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EFFECT OF LOCAL ADRENALINE AND HISTAMINE ON TUBERCULIN REACTIONS

BY

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The influence of vascular responses on tuberculin skin tests has been studied, by incorporating in the tests substances such as histamine and adrenaline which produce potent effects on blood vessels.

The investigation was carried out as follows:—

1. Effect of local injection of whealing agents on the intradermal tuberculin (Mantoux) test.
2. Effect of local injection of adrenaline on (A) the intradermal tuberculin test and (B) the tuberculin patch-test.

PART I.

WHEALING AGENTS AND THE MANTOUX-TEST

The simultaneous injection of high concentrations of local anaesthetic or antihistaminic drugs into Mantoux-tests together with the tuberculin has been reported by Lecomte (1952) to produce inhibition of the reaction, and he suggests that this is due to an anti-inflammatory or anti-allergic action. But, these substances are also whealing agents in the concentrations that he found to be effective and since whealing has been reported by Abrahamson and Engel (1938) and Pepys (1951) to produce considerable and rapid enhancement of the escape of substances from the skin, the escape of the tu-

berculin would appear to be a more likely explanation for the inhibition. Preliminary studies in which amethocaine 5 %, the antihistamine drug promethazine 1 % (Phenergan), and histamine diphosphate 1/1000 were injected into Mantoux tests, immediately after the injection of the tuberculin, showed that the histamine was equally effective in inhibiting the tuberculin reaction.

Materials and Methods.

Mantoux tests were carried out on 25 patients by intradermal injection of 0.10 ml. Old Tuberculin (Human T. Burroughs Wellcome) to be termed O.T. Five subjects were tested on the forearm with O.T. 1/100, and the remainder on the back with O.T. 1/1000 and 1/10,000. Injections of 0.10–0.20 ml. of histamine diphosphate and amethocaine were used to produce whealing in the tests to be described; promethazine was omitted owing to the local discomfort it produced. The whealing agents were injected into the tuberculin test sites separately from the tuberculin and equal volumes of saline were injected into control tests in corresponding sites. The reactions were read at 48 hours.

Results.

(A) In the 5 cases tested with O.T. 1/100, injections of 0.20 ml. histamine 1/1000 and 0.20 ml. amethocaine 5 % both produced complete inhibition of the reaction in 3 cases and almost complete inhibition in 2. The control reactions were very vigorous showing vesiculation or necrosis (Fig. 1). A greater area of erythema appeared at the histamine treated test in several cases, but the induration was negligible and was not comparable with the control. Similar results were obtained with other vigorous reactors and suggested that the histamine wheal by diffusing and diluting the tuberculin had produced a larger area of lower concentration.

(B) The injection of increasing dilutions of the whealing

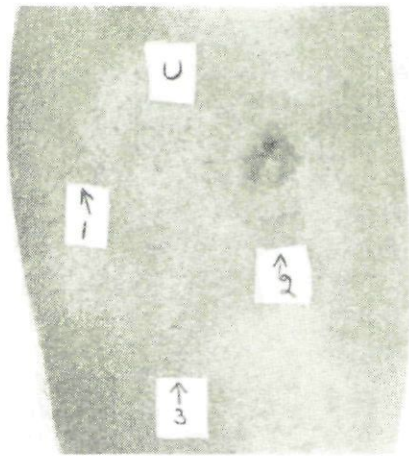


Fig. 1.
Effect of whealing agents on the Mantoux test.

Patient U. tested by intradermal injection of 0.10 ml. O.T. 1/100 at sites 1, 2 and 3.

Test 1. Inhibition of reaction by injection of 0.20 ml. amethocaine 5 %.

Test 2. Control test into which 0.20 ml. normal saline was injected shows vigorous necrotic reaction.

Test 3. Inhibition of reaction by injection of 0.20 ml. histamine diphosphate 1/1000.

agents in saline into Mantoux tests showed that the stronger the whealing agent and the larger the wheal produced the greater the inhibition of the reaction. (Table 1). Complete inhibition of 14 out of 26 individual tests was produced by the injection of 0.20 ml. amethocaine 5 % producing a wheal 427 sq. mm. in size, or 0.10 ml. histamine diphosphate 1/1000 producing a wheal 467 sq. mm. in size, whereas lower concentrations did not inhibit any of the tests completely.

