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STUDIES IN TOBACCO HYPERSENSITIVITY

II. THROMBOANGIITIS OBLITERANS WITH POSITIVE URTICARIAL SKIN REACTIONS AND NEGATIVE REAGIN FINDINGS

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In previous publications (1, 2 and 5), attention has been called to the fact that patients suffering from thromboangiitis obliterans have a skin hypersensitiveness to tobacco and, in some cases, to other allergens (frequently inhalants (1, 5)). This is demonstrable by the fact that these patients react with immediate wheal reactions to the intradermal injection of the allergens in question.[2]

In the following, we report the results of passive transference experiments with the sera of 22 unselected consecutive cases of thromboangiitis obliterans; as well as with the sera of 3 patients suffering from other conditions, who also had a marked immediate wheal reaction to intradermal skin tests with tobacco.

The technic which we have employed in our passive transference experiments is one which has been used by one of us (S.) in many hundreds of experiments, during the last eight years. We believe that

[1] We wish to thank Drs. Saul Samuels, H. Harold Gelfand and N. Nathaniel Smith of the German Polyclinic for placing their clinical material at our disposal.

[2] Although many years of diligent research have been devoted to the subject, the question has not yet been answered, as to why only certain individuals become sensitized in asthma, hay-fever, etc. It is not surprising, therefore, that the underlying causes of this more recently studied hypersensitiveness are also beyond our knowledge. We have not discussed the question from this viewpoint because, as yet, too little is known concerning tobacco hypersensitivity.

However, it is probable that the intensity of contact and the quantity of allergen play a definite rôle in the sensitizations to tobacco.

This may constitute one reason why the subjects of thromboangiitis obliterans, who are frequently very heavy smokers (Barker), have a higher percentage of positive skin tests to tobacco than any other group we have examined (see page 88).

accurate results and the avoidance of false positives can best be accomplished by this method. The procedure is as follows: One takes, at approximately the same time, the blood of the patient to be examined and, as control, the blood of a normal, non-sensitive individual, previously found negative to skin tests with the allergen or allergens in question; the bloods are allowed to clot; they are centrifuged and the serum is then removed and kept on ice, in sterile containers.[3]

The test individuals to whom the attempted passive transference is to be made must have been previously skin-tested and must have been found to be negative to the given allergen or allergens. They must also be found to be free from dermographism or traumatic whealing. The skin sites used should, of course, be free of hypertrichosis, acne, etc.

For the purpose of the experiment it is usually best to select a large area of clear skin, so that the sera may be injected into a sufficient number of sites, permitting convenient and accurate simultaneous observation. The serum being investigated and the normal control serum are injected intradermally in quantities of 0.1 to 0.2 cc. in exactly symmetrical sites, i.e., if for instance 0.1 cc. of the one serum is injected in the skin over the left scapula, 0.1 cc. of the other serum must be brought into the skin of the corresponding area over the right scapula. Sufficient sites should thus be injected to carry out the contemplated experiments and the necessary controls. A minimum of three sites is required:

1. The site at which the serum being investigated for reagins will later be tested by injection of the allergen in question;

2. A normal serum site, which should be symmetrically placed to site 1, in which the allergen in question will subsequently be injected in the same amount and concentration as at site 1; and

3. A second site prepared with the serum being investigated, which will later be injected with a control substance, such as normal saline solution, or an allergen to which neither the donor of the serum being investigated, nor the donor of the normal serum, nor the recipient of the passive transfer experiment has reacted.

Site 3 serves the purpose of proving that a specific hypersensitivity is being transferred, and not simply a non-specific quality of the serum to produce whealing subsequent to any form of injection or trauma.

[3] We have not mentioned the many other obvious precautions for sterility of the sera. All donors must have negative Wassermann reactions. The sera may be passed through an ultra-filter, or 0.5 per cent phenol may be added. Neither of these measures interferes with the experiment.

All the serum sites must be clearly marked, either with adhesive tape or by some other means, so that they can readily be found twenty-four to forty-eight hours afterwards. The allergen injection and the control injection are made twenty-four to forty-eight hours after the serum injections. At least two, and preferably more, different test individuals must be used for each experiment, so that a false negative finding may not be caused by the chance use of a test person refractory to passive transference.

The passive transference is considered successful only when site 1 shows a definitely stronger reaction regarding growth of wheal and/or erythematous flare than the other sites. To obviate false whealing, not more than 0.01 cc. of the allergens should be injected.

Employing the above technic, we carried out passive transfer experiments with the sera of 22 patients suffering from typical and proven thromboangiitis obliterans (T. A. O.).

Nineteen of these had reacted to tobacco extracts with immediate wheal reaction of from + to +++ (+). (See table 1.)

We also attempted passive transference with the sera of 3 patients without thromboangiitis obliterans, who had, however, given marked wheal reactions to direct intradermal tobacco tests. One was a man with chronic rheumatic heart disease (patient 24 in table). The second was a middle-aged woman with a neuritis of the right arm and shoulder, clinically proven to have been repeatedly precipitated by the use of tobacco (patient 23 in table). The third was a case of coronary disease with anginal pains (patient 25 in table).

