

concerns the supraduodenal artery, described by Wilkie, of Edinburgh, which in wasted infants may be obliterated by the downward pull of the viscera leading to necrosis in the part of the duodenum it supplies—namely, the upper part of the posterior wall.¹² This mechanism was suspected in Case 2 of this paper. Possibly Case 2 illustrates another point, —namely, the familial incidence of duodenal ulcer in infancy. Rogers¹² has recorded the condition in two successive infants in the same family. In conclusion we should like to refer to the fact that most of the recorded cases have been discovered at autopsy, and that it must remain a little uncertain to what extent they may have been due to post-mortem changes. In the stomach and œsophagus post-mortem digestions are common; in contrast the duodenum is peculiarly free from them. This evidence encourages us to attribute to these ulcers an ante-mortem origin.

SUMMARY

(1) Two infants, 10 weeks and 2 weeks respectively, died of duodenal ulceration. (2) The clinical picture resembled that of other cases (circa 200) recorded in the literature—namely, failure to thrive, vomiting, and pain after food. Melæna or hæmatemesis seem to occur in about half the cases, and diarrhœa also in about half. The infants are always very wasted and they are rarely above 5 months of age. (3) The diagnosis is one of great difficulty during life; 160 or more of the 200 recorded cases have been recognised in the post-mortem room. There is reason to suppose that the diagnosis should be made more frequently, and it is suggested that it should be considered in all infants below the age of 5 months who are declining in a state of atrophy. (4) The prognosis is very poor; death usually results from inanition, occasionally by perforation (eleven recorded instances) or by massive hæmorrhage. (5) The pathology of the condition is that of a single or multiple ulceration, always lying on the posterior wall of the duodenum between the pylorus and the ampulla of Vater. (6) The pathogenesis is in doubt; various hypotheses are considered.

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AUTOGENOUS URINARY PROTEOSE IN RHEUMATOID ARTHRITIS

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Barber and Oriel,¹ in 1930, pointed out that in eczema of internal origin, and other allergic diseases, a substance could be isolated from the patient's own urine, which substance when injected intradermally gave a skin reaction similar to the injection of an antigen into an allergic patient who had been sensitised to that antigen. They further suggested that by means of this substance, which appeared to be complex in composition and in the nature of a proteose, the patient could be desensitised. They have since stated² that in allergic cases a specific reaction is evoked by the intradermal injection of the patient's own "proteose." Criticisms have not been lacking, but these appear to hinge mainly on the question of the cutaneous and dermal reactions evoked by the proteose, and the absolute specificity of the test. Freeman³ is of the opinion that there is no specificity, and has shown graphically that no difference can be detected in the skin reactions of allergic patients injected with autogenous proteose and normal controls injected with the same proteose. Murray Lyon, Percival, and Stewart⁴ take the same view.

Of recent years the relationship between allergy and rheumatism has been often stressed, and the position is reviewed by Poynton and Schlesinger⁵ chiefly with regard to acute rheumatism. They base such evidence as exists for this relationship on analogy, experimental evidence, and clinical observation. Barber¹ considers that in rheumatoid arthritis, while the primary antigen may be a streptococcus or other organism, the arthritis itself may be an allergic reaction towards a secondary antigen derived from the action of the organism on the patient's tissue. The same observer, in treating cases of psoriasis arthropatica with proteose, found that:

"In these cases, without exception, a striking feature has been the susceptibility of the affected joints, even to minute doses. An injection of 0.1 c.cm. of a one in a million dilution" (of proteose) "is apt to provoke a sharp focal reaction in the joints with a general but transitory feeling of malaise. The results of treatment in psoriasis arthropatica, and in rheumatoid arthritis uncomplicated by psoriasis, have been very encouraging, but the effect has been more noticeable on the arthritis than on the psoriasis."