(C) The injection of the whealing agents 1 hour before, at the same time, and at intervals of 5, 10, 15 minutes and $\frac{1}{2}$ –2 hours after the injection of tuberculin showed that the most effective inhibition was produced by injections given

TABLE I
Effect of scheduling agents on the intradermal tuberculin (Mantoux) test.

Whealing agents	Conc.	Average size of wheals, sq. mm.	Decrease in size of tuberculin reactions					
			No. of cases	Complete inhibition	75—100 %	50—75 %	25—50 %	Slight or no decrease
Amethocaine 0.20 ml.	5 %	427	12	8	3		1	
Amethocaine 0.20 ml.	0.5 %	224	2		1			1
Histamine Diphosphate 0.10 ml.	10 ⁻³	467	14	6	5	1		2
Histamine Diphosphate 0.10 ml.	10 ⁻⁴	307	6		2	2		2
Histamine Diphosphate 0.10 ml.	10 ⁻⁵	225	6			2	2	2
Histamine Diphosphate 0.10 ml.	10 ⁻⁶	169	6			2	1	3

Tuberculin tests carried out by intradermal injection of 0.10 ml. Old Tuberculin 10^{-3} and 10^{-4} ,
 All areas calculated according to the formula, $\pi r^1 \times r^2$.

before or at the same time as the tuberculin. Even a short delay of 10–30 minutes resulted in far less inhibition.

The amount of inhibition produced by the whealing agents thus depends on the size of the wheal produced, on the degree of hypersensitivity of the subject to the tuberculin injected, and on the time interval between the injection of tuberculin and the production of the wheal.

PART 2 A.

LOCAL ADRENALINE AND THE MANTOUX-TEST

Materials and Methods.

Mantoux tests were carried out by injection of 0.10 ml. O.T. 1/10,000 in 28 patients, 5 of whom were tested with O.T. 1/1000 as well. Injections of 0.05–0.10 ml. of Liq. Adrenaline HCl. (B.P.) were given into the Mantoux tests and equal volumes of normal saline were injected into control tests in corresponding sites, and the reactions were read at 48 hours.

(A) Injection of 0.10 ml. Liq. Adrenal. HCl. 1/1000 into Mantoux tests immediately after the injection of the tuberculin produced complete inhibition in 13 out of 33 tests, and in 11 out of the 13 the corresponding control reactions were below 100 squ. mm. in size. An increase in area of reactions was seen in those cases where control reactions were large (Table 2). The influence of the size and intensity of the control reactions on the degree of inhibition is further evident in the 5 cases tested with both O.T. 1/10,000 and 1/1000. Of these 1 showed complete inhibition at both tests; 1 showed complete inhibition with the O.T. 1/10,000 and a 78 % decrease with the O.T. 1/1000; 1 showed a 50 % decrease with the O.T. 1/10,000 and no decrease with the O.T. 1/1000, and in the 2 cases who reacted vigorously to both concentrations of the O.T. no inhibition was produced at either test.

(B) The injection, in 8 cases, of increasing dilutions of

TABLE 2
Effect of local adrenaline on the Mantoux-test.

Degree of inhibition	No. of tests	Size of control reactions in squ. mm.		
		up to 100	101-300	301-400
Complete	13	11	2	
75-100 %	3		3	
50-75 %	5	1	3	1
25-50 %	3		2	1
Slight or no change	2	1	1	
Increase in size	7	1	2	4

Total no. of tests = 33, carried out by injection of 0.10 ml. Old Tuberculin 10^{-3} or 10^{-4} , followed by injection of 0.10 ml. Liq. Adrenaline HCl, 10^{-3} into tuberculin test.

TABLE 3
Concentration of local adrenaline and effect on the Mantoux-test.

Conc. of Liq. Adrenal. HCl. in normal saline	Decrease in size of tuberculin reactions				
	Complete inhibition	75-100 %	50-75 %	25-50 %	No change or increase
10^{-3}	3		1	1	3
10^{-4}	2	1	1		4
10^{-5}		2		1	5
10^{-6}		1	1		6

8 cases tested with injection of 0.10 ml. Old Tuberculin 10^{-4} followed by local injection of 0.10 ml. Liq. Adrenaline HCl.

Liq. Adrenal. HCl. in normal saline into Mantoux tests showed that the stronger the adrenaline the more effective the inhibition (Table 3).

(C) In 18 cases timed injections of 0.10 ml. Liq. Adrenal HCl. 1/1000 were given into Mantoux tests immediately, and 2 and 3 hours after the injection of the tuberculin, and equal volumes of saline were injected into control tests in corresponding sites.

