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CLINICAL SENSITIVITIES TO GELATIN AND OTHER MEAT PRODUCTS

By

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Gelatin is generally considered to be non-antigenic in animals and it has therefore been assumed that it is non-antigenic in man also (Spain et al. 1939, Wilson and Miles 1946, Cooke 1947). In consequence, gelatin sensitivity is rarely sought in allergic patients and may well have been overlooked. So certain are allergists on this point that gelatin is now being introduced as a carrier for A.C.T.H. (Gay and Murgatroyd 1952).

Extensive animal work has been done to test whether gelatin can produce anaphylactic shock or stimulate the production of specific antibodies. The most convincing reports are those of Starin (1918), Polettini (1931), Taylor et al. (1943), Pugsley et al. (1943), Robschweit-Robbins et al. (1944), Wormall (1944) and Vanderbrook et al. (1947). None of these authors was able to demonstrate the presence of precipitins or complement-fixing antibodies, nor could they produce anaphylactic responses. The only positive evidence that any response is made by the body to the injection of

gelatin is contained in papers by Arthus (1908), Abderhalden (1910) and Ascoli and Izar (1910). The matter has naturally been carefully investigated in connection with plasma substitutes for transfusion work (Amberson 1937, Taylor and Waters 1941, Waters 1941, Gordon et al. 1942, Parkins et al. 1943, Randolph 1947, Skinsnes 1947). These authors in general consider that gelatin is innocuous and fails to give rise to anaphylactic responses. It is known however that gelatin can act as a hapten and becomes antigenic when coupled to other substances such as diazotised aniline, arsanilic acid, etc. (Landsteiner 1919, Adant 1930, Bruynoghe et al. 1930, Hooker and Boyd 1933, Hopkins and Wormall 1933, Clutton et al. 1938, Mori 1939, Haurowitz et al. 1943, Wormall 1944). Pure gelatin is however thought to be non-antigenic in man and unable to give rise to allergy, and a number of theories have been advanced to explain this peculiarity (Wormall 1937, Haurowitz et al. 1943, Wormall 1944). Cases apparently sensitive to gelatin have been explained as being due not to the gelatin itself but to other proteins of the animal from which the gelatin was derived, small quantities of these being carried over to the finished product (Rowe 1937, Urbach 1946, Randolph 1947). This type of sensitivity undoubtedly exists and is illustrated by *Case b*, although it cannot explain the results obtained in the following case.

Case a.

A young woman of 22 complained of urticaria and angioneurotic oedema associated with some meals. She was engaged to be married and the attacks were particularly marked when she ate in her fiancé's company in restaurants. Attacks came on very soon after the beginning of a meal, the first sign being irritation of the mouth and lips, followed by swelling. She had observed that roast meat did not affect her in this way but that boiled and stewed meats were particularly irritating, and that soups and gravies made from

stock also produced this effect. Skin testing by the prick method with extracts of foods likely to have been the cause, including meats, gave negative responses and it appeared that the condition might be classed as psychogenic. Nevertheless, further questioning showed that she was not particularly "squeamish" about food, having no objection to other substances of slippery texture such as boiled onions, macaroni, etc., and that the attacks did not occur after knowingly eating roast horse meat. One other group of foods also caused symptoms—sweets such as ice-cream, "jellybabies", table jellies and trifles containing jelly. A series of extracts was prepared of gelatin, peptone, ice-cream and also of various proprietary substances which would normally be used in gravies, such as Oxo, Marmite and Bisto. On testing with these six substances positive reactions were obtained to them all, the largest being to gelatin itself. Negative reactions were obtained to the mould groups. Hyposensitisation with gelatin caused a reduction of the skin reaction and a disappearance of clinical symptoms. After four and a half years symptoms began to return, the skin reactions increased in size and it was found necessary to repeat the hyposensitisation. This time she has obtained only partial relief, being able to eat without symptoms small quantities of meats and gravies, although a spoonful of jelly will give rise to swelling of the eyelids, lips and throat within 5 minutes.