In another communication Barber² again stressed this point: "in certain cases of rheumatoid arthritis it was necessary to be extremely careful in regard to dosage, for a slightly excessive dose would produce in a few hours an acute flare up in the affected joints." Douthwaite⁶ stated that all true cases of active rheumatoid arthritis "have a urinary output of proteose which is capable of causing a flare up of joint manifestations if introduced subcutaneously even in infinitesimal quantities." Oriel, in a personal communication stated:

"In rheumatoid arthritis we find the patients very sensitive to the injections, especially the acute cases, and if you call the first solution one in a thousand, I should advise commencing treatment with about 0.05 c.cm. of the 1/10 million dilution . . ."

We would here remark that these observations in cases of rheumatoid arthritis are in striking

contrast to the results we have obtained, for, as will be apparent later, over half of our cases of rheumatoid arthritis gave no reaction at all on the injection of 1 c.cm. of the strongest dilution—i.e., 1 in 1000—and that in addition none of our cases gave a positive intradermal reaction.

SKIN REACTIONS

Pearson,⁷ working on proteose in asthma, has defined a positive skin test as a strong large wheal with pseudopodia and definite persistent erythema. This definition is in keeping with that laid down by Rackeman,⁸ Coca,⁹ Bray,¹⁰ and other authorities on allergy; throughout our investigations our criterion for a positive skin reaction has been a definite blanched wheal (as apart from the injection bleb caused by the intradermal injection) and a definite persistent zone of erythema.

While we do not wish to consider in this paper any conditions other than rheumatoid arthritis, we would mention that we have had, using the same technique as described below, some markedly positive intradermal reactions in a limited number of cases suffering from the eczema-asthma-hay-fever syndrome.

We agree with Freeman³ that the injection of the proteose appears to produce a "wheal," but if an ink ring be made round the injection site it will be seen that the convexity of the injection bleb is increased, in other words any increase that takes place is at right angles to the skin. An exactly similar phenomenon may occur in the control injection bleb. Slight and transient erythema was present in many of our cases, but there was little or no difference between the proteose erythema and control erythema in the same patient.

It appeared to us that to compare tests on the skins of patients with rheumatoid arthritis, whose skins are subject to trophic changes, with tests on the skins of healthy normals was not a fair criterion. We therefore compared the reactions on the two arms of the same patient, selecting as far as possible exactly corresponding sites on the flexor surface of the two forearms, avoiding too close proximity to the ante-cubital fossæ.

One arm was tested with proteose plus alkali plus buffer solution, and the other arm with alkali plus buffer solution in a corresponding strength. A fine gauge needle and a 1 c.cm. syringe graduated in hundredths were employed. Exactly 0.05 c.cm. was injected intradermally. Throughout the series of cases autogenous proteose was used. The initial injection consisted of 1 in 10 million dilutions of the proteose and control solution respectively. If no reaction appeared within ten minutes, a ten times stronger dilution was then injected, and so on until the 1 in 1000 ("stock") solution was reached.

After experience of several cases and consistently negative results, it became our custom in order to save time to inject all five dilutions from 1 in 10 millions to 1 in 1000, commencing with the weakest dilution, of both proteose and control alternately, and observe the results. Close observation was kept on the injection sites for a matter of 15 minutes and thereafter at intervals up to 24 hours. Focal or general reactions that might fairly be attributed to the injections of proteose were watched for, but with one exception none appeared. This exception was a delayed reaction as described by Lyon, Percival, and Stewart.⁴ These observers, it should be noted, regard the initial skin reaction "merely as a slight exaggeration of the phenomenon frequently observed to follow any type of intradermal injection." Oriel,¹¹ however, appears to rely on the initial skin reaction, and, as pointed out by Freeman¹² and Burgess,¹³ all claims for the specificity of proteose have been on this basis.

In all, we have tested the reactions to autogenous proteose in 50 hospital in-patients suffering from rheumatoid arthritis. All these cases were selected, in that they were clinically and radiographically true rheumatoid, and "active" in that they had pain, swelling of joints, and low suspension stability of the erythrocytes; the majority had, in addition,

intermittent low-grade pyrexia. It is obvious, therefore, that all these patients' proteoses were isolated during an apparently active phase of the disease.