The results were as follows:—

4 cases with weak to moderate control reactions ranging from 24-94 squ. mm. showed complete inhibition up to 3

hours; 4 with slightly stronger reactions ranging from 39-132 squ. mm. showed complete inhibition up to 2 hours with decreased reactions at 3 hours; 2 with reactions of 63 and 94 squ. mm. showed inhibition only with the first injection of adrenaline; 5 with reactions ranging from 150-755 squ. mm. showed a decrease of 43-48 %; 2 with reactions of 130 and 414 squ. mm. showed no change. 1 case showed an increase in size of the reaction from 75-560 squ. mm. resembling the reactions found in tuberculin patch tests on adrenaline pre-treated skin, which will be described.

The latest time for complete inhibition of moderate reactions up to about 130 squ. mm. in size by the local injection of adrenaline 1/1000, appeared to be between 2 and 3 hours. The inhibition depended on the concentration of the adrenaline and the degree of hypersensitivity of the subject to the tuberculin.

Histology of adrenaline inhibited reactions.

The histology of adrenaline inhibited and control tuberculin reactions was studied in 3 cases. Biopsy specimens were taken under local anaesthesia 3 to 24 hours after testing, from tests performed over the deltoid region. The skin removed was 10 mm. $\times$ 3 mm. in size and extended well down to the subcutaneous tissue. The skin was fixed in Zenker's solution and 15-20 sections 5 μ thick were cut from each block, and, were examined after staining with haematoxylin and eosin. The appearances were very similar in all cases, and Fig. 2 (a) shows that at 3 hours there was a moderately vigorous cellular infiltration with neutrophile and mononuclear cells at the control test, and a very scanty cellular infiltration at the adrenaline inhibited test, Fig. 2 (b). Fig. 3 shows a similar disparity of cellular infiltration at 24 hours, the control (Fig. 3 (a)) showing both perivascular foci of mononuclear cellular infiltration with the cells lying in fairly dense almost concentric layers, and infiltration into the surrounding tissue, whilst at the adrenaline treated test there is a

Fig. 2 (a) + (b). *Histological appearances of control and adrenaline treated Mantoux tests at 3 hours. (H and E. $\times 120$).*

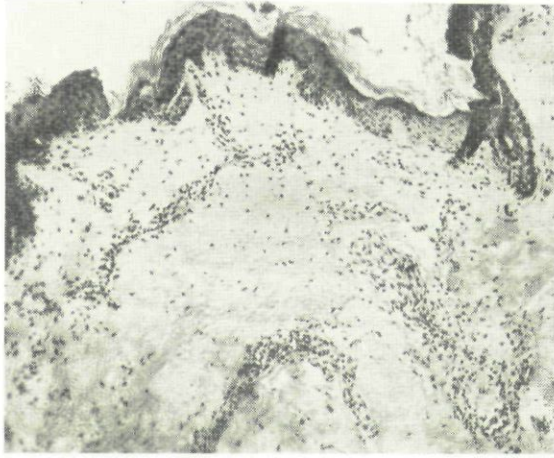


Fig. 2 (a).

Control test shows moderately vigorous cellular infiltration consisting of neutrophile and mononuclear cells. The infiltration is related to the vessels and extends into the tissues.

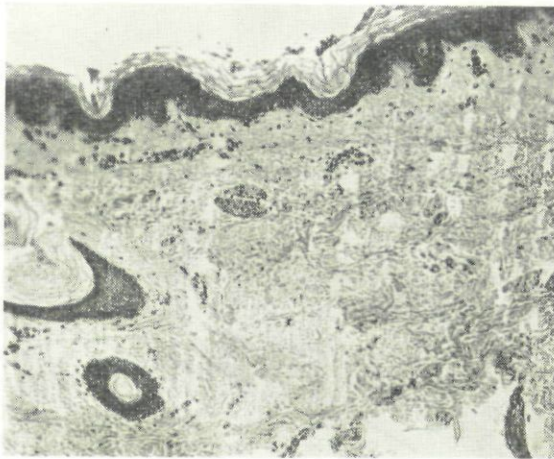


Fig. 2 (b).

Adrenaline treated Mantoux test shows very scanty cellular infiltration in comparison with the control test from the same subject and taken at the same time.

