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ON THE PROPHYLACTIC POSSIBILITIES IN ACTH ALLERGY

By

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The incidence of allergic reactions to ACTH has soon followed the introduction of the drug. The first data are summarized by *Roskam et al.* (1) and by *Serafini & di Nardo* (2). The symptoms elicited by ACTH on an allergic basis are local reactions (3-4) and urticarial-edema cases including the serum sickness type (1, 5). Further asthma (2) and, as the most severe type, anaphylactic shock can develop as signs of sensitivity to ACTH (6-13). Some shock cases were fatal (14-21). As more seldom occurring manifestations, fever (22) and contact dermatitis (23) are mentioned and even cases showing a paradox Thorn test, i.e. increase of eosinophils instead of decrease after an ACTH administration are held as allergic manifestations by some authors (24-25).

The number of reported ACTH-allergic cases has become large. *Brown* (26) quotes that 2 per cent of an allergic population is apt to exhibit hypersensitivity to ACTH. The more thoroughly investigated cases with ACTH sensitivity in the literature (4, 5, 14, 22-23, 27-37) are summarized in Table 1.

According to the data of Table 1, the greatest part of the investigated cases reacted to ACTH and pituitary extracts of different species, whereas in some cases the ACTH sensitivity was due to sensitization to animal tissue. Passive transfers with the appropriate allergens were in general positive. The occurrence of antibodies to ACTH by the neutralisation technic was

TABLE I
Reports from the literature on skin tests in patients with ACTH allergy.

Number of cases	Patient material	Symptoms					Immediate skin tests					Pas- sive trans- fer	Author		
							Acth extracts			Other hypo- physis ex- tracts	Animal tissue				
							Pig	Beef	Whale		"Puri- fied"			Pork	Beef
2 of 19	rheumatoid arthr.	+		+				+					—		(27)
6 of 208	"	+		+				+	—				—		(28)
1 of 208	"	+						+	+		+		—		(28)
6 of 113								+	+				—		(29)
1				+				+	+		a	+	—		(14)
1	psoriasis	+						+	— ^b	+		—	— ^{b, c}		(30)
1								+							(23)
6															(31)
5 of 600					+						—		+	+	(5)
1				+				+	+		+	+			(32)
3 of 25		+		+				+		+		+			(33)
1	polyarthritis	+	+					+							—
3		+						+					2 : +	1 : +	+
1	polyarthritis	+		+				+			+	+			(22)
10 of 106	asthma	+	+					+		+	+	+			(35)
11		+	+					+					+	+	(36)
8 of 144	asthma	+	+	+				+	+	+		+	—	—	(37)
		+	+	+				+	+	+		+	4 : +	4 : +	(4)

a: reaction to peptide preparations of the hormone was positive.

d: positive i.c. test to inactivated ACTH.

b: only patch test was done.

c: passive transfer with an other brand was negative.

c: per os provocation test.

shown by Inderbitzin (22). Allergic reactions to pituitary extracts originating from different parts of the pituitary gland on the same person have already been found by other investigators (38-40, 14).

In addition to these reports, some other findings should be mentioned. In some cases hypersensitivity to ACTH was suspected in spite of negative skin reactions (27, 41) although this is unlikely according to *Arnoldsson* (4). Another important question is that positive skin reactions to Corticotropins may occur in patients receiving ACTH but not showing clinical allergic manifestations due to ACTH. Such cases without established ACTH allergy are mentioned by *Brodwall* (33), these patients reacted to whale extracts. *Arnoldsson* (36) describes 27 patients of his series belonging to this group and in further investigations (4) 20 cases of this kind and 6 doubtful cases. These patients reacted to beef, whale and especially to pig ACTH preparations, whereas hypersensitivity to pig and beef tissue was found in 3 and 2 cases, respectively.