PREPARATION AND PROPERTIES OF THE "PROTEOSE"

The "proteose" dilutions were made by Oriel's technique as follows.

The 24-hours' output of urine collected in a Winchester quart bottle containing a few drops of chloroform was rendered acid to Congo red by addition of 25 per cent. sulphuric acid (1 to 3 c.cm. usually necessary), filtered through a close filter, 400 c.cm. filtrate placed in a separating funnel with 100 c.cm. ether and well shaken for some minutes. On standing, the ether layer either showed a gelatinous lower stratum or became semi-solid throughout. After running off the urine the ethereal layer was run into a stoppered measuring cylinder, an equal volume of alcohol added, and the mixture allowed to stand until the white flaky precipitate which invariably formed had subsided. From the twenty-sixth case onwards 10 to 15 minutes only were allowed for this subsidence, in order to avoid prolonged contact of the precipitate with the alcoholic liquid. (An experiment with a case, however, in which half was allowed 10 minutes contact with alcohol and the other half 24 hours, showed no difference as regards skin tests in the "proteose" dilutions made from each.)

The supernatant liquid was pipetted off, the remainder transferred to a centrifuge cell, and after centrifuging, washing with distilled water, and again centrifuging, the precipitate was treated in the cell with 0.5 to 1.0 c.cm. N/10 NaOH, made up to 10 c.cm. with buffered phenolated saline of pH 7.6, and again centrifuged. The clear liquid was transferred to a vaccine bottle and regarded as No. 1 (stock) dilution of nominal strength 1 in 1000. From this successive tenfold dilutions 2, 3, 4, 5 were made with phenolated buffered saline, the weakest, No. 5, being 1 in 10 millions. In all such cases dilutions were made from the readily soluble portion of the precipitate.

Previous workers have made determinations of the nitrogen content of the stock dilution of so-called "proteose" and the ratio it bears to the total nitrogen of the urine in various stages of allergic disease, but these determinations seem to have been made on the stock solution itself.

Murray Lyon, Percival, and Stewart,⁴ who employ the dried precipitate for making their dilutions, state only the total N in the proteose precipitate and its ratio to the total N in the urine, and do not give the percentage of N in the dried precipitate, which, if the precipitate is anything like a pure proteid, should approximate to the usual $100 \div 6.25$ content.

To throw light on this point, a separate portion of the urine was set aside in 12 successive cases, and the washed alcohol precipitate, obtained as above stated, was collected on a weighed dried filter, dried at 100° C., weighed, and the nitrogen percentage determined by Kjeldahl's process (Table I.). In 10 of the 12 cases this nitrogen percentage is not consistent with the precipitate containing even 50 per cent. of a pure proteid. The ratios of precipitate nitrogen to total nitrogen are of the same order as many of those given by other observers, but there is no case among the 12 of the very high ratios observed in acute attacks of allergic disease.

The heat test for proteoses was applied to the urine of each patient. About 2 in. of perfectly bright filtered urine was placed in each of four test-tubes, the fourth being a control. One drop 33 per cent. acetic acid was added to No. 1 tube, two drops to No. 2, and nothing to the third. The three tubes and a thermometer were immersed in a bath of distilled water and gradually heated. Except in the third tube no cloudiness appeared in any case until the temperature rose above 50° C.—cloudiness appearing between 50° and 60° was registered as positive for proteoses, and its degree estimated by comparison with the control tube of unheated urine by illuminating the four tubes in a row against a black background as in Dreyer's agglutination technique. Whenever the third tube alone showed turbidity, one drop of acetic acid at once removed it, as it was then due to a trace of phosphate precipitated by the effect of heat on nearly neutral urine. On further heating the three tubes from 70° to 100° perfect clearing up of the proteose cloudiness was never seen, presumably because a trace of

coagulable albumin not detectable by any less delicate mode of observation was in many instances present in addition to the proteose. The results obtained were as follows:—

No. 1 tube with one drop of 33 per cent. acetic acid : 26 per cent. positive, 74 per cent. negative.