Fig. 3 (a) and (b). *Histological appearances of control and adrenaline treated Mantoux tests at 24 hours. ($\times 90$).*

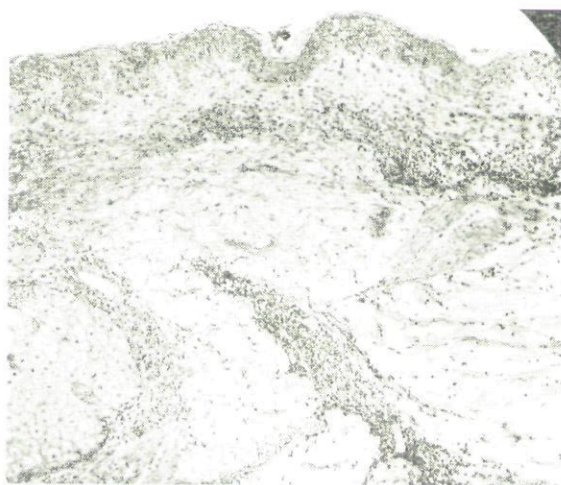


Fig. 3 (a).

Control test shows fairly vigorous mononuclear cellular infiltration, both perivascular and into the tissues.

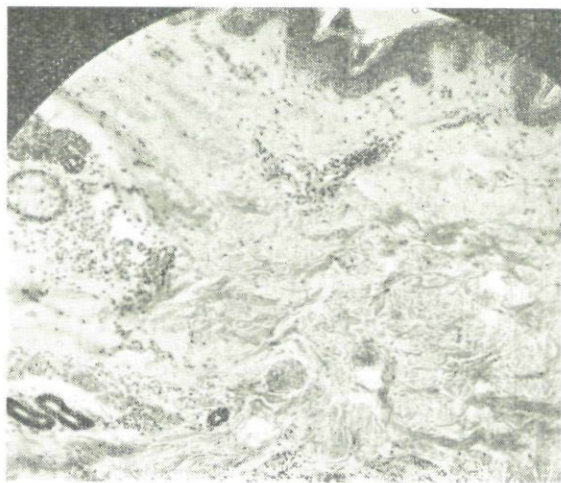


Fig. 3 (b).

Adrenaline treated test shows marked decrease in cellular infiltration as compared with the control. Both specimens were taken from the same subject tested at the same time.

mild scattered cellular infiltration. Control tests carried out at the same time gave reactions ranging from 38-78 squ. mm. The significance of the cellular infiltration will be discussed.

PART 2 B.

EFFECT OF LOCAL ADRENALINE ON THE TUBERCULIN PATCH TESTS

Materials and Methods.

The Vollmer patch tests used for testing contain 3 squares of filter paper saturated with human and bovine tuberculin and the synthetic culture medium respectively. In many cases multiple parallel tests were carried out on the back, by applying patches to normal untreated skin and to skin into which 0.05 ml. normal saline or Liq. Adrenaline HCl. (B.P.) 1/1000 had been injected immediately before the application of the patch. Patch tests were applied either over the puncture wound of the injecting needle, or over unbroken skin into which the saline or adrenaline had been injected by passing the needle horizontally under the skin and lifting the tip towards the surface so as to arise a bleb. Reactions were read 2 and 5 days after testing.

Results.

The results of the tests in 16 cases are recorded in Fig. 4. 9 out of 16 tests on normal untreated skin were positive but the reactions were small, 8 out of 9 being less than 12 squ. mm. and one 38 squ. mm. in size. 14 out of 16 tests on saline pretreated skin were positive and 12 of these were at patch tests performed over the puncture wound. The size of the reactions was less than 20 squ. mm. in 9 cases, the other three being 63, 189 and 212 squ. mm. in size. Positive reactions were obtained at adrenaline treated areas in all 16 cases, and in 14, in whom the tests were performed over the puncture wound, the reactions were below 20 squ. mm. in 4 cases; 5

