on the other hand can be begun at any time, no laboratory preparation is necessary, the same degree of therapeutic value is obtained, and the treatment is relatively cheap.

Conclusions

1. Investigations here described, together with a study of the literature, tend to confirm the view that the zone of erythema obtained at the site of intradermal injection of urinary proteose is probably nothing more than a local toxic reaction and is not in any way specific.

2. The therapeutic benefit obtained with injections of autogenous urinary proteose in cases of asthma is about the same as that obtained with peptone. Any specificity which may be claimed for the former method does not outweigh the many advantages of a simpler and more general form of desensitization such as can be obtained with peptone.

3. The therapeutic results obtained in cases of urticaria are encouraging, and of sufficient interest in our opinion to warrant further investigation.

In conclusion, we wish to record our sincere thanks to Dr. W. Howel Evans for preparing the proteose in each case, and to Dr. R. Kemp for his help in supervising the peptone injections.

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THE VALUE OF OLEOTHORAX IN OBLITERATIVE PLEURISY

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The ingenious idea of Bernou of employing large quantities of oil in the pleural cavity was, unfortunately, overdone and exploited in certain quarters with an uncritical enthusiasm, with the result that opinion veered the other way until the method appears to have become almost entirely discounted. This is to be regretted, for though a minor procedure, it occupies a position of great importance, used strictly within its proper indications and limitations. If oblitative pleurisy is taking place with dangerous prematurity in the course of artificial pneumothorax, oil in the pleural cavity is the only thing that will keep the pleural layers apart, and so save the patient from a thoracoplasty. As the obliteration of the pleura proceeds so will the oil be driven to the upper zone of the chest, where collapse is most commonly wanted. It will be held there under considerable pressure, and, contrary to what Mr. Morrison Davies wrote in an excellent contribution to the *American Journal of Thoracic Surgery* in December, 1935, I believe that it is the high-pressure oleothorax that is of the greatest value.

The division of adhesions in cases of incomplete pneumothorax may itself start the process of oblitative pleurisy. Then, although the intervention may have given

complete rest to the lung, closed all cavities, abolished all symptoms, and led to the complete disappearance of tubercle bacilli, the inexorable and irresistible march of the pleural symphysis may, as it reaches the higher zones of the thorax, reopen the cavities, tear apart quiescent and healing areas, and so start the disease process all over again.

If it is evident that the pleural obliteration is progressive, or if it is possible that the premature re-expansion of the lung will reactivate the disease, something must be done to prevent it. There are only two possible courses: one is thoracoplasty, and the other is to establish an oleothorax. Of the two oleothorax is obviously to be preferred.

Oil is incompressible and practically unabsorbable, or absorbed only over a very long period. It is driven to the upper part of the thorax, where it is most usually wanted, and there it will remain unchanged and unnoticed by the patient for many years.

The objection raised is that it may rupture into the lung. I believe that this is putting the point the wrong way round. The lung, if the seat of active tuberculosis, may rupture into the oil, just as a spontaneous pneumothorax may occur with or without an artificial pneumothorax, with or without pleural fluid, and with or without an oleothorax. At the same time it cannot be denied that oil under considerable pressure over a softened area of diseased lung could burst through. If this happens it is an unpleasant and sometimes a grave event. With a thickened pleura, however, which usually exists under the conditions for which I advocate oleothorax, I believe this accident to be rare; moreover, it is a risk most patients would be prepared to take if they understood the alternative. At the very first suspicion of oil in the expectoration the oil in the pleura must, of course, be immediately replaced by air.

Conditions Necessary for the Establishment of a Successful Oleothorax

There are two essentials in my opinion: a rigid mediastinum, and a pleural cavity of strictly limited capacity. The first is obvious; the second perhaps not.

In the early days I tried therapeutic oleothorax as a substitute for pneumothorax, and I found that three pints of oil would not half fill the hemithorax. To maintain an adequate lung collapse by oil with a non-rigid mediastinum and a completely free pleura would take, in an average case, probably six to eight pints, and this would seem highly undesirable. With a mobile mediastinum no amount of oil would be effective without producing, simultaneously, gross mediastinal displacement. Hence it can be seen that commencing or, better, partially developed oblative pleurisy provides the ideal conditions for oleothorax. The mediastinum is fixed, the pleura is probably thickened and unyielding; the capacity of the pleura is limited and progressively becoming smaller.

Nevertheless I have cases where an oleothorax was performed as a substitute for pneumothorax. One patient was a child, aged 7, whose case I published in the *British Medical Journal* (June 18th, 1932). There was acute phthisis and extensive cavity formation. Artificial pneumothorax treatment was given, and a huge central cavity would not close because of adhesions. These were divided and the cavity closed. The child so dreaded the refills of air that I decided to perform an oleothorax. This was done in 1931, and the child to-day is perfectly well, living the normal life of a schoolgirl, with the oil still present. It has apparently become encysted from apex to base. She has never had any recurrence of symptoms.