No. 2 tube with two drops of 33 per cent. acetic acid : 48 per cent. positive, 52 per cent. negative.

Notes on the alcohol precipitate.—All urines gave an alcohol precipitate from the ether extract of 400 c.cm. of urine. In only one case was this very slight; in another case it measured 10 c.cm. in the graduated cylinder, but it generally ranged from 1 to 5 c.cm.

All the stock dilutions examined gave at least a trace of reaction with the general tests for proteins tried—viz., Millon, Esbach, salicyl sulphonic acid, Spiegler—but this proves nothing as to proteose. It should be noted that this is in contradistinction to the negative results obtained by Haviland Minchin's¹⁴ tests on the proteose obtained from patients suffering from idiopathic epilepsy.

Many urines which, when filtered, were perfectly clear, gave no cloud with salicyl sulphonic acid, either immediately or after standing half an hour, and would consequently be returned negative for albumin for clinical purposes, nevertheless showed cloud after standing for some hours.

Some of the alcohol precipitates, when only 10 to 15 minutes is given for subsidence, readily dissolved after centrifuging and washing in 0.5 to 1 c.cm. N/10 NaOH, and may be presumed to be fairly homogeneous. Others, especially after some hours are allowed for subsidence, are, on centrifuging, manifestly not homogeneous; frequently there is a non-flocculent, heavier, sometimes pigmented layer at the bottom, and the flocculent and non-flocculent portions do not entirely dissolve in 3 or 4 c.cm. N/10 NaOH, but sometimes require a few drops of N/1, or even 10 per cent. soda for solution.

RELATION OF PROTEOSE THERAPY TO PROTEIN SHOCK

—	Heat test proteose. Acetic.		Albumin tests.	Urine in 24 hrs. c.cm.	Total N 24 hrs. g.	Proteose ppt. 24 hrs. g.	N% in "proteose."	Proteose N % of total.
	1 dp.	2 dps.						
7 Camb. . .	—	—	+++	900	11.25	0.1435	10.20	0.13
1 Prince . .	—	—	trace	600	6.14	0.0697	4.36	0.49
10 Colston	—	—	---	650	8.38	0.2798	6.75	0.23
10 Prince . .	+	+	+	750	4.88	0.2730	4.00	2.24
14 „ . .	—	—	? tr.	1500	10.80	0.1912	4.00	1.77
5 Perry . .	+	+	+ tr.	950	5.85	0.1757	3.98	0.12
8 „ . .	—	—	—	1200	4.26	0.1590	3.83	0.16
6 Colston	—	+ ?	+ ?	1000	10.57	0.1600	7.11	1.08
8 „ . .	+	+	—	1150	6.16	0.0708	17.90	0.20
2 „ . .	+	+	trace	480	3.46	0.0974	4.32	0.12
11 „ . .	+	+	trace	1100	8.25	0.1254	5.51	0.08
15 „ . .	+	+	+++	650	5.33	0.1664	6.12	1.88

dps. = drops.

In order to test whether injection of proteose was in any way comparable to protein shock therapy, the protein nitrogen was estimated in an "antisepsis" vaccine of Parke, Davis and Co., and the value arrived at was that each coccus = 1/5250 mg. N. A similar estimation was done on Warren Crowe's *Micrococcus deformans* vaccine, and each coccus there was found to contain 1/9217 mg. N.

Note.—These results are assuming that all the N found (after deduction for controls) is due to the cocci. Some of the N found probably comes from the culture medium during the contact of the normal saline with the slope, or from the

employment of non-N free water when making the emulsion of cocci for the vaccine.

Now if the soluble portion of the alcohol precipitate be assumed to be pure proteose, 0.05 of the 1 in 1000 (stock) dilution is = 0.008 mg. N, which value is roughly comparable to about 100 cocci, and thus 0.05 of the 1 in 1 million dilution has a nitrogen value similar to that of one coccus.

Our figures given in the above Table indicate that the soluble alcohol precipitate instead of giving figures in the neighbourhood of 16 per cent. of the total nitrogen, thus being indicative of pure proteose, range from 3.83 per cent. to 17.90 per cent. with a mean of 6.50 per cent.