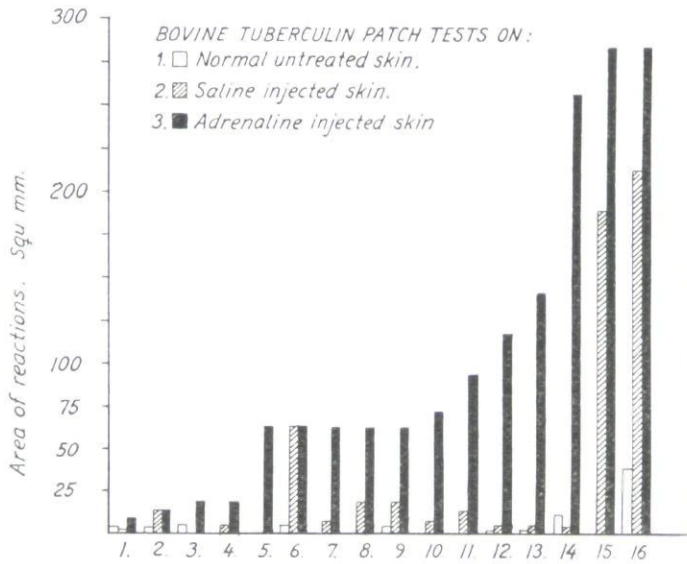


Fig. 4.

were 62–63 squ. mm.; 2 were 94 squ. mm.; 1 was 212 squ. mm. and 2 were 283 squ. mm. in size. In the 6 cases in whom patch tests were performed on unbroken skin into which saline or adrenaline had been injected, 2 positive reactions 5 and 6 squ. mm. were obtained on saline pretreated skin, whilst the 5 positive reactions obtained on adrenaline pretreated skin ranged from scattered papules to 24, 50, 142 and 257 squ. mm in size (Figs. 5 and 6). Three illustrative cases gave results as follows:—

Tests on:—

	Control untreated skin	Saline pretreated skin	Adrenaline pretreated skin
1	9. squ. mm.	5. squ. mm.	186 squ. mm.
2	0. squ. mm.	7. squ. mm.	146 squ. mm.
3	0. squ. mm.	0. squ. mm.	On puncture, 63 squ. mm. On unbroken skin, 0. squ. mm.

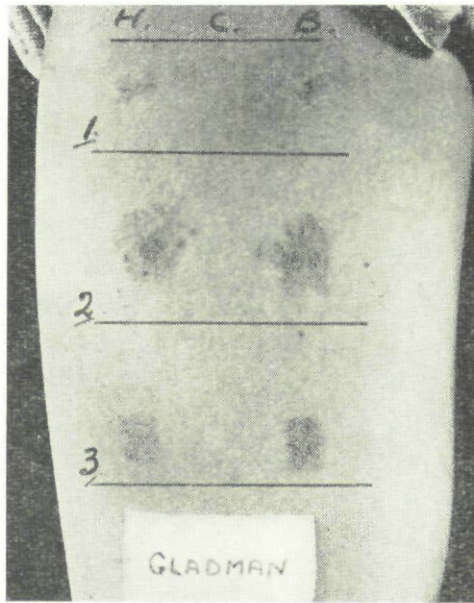


Fig. 5.

Effect of local adrenaline and saline injection on the tuberculin patch test.
(Tests applied "over the needle puncture wound").

H = human tuberculin patch test.

C = control synthetic medium patch test.

B = bovine tuberculin patch test.

1. Tests on normal untreated skin show weak papular reactions.
2. Tests on adrenaline pretreated skin show considerable enhancement of the reactions, with widespread distribution of the papules and erythema.
3. Tests on saline pretreated skin show that the puncture wound by itself enhances the reaction. The reactions are plaque like and are slightly larger than the patch tests applied. This contrasts with the extension of the reactions at the adrenaline treated site, far beyond the area of application of the patch test.

All control tests were negative.

The most vigorous reactions were thus obtained when the patch tests were applied over the puncture wound of adrenaline treated sites, at which reactions appeared as early as 24 hours after testing, the reactions at other sites appearing 3

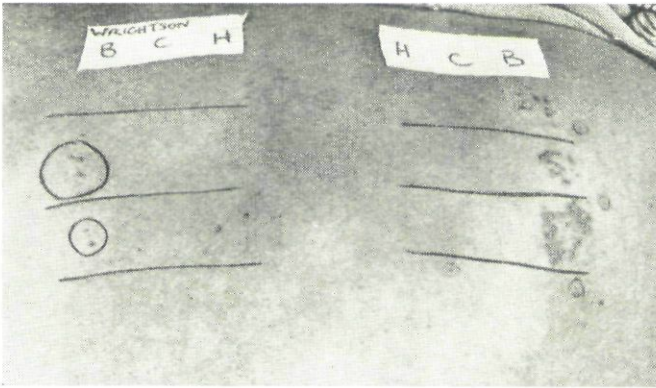


Fig. 6.

