

STUDIES IN CONTACT-DERMATITIS*

VIII. THE EFFECT OF FEEDING OF ANTIGEN ON THE SUBSEQUENT DEVELOPMENT OF SKIN SENSITIZATION

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IN EXPERIMENTS on the guinea pig, Chase¹ demonstrated that feeding of certain chemicals to the nonsensitive animal established a blocking effect of substantial degree against subsequent sensitization of the skin by the same agent. A 1 per cent solution of dinitrochlorobenzene in olive oil in amounts of 0.3 ml. was fed the animals from the tip of a pipette. The feedings were made daily for 6 days, and were followed by a rest period of 8 days. After 2 or 3 such courses and a rest period of 2 weeks, the animals were given 6 or more intracutaneous injections of the antigen over a period of several weeks. Two weeks after the final injection a contact test was performed. A blocking effect was demonstrated. Though it was not absolute, it was of significant magnitude in a large number of animals, it was specific, and it was durable (up to 31 weeks).

This work naturally raised the question of the role of the ingestion of antigen as an inhibitor of skin sensitization in human beings. In re-examining notes on unpublished experiments in 1937 on sensitization of the human skin with krameria^{2, 3} I found that a group of 9 subjects had been given krameria orally prior to an attempt to induce sensitivity of the skin to the same excitant. This particular experiment had been carried out to determine whether the ingestion of krameria would influence the development of skin sensitization. Since complete inhibition had not been demonstrated, and since the majority of the subjects had become sensitized at some stage in the investigation, the study was discontinued.

After Chase's reports on animals, my findings were re-analyzed. Though the data suggested that some inhibitory effect had been produced by the prior ingestion of the antigen, the evidence could not be evaluated fully since planned controls had not been included. Therefore the investigation was resumed recently under more favorable experimental conditions. The findings in this study are presented in this report.

The subjects employed were adults, either patients in the allergy clinic under treatment for hay fever, allergic rhinitis, and asthma, or mothers of allergic children. While it was originally intended to include at least 20 test subjects and a like number of controls, the final number who cooperated up to the completion of the experiment was smaller.

There were 11 test subjects, 1 male and 10 females, ranging in age from 17 to 54 years. Twenty-four ounces (710 ml.) of the official tincture of krameria (U.S.P.X) was established as the total dose. It was to be taken over a period of 8 weeks. Each subject was instructed to drink 1 teaspoonful (approximately 4 ml.) of the medication diluted in 1 ounce (30 ml.) of water 15 minutes before meals. One-half of the subjects were to continue this procedure for the full

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dose. In the other subjects there were alternate periods of ingestion of the excitant followed by rest periods as follows: 1 teaspoonful (approximately 4 ml.) of the drug was to be taken 3 times daily for 2 weeks, then after a rest period of 1 week, 2 teaspoonfuls (approximately 8 ml.) of the medication were to be taken for 1 week, followed by another rest period of 1 week. This schedule was followed until the full dose had been taken.

The alternate plans had been prescribed in order to determine any difference in protective effect in respective groups. Actually it was possible to persuade only 4 of the subjects to take the drug continuously, and 7 took it in interrupted courses. In a few instances there were slight variations from the established procedures, but the general plan was carried out for the most part.

The procedure of sensitization was begun 2 weeks after the last dose of the drug had been taken. The fluidextract of *krameria* (N.F. VII) was used as the antigen. This preparation represented 1 Gm. of the dried drug in 1 ml. of the vehicle which contained 60 per cent alcohol. The tincture employed in the feeding experiments contained an amount of drug which compared to that in the fluidextract in the ratio of 1:5.

To induce sensitization a one-half inch square of white blotting paper was saturated with 3 drops of the excitant and applied as a patch test to the unbroken skin of the arm for 24 hours. If no reaction ensued the application was repeated at an adjacent area for the same period. In the absence of a reaction, this procedure was repeated each week. In a few instances there were unavoidable minor variations from this plan (see Table I).

There were 10 control subjects, all women, ranging from 27 to 56 years of age. Sensitization was induced in a manner identical with that employed in the treated subjects. There was an occasional unavoidable deviation from the general plan (see Table II). It was not believed that such minor deviations could influence the final outcome.

RESULT

Test Subjects.—Sensitivity was induced following from 1 to 4 applications of the excitant (Tables I and II). It occurred after 4 patch tests in 3 subjects, after 3 in 2 subjects, after 2 in 4 subjects, and after a single application in 2.

The intensity of reactions was graded in 3 degrees: a mild response consisted of erythema and infiltration; a moderate, of papule and early vesicle formation; and a marked, of distinct vesiculation. There were 4 mild, 5 moderate, and 2 marked reactions. As another index of intensity of reaction, spontaneous flare-up³ occurred in 4 subjects (Table I).

Control Subjects.—Sensitivity was induced in the controls after from 1 to 5 applications of the antigen (Tables II and III). It occurred after 5 patch tests in 1 subject, after 4 in 3 subjects, after 3 in 2 subjects, after 2 in 3 subjects, and after a single application in 1. There were 3 mild, 4 moderate, and 3 marked reactions. Spontaneous flare-up occurred in 5 subjects.

DISCUSSION

I realize that a series of 11 test and 10 control subjects is a small one indeed. It was difficult, however, to get thorough cooperation in a large group of human

TABLE I.