TESTS IN RHEUMATOID ARTHRITIS

Intradermal skin test.—Fifty cases were tested with all five dilutions of autogenous proteose, and gave negative results.

Scratch test.—Twenty-six cases were tested by this method with 1 in 1000 dilution of proteose, and proved negative.

Patch test.—Thirteen cases were tested by patches applied above the breast on either side, and left in situ for 48 hours. All were negative, with one exception.

This patient developed marked erythema under the proteose patch, and also had areas of vesiculation under the patches on both sides. It is interesting to note that when a week or so later the same patient had Scott's dressing applied on her wrist for a matter of 12 hours, a scarlet erythema with exfoliation occurred over the same wrist, with large areas of scarlet erythema over her abdomen and both legs.

As mentioned previously, Barber, Oriol, and Douthwaite have stressed the extreme toxicity of autogenous proteose. To test this we injected subcutaneously a 1 c.cm. of the strongest—i.e., the 1 in 1000—dilution of proteose into the right arm of 14 patients. Out of the 14 cases of rheumatoid arthritis, over half (8) had no focal or general reaction whatsoever, whilst in the other 6 the symptoms charted below do not indicate that degree of toxicity of the proteose that we had been led to expect:—

Case 1.—Pain in right hand which started five to six hours after injection, and lasted about two days.

Case 2.—Muscles of right arm stiff and hands more painful.

Case 3.—Marked pain in right arm and right hip.

Case 4.—Right arm swollen. Headache and temperature over 100° C. on evening of injection.

Case 5.—Pain in right arm.

Case 6.—Stiffness of right arm and rise of temperature to 99.5° C.

Whilst we are forced to conclude from our investigations that urinary proteose does not give similar cutaneous and dermal reactions to the injection of an antigen into a patient sensitised to that antigen, this does not necessarily negative its possible therapeutic value. We feel that this point—namely, that the injection of proteose, although possibly being in no way specific for a certain disease, may yet have therapeutic value in that disease—is at times apt to be overlooked by Oriol's critics. For instance, we have dealt successfully by means of autogenous proteose with cases of hay-fever which had derived no benefit from other and varied forms of treatment. But in a number of these successful cases the skin reactions were at all times negative.

The difficulty, however, arises as to the indications for the correct dosage to promote amelioration or effect cure. In rheumatoid arthritis one must needs fall back on the patient's focal and general reactions to assess the optimum dosage. It is extremely

difficult, as is well known, to assess whether any slight rise of temperature, malaise, or increase of pain in true active rheumatoid arthritis is due to excess in any particular treatment. For patients with rheumatoid arthritis have alternating periods of malaise and well-being, and, further, intermittent rises of temperature and increase in local pain will occur, even if they are in bed without any form of treatment. To cite an example: one case complained bitterly that the patch test (although negative) caused her marked exacerbation of her arthritic pain, whereas she felt no ill-effects at all from the subcutaneous injection of 1.0 c.cm. of 1 in 1000 proteose.

One experiment we tried may be quoted. Twelve patients with true active rheumatoid arthritis were selected on admission. Of these, six were chosen at random and placed on the appropriate hydrological treatment to serve as controls; the other six were given no other treatment save injections of proteose at weekly intervals, commencing with 0.05 c.cm. of the 1 in 10 million dilution, and given a similar quantity of a ten times stronger dilution each succeeding week. At the end of six weeks a note was made of subjective symptoms of all twelve patients. All six of the patients treated by hydrology were improved, whereas of the remaining six who had received proteose injections, one patient felt better, one felt worse, and the other four said there was no change in their condition since admission. This experiment was not of help, and only served to show that, if it be that proteose gives therapeutical results in rheumatoid arthritis, we had employed wrong dosage or not allowed sufficient time for therapeutic results to mature.