Several data of Table 1 speak in favour of the role of the impurities in ACTH allergy. Positive skin reactions to impurities were seen by *Bieliczky* (42) who, however, observed positive skin reactions in controls and by *Duchaine et al.* (25). The latter observed patients reacting to both ACTH and impurities by skin tests. The positivity of skin reactions could not be prevented by inactivation of the preparation (22, 43). The role of pyrogenic substances could be excluded (20). Sensitivity reactions to gel or to gelatin of the repository preparations could not be found in a single case (24, 13, 44-45), but *West* (44) describes a local reaction due to the phenol antiseptic. To a highly purified (Corticotropin A₁) preparation no reactions could be observed in patients not tolerating the cruder Carboxycelluloze (COC)-purified ACTH (44). The allergenic role of protein or peptide contaminations was especially emphasized by *Arnoldsson* (4) who further could not obtain reactions to human ACTH preparations in his Corticotropin-allergic cases.

THE AUTHOR'S INVESTIGATION

It will be seen therefore, that much work has already been done in the field of ACTH allergy. The aim of this publication is to discuss the problems of prophylactic measures on the basis of investigations in three ACTH-allergic patients. The brief history of these patients is as follows:

Case 1. A 30-year old woman who since 1953 had disseminated lupus erythematosus and joint complaints. Nivaquine and cortisone preparations were given and in 1957 ACTH-injections with good therapeutic effect. ACTH was therefore continued at intervals of one week. In the summer of 1958, she experienced headache and vomiting for which reason nivaquine side effects were suspected so that this treatment was stopped. The ACTH therapy was interrupted, and the patient was hereafter given ACTH only twice. On both occasions, urticaria developed after the ACTH-injection.

In her history a rhinitis, presumably on a nonallergic basis and urticarial eruptions after raspberry were noticed.

Case 2. A woman, 49 years of age with rheumatoid arthritis since 1954. In 1954 she was first treated by ACTH therapy. In 1955 a treatment with a pig extract was started but the patient responded with urticaria to the drug and consequently it was stopped. In 1958, a whale ACTH preparation was tried intracutaneously but a local reaction followed. The patient in 1960 developed a suspected Addisonism, however the diagnostic ACTH-test could not be made owing to her allergy to this drug.

The patient had earlier had a gold dermatitis, and in the summer of 1960, she had an urticarial rash the cause of which was possibly the eating of strawberries. Although the patient received at the same time tresochin and dicoumarine tablets, the exposition and thrombocytopenic tests for these drugs were negative.

Case 3. A woman of 31 years of age was examined for a suspected pituitary hypofunction. In the autumn of 1959, she had a pig ACTH preparation but even after the first injection

a local reaction appeared after some hours. Owing to good therapeutic results, the injections were continued but local reactions, becoming gradually less obvious, followed each injection. After about one month, an asthmatic attack followed and the treatment was stopped.

The patient had already a tendency to have infections of the upper respiratory tract with coughing. The asthma attacks continued even after the ACTH was stopped. On the basis of the history and positive bacterial reactions with an intracutaneous test, the diagnosis of asthma of the endogenic type was made.

The results of the investigations of ACTH allergy are summarized in Table 2. It will be seen that all three patients reacted to ACTH and pituitary preparations of different sources. The passive transfer with pig extract was likewise positive. Case 3, experiencing clinical signs of both the immediate and delayed type to ACTH reacted similarly in skin tests. No reactions were found to animal tissues. The pig ACTH preparations were of different brands including COC-purified pig extract.

None of these cases reacted to *human* ACTH preparation. This fact is in agreement with *Arnoldsson's findings* (4). This circumstance can therefore be taken into consideration as a possible prophylactic method for ACTH-allergic patients. However, the mass production of human ACTH preparation is impracticable. On the other hand, although a negative provocation test was seen after a small dose (2 units of human ACTH) in Case 1, the report of *Hale* (39) is of importance. He (39) found in a patient positive intracutaneous and passive transfer reactions to human pituitary extracts and therefore, the possibility of allergic reactions even to human ACTH extracts cannot be excluded.