SUBJECT	SEX	AGE	FEEDING METHOD*	DIAGNOSIS	APPLICATION 1		INTERVAL IN WEEKS BETWEEN APPL. 1 & 2
					DURATION IN DAYS	REACTIN	
S. B.	F	44	I	All. rhinitis polyps	1	0	2
J. F.	F	18	C	All. rhinitis	1	0	2
G. M.	F	19	C	All. rhinitis	2	0	2
I. F.	F	37	I	All. rhinitis	1	0	2
Y. K.	F	49	I	Br. asthma	1	0	2
R. G.	F	33	I	All. rhinitis	1	0	2
L. G.	F	17	I	Br. asthma	1	0	2
M. S.	F	49	I	Hay fever	1	0	2
A. C.	F	54	C	All. rhinitis	1	0	3
S. S.	M	39	I	Br. asthma	1	mod.	
A. G.	F	44	C	All. rhinitis Br. asthma	1	mod.	

*I = Interrupted.

C = Continuous.

TABLE II.

SUBJECT	SEX	AGE	DIAGNOSIS	APPLICATION 1		INTERVAL IN WEEKS BETWEEN APPL. 1 & 2	APPLICATION 2		INTERVAL IN WEEKS BETWEEN APPL. 2 & 3
				DURATION IN DAYS	REACTION		DURATION IN DAYS	REACTION	
J. M.	F	32	*	1	0	2	1	0	1
S. E.	F	38	*	1	0	2	1	0	2
M. W.	F	39	*	1	0	2	1	0	1
A. T.	F	38	Hay fever	1	0	2	1	0	1
E. D.	F	27	*	1	0	2	1	0	1
M. WE.	F	46	Hay fever	2	0	2	1	0	1
M. Z.	F	27	*	1	0	2	1	mod.	
B. Z.	F	27	*	1	0	2	1	mod.	
A. M.	F	28	*	2	0	2	1	mkd.	
F. R.	F	56	Hay fever	2	mild				

*Mothers of allergic children.

subjects because of the unpleasant taste of the drug and the discomfort brought on by the positive reactions on the skin. There were some who started the experiment but did not continue it to completion.

Careful examination of the results in this series, however, leads one to the conclusion that in terms of intensity of reaction and number of patch-test applications required to produce sensitivity there was no essential difference in the test and control groups.

Chase¹ observed that the protection afforded by prior feeding of antigen was not absolute; it remained possible that the protective effect could be over-ridden by intensive treatment with the allergen. In my study in 1937 on human subjects, neither the feeding of antigen nor patch-test treatment with it followed any established procedure. One got the impression, however, that some inhibitory effect might be present, but it was not definite because of lack of suitable controls. From the present series, no such difference in the end result could be demonstrated.

It is to be noted, moreover, that the feeding of antigen was stopped 2 weeks prior to the first sensitizing application of the excitant. This procedure had been adopted in order to parallel the general plan followed by Chase.¹ Whether

TEST SUBJECTS

APPLICATION 2		INTERVAL IN WEEKS BETWEEN APPL. 2 & 3	APPLICATION 3		INTERVAL IN WEEKS BETWEEN APPL. 3 & 4	APPLICATION 4		SPONTANE- OUS FLARE- UP AT SITE
DURATION IN DAYS	REACTION		DURATION IN DAYS	REACTION		DURATION IN DAYS	REACTION	
1	0	1	1	0	1	1	mod.	2-3
1	0	1	1	0	1	1	mod.	3
1	0	1	1	0	1	1	mild	
1	0	1	1	mod.				2
1	0	2	1	mkd.				1-2
1	0	1	1	mild				
1	mild							
1	mod.							
1	mkd.							

CONTROL SUBJECTS

APPLICATION 3		INTERVAL IN WEEKS BETWEEN APPL. 3 & 4	APPLICATION 4		INTERVAL IN WEEKS BETWEEN APPL. 4 & 5	APPLICATION 5		SPONTANEOUS FLARE-UP AT SITES
DURATION IN DAYS	REACTION		DURATION IN DAYS	REACTION		DURATION IN DAYS	REACTION	
1	0	1	1	0	3	1	mod.	4
1	0	1	1	mild				
1	0	1	1	mild				3
1	0	1	1	mod.				1-2
1	mkd.							1-2
1	mkd.							1

TABLE III. REACTIONS OF SENSITIZATION

	NUMBER OF TEST SUBJECTS	NUMBER OF CONTROL SUBJECTS
Number applications required to sensitize		
1	2	1
2	4	3
3	2	2
4	3	3
5		1
Intensity of reactions		
mild	4	3
moderate	5	4
marked	2	3
Total subjects	11	10

the continued ingestion of antigen would have altered the final outcome can be determined only by further study.

SUMMARY

Eleven adults ingested 24 ounces (710 ml.) of the tincture of krameria in teaspoonful doses (approximately 4 ml.) over a period of 8 weeks. Two weeks

later patch-test applications were made with the fluidextract of krameria. In the absence of any reaction they were repeated at spaced intervals until evidence of sensitization was demonstrated. There were 10 control subjects in whom repeated patch-test applications were made according to the procedure followed in the prepared subjects.

All test subjects and controls were sensitized. No difference existed in both groups, either in intensity of induced reactions or in the number of patch-test treatments required to provoke sensitization.

CONCLUSION

The feeding to human beings of an antigen, krameria, did not produce a blocking or inhibiting effect to subsequent skin sensitization with the same antigen.

REFERENCES

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3. Grolnick, Max: Studies in Contact-Dermatitis. IV. The Spontaneous Flare-up of Negative Test-Sites in Experimental Sensitization in Man, *J. Immunol.* 41: 127, 1941.