Serum was separated from 200 ml. of *Case a* blood and after successfully passing Wassermann and sterility tests was stored in the refrigerator.

This serum undiluted and diluted 1/5, 1/10, 1/20, 1/200, and 1/2,000 was titrated against gelatin solutions diluted 1/100, 1/200, 1/400, 1/800, 1/2,000 and 1/20,000 but precipitins could not be demonstrated.

To investigate the possible presence of circulating skin-sensitising antibodies passive transfer tests were carried out. Owing to the possible occurrence of serum jaundice it was considered unjustifiable to perform such tests, using the Prausnitz-Küstner technique, on normal healthy subjects, and

these tests were therefore performed on 4 non-atopic adult volunteers whose expectation of life was less than the incubation period of serum jaundice. (In fact, no jaundice appeared subsequently in any of them.) All 4 patients gave negative results when prick tested with normal saline, grass pollen, beef, mutton, pork, horse serum and gelatin extracts, and the histamine skin responses were within normal limits.

In 3 patients 0.05 ml. of *Case a* serum was injected intradermally into each of 4 sites on the flexor surface of the forearm, and 2 further sites were sensitised by the intradermal injection of 0.05 ml. of serum from a hay fever subject (W.R. negative) known to possess circulating pollen antibodies. After 48 hours (during which period gelatin-containing foods were forbidden) the first 4 sensitised sites were injected intradermally with 0.02 ml. of normal saline and 0.02 ml. of beef, mutton, and gelatin extracts. The last 2 sites were injected with 0.02 ml. of normal saline and 0.02 ml. of grass pollen extract (positive control). Each injection on a sensitised site was repeated on adjacent normal skin (negative control). Results were read after 25–30 minutes. Positive results were obtained with the gelatin and grass pollen extracts only. In each case the response at the site of the gelatin injection was about half the size of the grass pollen response (positive control), and the smallest response obtained to a gelatin injection consisted of a wheal measuring 0.5 cm. $\times$ 0.3 cm. surrounded by a zone of erythema measuring 1.5 cm. $\times$ 2.0 cm. At all the other injection sites there occurred either no reaction or else a small flare lasting from 5 to 20 minutes unaccompanied by whealing.

In the fourth patient 4 sites sensitised with *Case a* serum were prick tested 48 hours later with normal saline, beef, mutton and gelatin extracts. No responses were obtained but a positive control test using a known anti-grass pollen serum was not performed.

The gelatin extract was made by breaking up 10 gm. of chemically pure bovine ossein sheet gelatin in 100 ml. of Coca's extracting fluid. This was auto-

claved at 15 lbs. pressure for 20 minutes, thus dissolving the gelatin and sterilising the whole. The gelatin solution so obtained was diluted ten times with sterile normal saline and bottled. This "extract" did not solidify on cooling and was used for all skin testing purposes and (suitably diluted) for the precipitin titration i.c. and for hyposensitisation. It contained 0.01 gm. of gelatin per ml. (equivalent to 10,000 Noon units per ml.) and 1.215 mg. of protein nitrogen per ml.

This case shows that allergy to gelatin can exist with no accompanying sensitivity to other animal proteins, that it behaves like an ordinary protein sensitisation, giving an immediate type of skin response, that desensitisation can be undertaken, and that circulating skin-sensitising antibodies can be demonstrated.

The more common type of allergy, in which there is a sensitivity to an animal protein and also to the gelatin derived from it, is illustrated in the second case. Here it would have been impossible to provide convincing evidence that there was no carry-over of animal protein in the manufacture of the various products which had given rise to symptoms.

Case b.