Effect of local adrenaline and saline injection on the tuberculin patch test.
(Tests applied over "unbroken adrenaline or saline pretreated skin").

H = human tuberculin patch test.
C = control synthetic medium patch test.
B = bovine tuberculin patch test.

Tests in triplicate at adrenaline treated skin on the right side and at saline treated skin on the left side.

Adrenaline treated skin. The reactions to the bovine tuberculin patch tests are moderate to vigorous and show widespread extension of the papules beyond the area of application of the patch. The small rings encircle the point of insertion of the injecting needle and lie well away, $1\frac{1}{2}$ -2 cm. from the test area.

Saline treated skin. The scanty papular reaction at the lower two bovine tuberculin patch tests have been ringed to show them more clearly, and the considerable enhancement by the adrenaline pretreatment of the skin can thus be seen to be independent of the puncture wound, which can exert an enhancing effect as seen in Fig. 5.

All control and human tuberculin tests were negative in this case.

or 4 days later. Scarification of the skin is well known to enhance patch tests and this was evident at patch tests applied over the needle puncture wound, but the local adrenaline clearly exerted an additional enhancing action, which was seen in tests on unbroken adrenaline treated skin.

Fig. 7 (a) and (b). *Effect of local adrenalin and histamine on the escape of dye from the skin.*

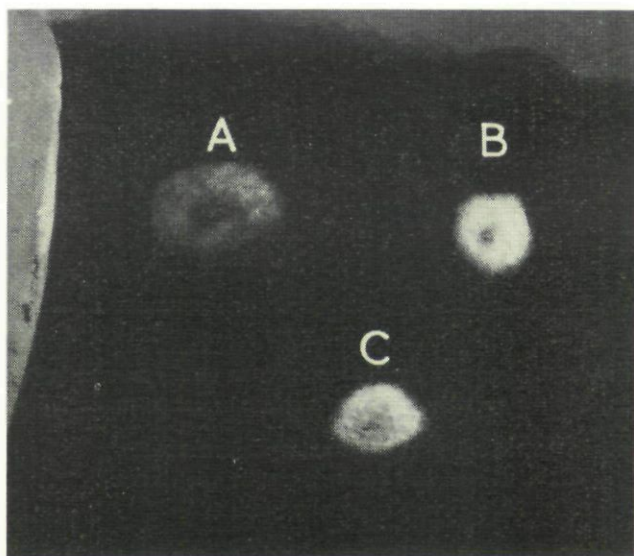


Fig. 7 (a).
One hour after testing.

- A. Intradermal injection of 0.05 ml. 5 % sodium fluorescein plus 0.05 ml. normal saline followed by 0.02 ml. Hist. Diphosph. 1/1000. Fluffy mottled appearance and enhanced escape of dye can be seen.
- B. Control test consisting of injection of 0.05 ml. 5 % sod. fluorescein plus 0.05 ml. normal saline. Some spread of dye forming homogeneous patch with clear central area at point of injection.
- C. Intradermal injection of 0.05 ml. 5 % sod. fluorescein plus 0.05 ml. Liq. Adrenal. HCl. 1/1000; appearances similar to those of the control.

Effect of local histamine and adrenaline on the escape of substances from the skin.

This was studied by injecting a 5 % sodium fluorescein solution in normal saline into the skin and observing it under the fluorescence lamp. Intradermal injections of 0.05 ml. of the fluorescein plus 0.05 ml. normal saline were given into two sites into one of which a further 0.02 ml. of histamine

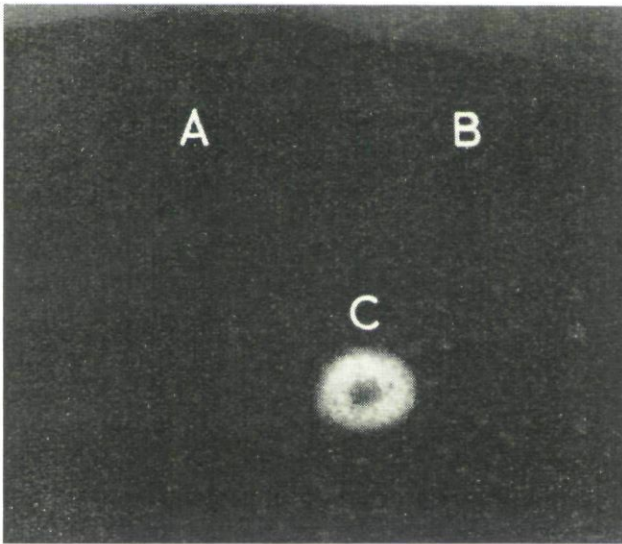


Fig. 7 (b).
Six hours after testing.