Two fractions obtained from a COC-purified pig ACTH preparation and separated by paper electrophoresis as a rapidly and a slowly "wandering" fraction was kindly supplied by a pharmaceutical laboratory. Of these the former even judged by its greater physiologic activity was a purer corticotropin

TABLE II
Skin and provocation tests in three patients with ACTH allergy.

0.05 ml from:	Scratch and i. c. reactions						Passive transfer with pig Acth		Provocation test with 25 E purified rapidly wandering fraction ¹			
	Immediate						Delayed					
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 1	Patient 2		
Pig ACTH 10 E/ml	++	+	+	—	—	+	—	—	—	—		
Whale ACTH 10 E/ml	++	++	+	—	—	+	—	—	—	—		
Pork extract 1 : 1000	—	—	—	—	—	—	—	—	—	—		
Sheep extract 1 : 1000	—	—	—	—	—	—	—	—	—	—		
Somacton (pig) 10 E/ml	++	++	+	—	—	+	—	+	+	—		
Prolactin (sheep) 10 E/ml	++	++	+	—	—	+	—	+	+	—		
Human ACTH 2 E/ml	—	—	—	—	—	—	—	—	—	—		
Purified ACTH rapidly ¹ wandering fraction 10 E/ml ...	—	—	—	—	—	—	—	—	—	—		
Purified ACTH slowly ¹ wandering fraction 3 E/ml	++	+	+	—	—	—	—	—	—	—		

¹ Fractions of COC-purified pig ACTH separated by paper electrophoresis.

preparation, whereas the "slower" contained contaminations with inactive proteins or peptides to a high degree. For the moment, no more chemical analytic data are available of these two fractions. The skin reactions were positive when the COC-purified pig product was used (before the starting of the paper electrophoresis) and to the slow electrophoretic fraction. However, no positive skin reactions were seen to the rapidly wandering relatively pure electrophoretic fraction. Provocation tests were made in Cases 1 and 2, whereas they could not be made in the third case. These tests were totally negative with 25 units.

In this way, a diagnostic test of great importance to the patient could be used without side effects in Case 2. Further, the allergenic role of protein or peptide impurities may be the explanation for the local reaction appearing in Case 3 even after the *first* administration of ACTH. Although the patient did not have positive reaction to pork extract it seems likely that she earlier had had contact with animal tissues containing such or immunologically similar proteins and peptides, for example by eating pork or other meat. Even other authors have mentioned without comment, that their patient reacted after the first administration of an ACTH preparation (37, 46). On the basis of intracutaneous tests and passive transfer reactions, an irritative reaction can be excluded in the author's case.

Of general importance is that these test results corroborate once more the fact that in the most cases of ACTH allergy the decisive factor is neither the gland itself, nor the animal tissue but contaminations with inactive proteins or peptides. The prophylactic aim for ACTH allergy undoubtedly should be to find purer products and it is to be hoped that even the above cited purification leads to practical results. It may of course happen, that some patients sensitized to pork, react to every pig extract, and therefore whale seems to be better as a starting material for ACTH purification. Further, it may occur that certain patients who have been sensitized to cruder products even react to pure(r) ACTH. Finally for theoretical

reasons even a sensitivity to the gland product itself may exceptionally occur. But it can be assumed that when using pure ACTH products, the incidence of ACTH sensitivity will be decisively lower than now.

SUMMARY

After evaluation of the relevant literature three cases of ACTH allergy are mentioned two with urticaria and one with local reaction at the injection site and bronchial asthma. Intracutaneous tests with ACTH and pituitary extracts of different sources were positive, whereas no reaction to animal tissues were found. However, no reactions were found to human ACTH and to a purified porcine preparation separated by paper electrophoresis. Even provocation tests with 25 units of the porcine preparation were negative and in one case a diagnostic ACTH test could be made without side effects. In this way, the allergenic role of contaminations with inactive proteins and peptides is corroborated. The production of human ACTH preparation is impracticable, however, the purification of the ACTH products promises a decrease of the incidence of ACTH allergy.

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