With the exception of 2 sera, patient 8 (thromboangiitis obliterans) and patient 24 (rheumatic heart disease), *none of the 25 cases investigated had demonstrable reagins to tobacco.*

Each serum was injected into at least 2 test individuals; some sera were injected into as many as 10 and 12 test individuals; and the average number of test individuals used for the attempted passive transference with each serum was 5. From some donors several specimens of blood were taken and examined.

The following extracts were used in our experiments: (*a*) Lederle's combined tobacco allergen, undiluted; (*b*) Arlington and Company's combined tobacco allergen, 1:100; (*c*) an extract

TABLE 1

Results of direct tests and passive transference experiments of tobacco hypersensitivity

PATIENT	DIAGNOSIS	RESULTS OF DIRECT TEST WITH TOBACCO	RESULTS OF EXPERIMENTS IN PASSIVE TRANSFERENCE OF TOBACCO HYPERSENSITIVITY		REMARKS
			Negative	Positive	
1. Sol. Alb.	T.A.O.	++	In 5 test individuals		
2. Sol. Blo.	T.A.O.	++	In 5 test individuals		
3. Ab. Her.	T.A.O.	(+)	In 8 test individuals		
4. Ab. Kat.	T.A.O.	(+)	In 8 test individuals		
5. Alex. Lam.	T.A.O.	+	In 5 test individuals		
6. Rafalowitz.	T.A.O.	+++ (+)	In 10 test individuals		
7. Sam. Rot.	T.A.O.	0	In 2 test individuals		
8. Max. Sil.	T.A.O.	+++	In 5 test individuals	In 7 test individuals	Direct tests with dust, feathers and kapok also positive. Reagins to dust giving stronger passive transference than those to tobacco.
9. Rubin. Z.	T.A.O.	++	In 5 test individuals		
10. Barney. Zu.	T.A.O.	0	In 2 test individuals		
11. P. Torr.	T.A.O.	++	In 3 test individuals		
12. Cl. Mc.	T.A.O.	0	In 2 test individuals		
13. Mur. Kr.	T.A.O.	+	In 5 test individuals		
14. L. Mil.	T.A.O.	+	In 5 test individuals		
15. Ab. Cla.	T.A.O.	+	In 5 test individuals		
16. H. Hec.	T.A.O.	++	In 5 test individuals		
17. Wm. Bri.	T.A.O.	+	In 5 test individuals		
18. Her. Schi.	T.A.O.	+++	In 5 test individuals		
19. Ph. Ele.	T.A.O.	+	In 5 test individuals		
20. Ab. Nic.	T.A.O.	++ to +++	In 3 test individuals		
21. Morris. K.	T.A.O.	+	In 3 test individuals		
22. Ar. Lev.	T.A.O.	++	In 4 test individuals		
23. O. Irish.	Neuritis (tobacco?)	++	In 3 test individuals		
24. M. Tau.	Chronic rheumatic heart disease and echinococcus cyst	+++	In 5 test individuals	In 4 test individuals	Possibility that echinococcus sensitization was of some significance in production of reagins to tobacco?
25. Nuren.	Coronary disease and anginal pains	++	In 4 test individuals		

from Prince Albert tobacco, prepared by Dr. W. C. Spain of the Post Graduate Hospital; (*d*) Camel tobacco extract, from the cigarette; (*e*) Chesterfield tobacco extract, from the cigarette; (*f*) Old Gold tobacco extract, from the cigarette; (*g*) Lucky Strike tobacco extract, from the cigarette; (*h*) Murad tobacco extract, from the cigarette; (*i*) extract of pure Havana tobacco; (*j*) extract of pure Connecticut tobacco, and (*k*) a 0.4 per cent solution of nicotine sulfate. (The last named gave no definitely positive reactions in any of the cases investigated; and there were no reagins to nicotine in any of these cases, including the 2 with reagins to tobacco (1).)

The 2 cases with positive reagin findings to tobacco were the following: (*a*) (Max. Sil. No. 8 in the table), a case of thromboangiitis obliterans and without personal or familial atopy. This case was positive upon direct testing, not only to tobacco, but also to house dust, feathers (duck and chicken), and kapok. He also had reagins which gave a very strong passive transference to house dust. (*b*) (M. Tau. No. 24 in the table), a case of rheumatic cardiac disease, also "non-atopic," and with a positive immediate wheal reaction to tobacco and positive passive transference with his serum to 5 test individuals. (It is essential to note that this case also had an echinococcus cyst—polyvalence of sensitization brought about by echinococcus? (Casoni).)