Disappearance of dye at (A) histamine and (B) control tests. At (C) the adrenaline treated site, the dye has persisted as a still dense and homogeneous patch showing only a slightly hazy outline with a clear central area at the point of injection. The dye appears to have spread superficially in the skin and covers a wider area.

(The photographs were taken by means of an electronic flash through a Wood's filter.)

diphosphate 1/1000 was injected. An injection of 0.05 ml. fluorescein plus 0.05 ml. Liq. Adrenaline HCl. 1/1000 was given into a third site. Fig. 7 (a) shows the appearance 1 hour after testing, by which time the histamine treated area showed a fluffy mottled appearance with enhanced escape of the dye into the deeper tissues. The other two tests showed only an increased area of dye, but the control site later developed a fluffy appearance like that of the histamine treated test, though with a more gradual escape of the dye. At 6 hours (Fig. 7 (b)) both the histamine treated and control tests had lost virtually all the dye, whereas the adrenaline treated site

showed a clearly outlined homogenous superficial patch of dye which had spread horizontally in the skin and at which the dye was still visible 10-14 hours after testing, with complete disappearance after 20 hours.

DISCUSSION

There are several problems of interest arising out of these findings.

(A) Local injection of histamine or adrenaline, which produce opposing vascular effects, both inhibit the intradermal tuberculin test.

(b) Local adrenaline inhibits the intradermal tuberculin test and enhances the tuberculin patch test.

1. *Inhibition of the Mantoux test by whealing.*

Whealing enhances the absorptive velocity of the skin, and in this case the escape of the tuberculin antigen from the test site would prevent the reaction. In many conditions in clinical practice, in which negative reactions are obtained, a similar mechanism seems to be involved. In cachexia, in premenstrual and pregnant females, in infectious diseases and in pyrexial illnesses the inhibition of the tuberculin reaction has been explained, in a vague manner, as an anergic reaction. Gernez and Marchandise (1935) and Seeberg (1947) found that in these conditions, as measured by the Aldrich McClure test, the absorptive velocity of the skin was increased. This test consists of the timing of the rate of absorption of the bleb raised by intradermal injection of 0.10 ml. of normal saline. They found that in all the above conditions the absorptive velocity of the skin was increased and "pari passu" the tuberculin reaction was decreased. Gernez and Marchandise also showed that the production of artificial pyrexia was associated with an increased absorptive velocity of the skin,

and if produced within 5-7 hours of the tuberculin injection it inhibited the reaction. This effect, like that of the whealing appears to be due to the decrease in the local concentration of the antigen and not to any immunological mechanism.

2. *Inhibition of the Mantoux test by local adrenaline.*

The vasoconstriction produced by the high concentrations of adrenaline used here results in visible blanching which persists for 10-12 hours. This is associated with a decrease in blood flow through the skin and as a result a decrease in the passage of circulating substances and cells into the tissues, which has been amply demonstrated by Evans, Miles and Niven (1948) in investigations of the influence of local adrenaline on experimental infection in the guinea pig. There are two possibilities to be considered at this point. If the early cellular infiltration is a non-specific inflammatory response to the injection of tuberculin, the vasoconstriction would be exerting an anti-inflammatory effect by preventing the emigration of circulating cells into the part. If, on the other hand, the early cellular infiltration is participating specifically in the reaction, the vasoconstriction would be preventing the initiation of the reaction by retarding the passage of these cells into the tissues. The latter possibility, namely that the lymphoid cells or circulating lymphocytes are acting as carriers of antibody in tuberculin hypersensitivity is indicated by a brief survey of the available evidence.

(a) Lymphoid cells and circulating white blood cells, in particular the lymphocyte (Wesslen 1952), have been reported to produce passive transfer of tuberculin hypersensitivity (Chase 1945, Lawrence 1949, 1952). The dose of cells injected was found to determine the degree of hypersensitivity transferred.

(b) Tuberculin has been reported to be toxic to tissue cultures of lymphoid cells and circulating white cells (Rich and Lewis 1932) and non-toxic for tissue cultures of skin

from tuberculin hypersensitive subjects (Cruickshank 1951, Everett et al. 1952).