Since then we have tried the effect of giving intradermally exceedingly minute doses—e.g., 0.02 of the 1 in 10 million—over long periods. Apparent success in one case encouraged us to persevere with other cases. We also tried varying the strength of the dosage and varying the time interval, persevering with individuals for periods up to four months, but without any therapeutic effect.

ALLERGIC HISTORY IN RHEUMATOID ARTHRITIS

A careful inquiry was made into the patient's (1) own history, and (2) family history, for:

(a) Any *allergic conditions* such as eczema, migraine, asthma, urticaria, or hay-fever. The results obtained were as follows: out of 50 cases of rheumatoid arthritis: (1) two gave a positive history (one had had migraine and the other hay-fever); (2) one said her mother suffered from sick headaches, possibly migraine.

(b) *Family history of "rheumatism."*—Inquiry was made back to two generations; 13 gave positive answers—e.g., sister had rheumatic fever, grandmother rheumatoid arthritis.

(c) *Patient's past history of rheumatic fever:* 4 of the 50 cases of rheumatoid arthritis had previously suffered from this.

SUMMARY AND CONCLUSION

1. Fifty cases of true active rheumatoid arthritis have been selected and autogenous urinary proteose vaccines have been prepared.

2. Adopting the usual standard for positive skin reactions, all the cases treated were consistently negative to intradermal, scratch, and patch reactions (with one exception in the latter group).

3. Some points in the preparation of the proteose are considered, and the question is discussed whether the substance isolated be of a proteose nature.

4. Inquiry was made into the patients' previous and family history with regard to allergy. The following facts were elicited: (1) previous history of allergy, 4 per cent.; (2) family history of allergy,

2 per cent.; (a) previous history of rheumatic fever, 8 per cent.; (b) family history of "rheumatism" (all forms), 26 per cent.

5. Attempts were made by treating patients over long periods with various doses and at various time intervals with the proteose to produce amelioration, but in only one instance was any apparent success obtained.

6. From this we draw the conclusions: (a) that autogenous urinary proteose does not produce skin reactions in rheumatoid arthritis similar to those produced by antigens in cases of allergy. Further, its toxicity in rheumatoid arthritis has been exaggerated. (b) As a therapeutic agent in the treatment of rheumatoid arthritis, urinary proteose appears to be useless.

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Clinical and Laboratory Notes

A CASE OF ADRENAL NEUROBLASTOMA

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THE case reported in THE LANCET of Nov. 19th (p. 1101) by Mr. Frank Law recalls one which I saw last year, which gave rise to considerable difficulty in diagnosis. In this particular case, however, histological examination of a subcutaneous nodule was of great help.

A male child, 17 months of age, was admitted to the Infants Hospital on July 11th, 1931. He had been brought by the mother because there had been anorexia and diarrhoea with loss of weight for the last four months, and because there were scattered over the body "lumps" which the mother averred had been present since birth.

On examination the child was seen to be very emaciated, his weight being only 15½ lb. instead of the average normal of 25 lb. at that age. The skin was dry, powdery, and of a slight but quite definite café-au-lait tinge. This pigmentation was most marked on the face and on the dorsal aspects of the hands. Apart from the pigmentation and the wasting, the child had a curiously repulsive aged facies. A non-medical friend, when shown the photograph, took it to be one of a famine coolie rather than that of a child of 18 months. The abdomen was distended but no definite tumour was felt at any time.

The most striking feature was the large number of subcutaneous nodules which were present. Most of these were on the chest wall, and appeared in certain areas to run in chains along the intercostal spaces. There was a definite chain running along the lower border of the scapula. These nodules were freely movable under the skin and varied in size from about 1½ in. long by ¾ in. across, to that of a small pea. There were similar nodules on the anterior abdominal wall and along the flexor aspect of the forearms. The glands in the axillæ and groins were also enlarged. The distribution of these nodules, the pigmentation, and the absence of any other definite symptoms suggested a diagnosis of von Recklinghausen's disease.

About three weeks after admission, other symptoms appeared which suggested very strongly involvement of the suprarenal gland. At this time there appeared a fine growth of downy hair over the greater part of the body