From these experiments, we reach the conclusion that the findings of passive transference antibodies to tobacco is by no means a regular occurrence in thromboangiitis obliterans, nor in any way characteristic of this disease. We found such tobacco reagins in only 1 out of 22 cases, in spite of repeated experiments, the employment of as many as 10 different test individuals per case, and 10 different tobacco extracts. In the 1 case of thromboangiitis obliterans in which tobacco reagins were found, this could not be a pathognomonic finding, for even stronger reagins could be demonstrated to house dust. We also report 1 case without thromboangiitis obliterans, with positive direct skin test and reagins *to tobacco.*

Our findings of the general lack of reagins, in spite of immediate wheal reactions to tobacco in thromboangiitis obliterans, is in contradiction to the results of Harkavy et al. (2). These

observers report that the wheal hypersensitivity to tobacco is associated with the presence of "atopic reagins" to tobacco in thromboangiitis obliterans; and that they were able to demonstrate such reagins in 13 out of 20 tobacco positive cases of thromboangiitis obliterans. And that: "The presence of reagins to tobacco in these thromboangiitis cases indicates that we are dealing with individuals who were in all probability atopic, and that the positive phenomena are true antigen-antibody reactions" (reference 2, page 106, lines 27–30).

We do not wish to enter into the possible explanations for these divergent results. We merely wish to point out that, while the subjects of thromboangiitis obliterans usually exhibit a distinct skin hypersensitivity to tobacco as evidenced by the response of the vascular system of the cutis with wheal formation upon intradermal skin testing, they are not, (by family or personal history or accompanying maladies), members of the atopic group in which reagins are usually found.

Our series of thromboangiitis patients had no more frequent findings of asthma, vasomotor rhinitis, or disseminated neurodermite, in themselves or in their families, than a control group of normal individuals. Corresponding to this absence of the personal or familial stigmata of atopy, we have demonstrated a general absence of reagins to tobacco in our patients with thromboangiitis obliterans. They did, however, have a markedly increased percentage of positive skin reactions of the wheal type upon direct intradermal testing with tobacco. (Our figures now read approximately as follows: Thromboangiitis obliterans patients, 77 per cent positive; adult non-smokers, 16 per cent positive; adult smokers (without thromboangiitis), 36 per cent positive (5).)

We do not think it necessary, at this point, to enter into a discussion regarding the differentiation of atopy from other forms of hypersensitivity with positive immediate wheal reaction, nor to discuss reagins, as to their being pathognomonic of atopy (Coca, 3). *However, our above reported results must classify thromboangiitis obliterans as a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of*

the skin to tobacco, but without any at present demonstrable connection with asthma, hay-fever, and disseminated neurodermite, etc., and, in our cases, without regularly demonstrable reagins.

It must be today regarded as an established fact that hypersensitivities of the type which Coca has called "atopic," that is, which are of familial occurrence and manifest themselves, in most cases, in the form of hay-fever, vasomotor rhinitis, bronchial asthma and disseminated neurodermite, are those in which positive wheal reactions, associated with passive transference antibodies, or reagins, are found with the greatest regularity. Nevertheless, positive wheal reactions are found in cases of human hypersensitiveness not of familal occurrence and without the characteristics of the so-called atopic group (3).

In some of these "non-atopic" urticarial hypersensitivities, passive transference antibodies are regularly encountered. Thus, for example, in the acquired hypersensitivities to intestinal parasites (Rackemann and Stevens, Brunner, W. Jadassohn, Fülleborn, etc.); and also in certain phases of acquired hypersensitivity to antitoxic horse serum (Tuft and Ramsdell, Ramel).

On the other hand, there is another group of hypersensitivities of non-atopic type, in which positive wheal reactions, but *no* circulating antibodies can be demonstrated. This holds true in many asthmatic and urticarial conditions due to drugs (3). The not infrequent asthmas due to aspirin belong in this category. A case of drug hypersensitivity of this type, recently observed, may be worth citing as an example: A twenty-two year old, "non-atopic" nurse, Miss Kl., suffered from asthmatic and gastro-intestinal attacks, as well as from severe urticaria, all clinically proven to be due to contact with sulfarsphenamine. A scratch test both with sulfarsphenamine and with neoarsphenamine on the patient's arm produced an extremely strong urticarial reaction and an asthma and gastro-intestinal attack. No reagins to sulfarsphenamine or to neoarsphenamine could be demonstrated in 4 attempted passive transference experiments with this patient's serum.[4]

[4] We are greatly indebted to Dr. Albert Pfeiffer of Albany for giving us the opportunity to study this instructive case.

In addition to such drug idiosyncracies with positive wheal reactions and no reagins, other forms of hypersensitivity with positive immediate reactions and negative passive transference experiments include certain phases of acquired serum hypersensitivity (Tuft) and the acquired sensitivity to pediculoides ventricosus (Grove, 4).

The results of our experiments incline us to include the tobacco hypersensitivity of thromboangiitis obliterans in the last group, i.e., among those with positive wheal reactions and negative findings of passive transference antibodies.

We wish to reiterate that, in doing this, it is not our purpose to state that the presence or absence of reagins constitutes a fundamental difference in principle between various forms of hypersensitivity with immediate wheal reaction; on the contrary, we wish to leave open the decision as to whether the positive or negative findings of reagins may not be a quantitative matter, or due to different phases in sensitizations of the same basic nature.

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(5) For further discussion of tobacco hypersensitivity, see SULZBERGER, MARION B.: Bulletin of the New York Academy of Medicine.

(6) For further discussion of reagins, their characteristics and their occurrence, the work of Brunner, W. Jadassohn, Fülleborn, Tuft and Ramsdell, Rackemann and Stevens, etc., see reference 3.