A widow of 26, in domestic service, gave a history of urticaria and angioneurotic oedema occurring within one to six hours of eating any meat. Twice she had lost consciousness and the attacks were often accompanied by generalised joint stiffness and pain lasting from 24 to 48 hours. From the age of two until she was eighteen the patient had had asthma, but had been free for the past eight years. The present symptoms had begun six years before, during her first pregnancy, and had never occurred except after eating meats and gravies. Pork was especially troublesome. On skin testing by the prick method positive responses were obtained to horse dander, cheese, milk, pork and rabbit flesh. The first three did not appear to be clinically significant. On further testing with gelatin, Oxo, Marmite and Bisto positive responses were obtained to gelatin and Marmite. The mould groups gave negative responses and therefore the skin response to

Marmite was not due to its yeast content. Although negative responses were obtained to beef, mutton and horseflesh the patient could not eat these meats.

A related condition has been found in the following case where there is sensitisation to the products of meat protein digestion without any direct evidence of sensitisation to the meat itself.

Case c.

This case presented a history suggestive of psychogenic asthma. An 18-year-old law student working for examinations had had asthma since childhood. He complained that recently the asthma had become very much worse. Attacks were particularly bad on Sunday afternoon after he had lunch with his family. During the week he was practically a vegetarian, avoiding meat products, and he claimed that any meat meal would give him an asthmatic attack within about 2 hours. Skin prick tests against various meats were negative, but as it had been made clear by *Case a* that sensitivity to parts of meat could occur he was tested with the same series of extracts and positive responses were obtained to Marmite and Oxo but not to gelatin. Testing with the mould groups gave negative results. It was thought that his sensitivity might be due to breakdown products of meat protein digestion, so a tryptic digest of beef muscle was set up at 30°C and samples were withdrawn after 0, 30, 60, 90, 120, 150 and 180 minutes. The samples were immediately heat sterilised (thus inactivating the trypsin) and their pH adjusted to 7.2, and they were then placed in sterile containers on ice until used for skin tests later. Positive skin responses were obtained with the 30-minute to 150-minute beef digest samples only. The first and last beef digest samples gave negative skin responses.

In a sequence of over 1,000 allergic cases, only 4 gave positive skin responses to gelatin with no positive skin responses to meat itself or to meat extracts not containing gelatin. 2 other cases gave positive skin responses to gelatin

and to meats. Of these 6 cases clinical symptoms were present in 2 only (*Cases a* and *b*).

DISCUSSION

In these cases we have therefore encountered 3 types of sensitivity to meat products. The first (recognised for many years) consists of those cases sensitive to meat itself and to its products (where it is probable that traces of unaltered protein or protein not sufficiently denatured to lose its specificity are present in these products). *Case b* is of this type. The second type consists of cases similar to those recorded previously by Stull and Hampton (1941) and by Cooke (1930, 1942), in which products of meat digestion give rise to symptoms but in which there is no direct evidence of sensitisation to the original protein (*Case c*). Finally there is a type, apparently not previously reported, in which there is a sensitisation to gelatin (or possibly to products of gelatin hydrolysis) in the absence of a reaction to the proteins of the parent meat or to meat products not containing gelatin (*Case a*). It is possible that the positive skin responses to gelatin were due to some product of gelatin hydrolysis and the positive response to peptone may be significant in this respect, although even if this were so it would make little difference to the practical applications of skin testing and the assessment of results, as clinically the patient would still be aware of a sensitivity only to gelatin itself.

From previous work already quoted it has been shown that gelatin alone cannot be made to give rise to anaphylaxis in animals, and in man it appears to be a rare allergen.

SUMMARY

3 cases are described illustrating different types of sensitivity to meats and their derivatives, including one case of sensitisation to gelatin in the absence of other demonstrable

protein sensitivities. This gelatin sensitivity was confirmed by successful hyposensitisation and by the demonstration of circulating skin-sensitising antibodies.

The incidence of positive skin reactions to gelatin in a series of over 1,000 allergic patients was less than 1 in 150, and the incidence of clinical sensitivity to gelatin was 1 in 500.

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