(c) "In vitro" lysis of circulating lymphocytes from hypersensitive subjects, within 20 minutes, by tuberculin has been reported. (Favour 1947).

All these findings suggest a direct participation of the circulating lymphocyte in tuberculin reactions as a carrier of antibody, and the exclusion of these cells by the vasoconstrictor effect of adrenaline may explain the inhibition observed. The role of local or resting reticulo-endothelial cells in the later stages of the reaction is not questioned and does not appear to arise here.

In comparing the inhibitory effects of histamine and adrenaline it seems likely that the histamine has modified the availability of the antigen, and the adrenaline the availability of the antibody.

3. *Enhancement of the patch test by local adrenaline.*

It seems strange that adrenaline inhibits the intradermal tuberculin test and yet enhances the patch test. As an explanation for this, it is suggested that the tuberculin penetrates slowly into, and escapes slowly from the epidermis. This escape would be retarded by the adrenaline produced vasoconstriction, just as was seen with the retention of the fluorescein. In this way the concentration of the tuberculin in the skin would increase steadily during the 10-12 hours of vasoconstriction, so that with the passing off of the vasoconstriction an optimal concentration of tuberculin would be present in the skin to provoke a reaction. The widespread papules seen in Figs. 5 and 6 suggest that the tuberculin has also spread superficially in the skin, just as was seen with the fluorescein under the influence of local adrenaline. The reaction may also be aided by the reflex vasodilatation which follows on the vasoconstriction and which can be seen as dusky erythematous spots in adrenaline blanched skin within several hours of the adrenaline injection. The influence of differences in the local

concentration of the tuberculin may explain the opposing responses, of the intradermal tuberculin test and the patch test, to the injection of adrenaline, and this may arise as follows:—

1. The tuberculin is at its highest local concentration at the intradermal test from the beginning, so that even with a retarded escape from the tissues the local concentration will have fallen, probably below the reacting level, before the vasoconstriction passes off. On the other hand, with the patch test the concentration of tuberculin in the epidermis must necessarily be increasing during the same period of time and it does appear to have risen above the reaction level.

2. The rate of escape of the tuberculin from the intracutaneous tissues would in any case be expected to be more rapid than from the epidermis. Thus, the time factor and the vasoconstriction produced by the adrenaline would appear to have hampered the access of antibody during the fall in concentration of the tuberculin in the intradermal test, whilst in the patch test an increased concentration of tuberculin in the skin would be favoured. The effect of adrenaline on the pH and the reducing intensity of the guinea pig skin described by Evans et al. should not be overlooked, but they suggest that the vasoconstriction, by hampering the access of circulating substances and cells into the skin, is the dominant factor in the enhancement of experimental infection by local adrenaline. It seems, too, that the vasoconstriction is the most significant element in the effects which adrenaline produces on the tuberculin skin tests.

The view that all the tissues of the body are hypersensitive in tuberculin hypersensitivity was put forward by Rich (1946) because tuberculin reactions can be elicited in the avascular cornea. This is in contrast to immediate type hypersensitivity reactions, such as the Arthus reaction, which cannot be elicited in the avascular cornea (Rich and Follis 1940) and in which the blood vessels are a shock organ. Whilst the blood vessels do not appear to be a shock organ in tuberculin reactions they participate in the production of the reactions by (a) acting as a "via media" for the antibody carrying cells and (b)

because of the influence of the circulation and lymphatic absorption on the retention of the antigen at the test side. In tuberculin reactions of the cornea it has been reported that the earliest cellular response is at the limbal vessels (Long, Holley and Vorwald 1933). In the case of the epidermis there is a view that the epidermis participates directly in delayed type reactions, such as the patch test tuberculin reaction. In this instance as well, the functional participation of the blood vessels requires consideration. It seems possible that the slower penetration and absorption of substances from the epidermal tissues may have created the impression that they are participating as a source of reacting antibody, though there is evidence that chemical contact sensitizers may be made fully antigenic by combination with protein in the skin. (Eisen, Orris and Belman 1952). The findings described suggest, that the delayed nature of the tuberculin reaction may be due in part to the time required for the arrival and migration of sufficient antibody carrying cells into the tissues, and for their reaction with the antigen so as to excite an inflammatory response.

SUMMARY

1. The local injection of whealing agents such as histamine into Mantoux tests inhibits the reaction, by enhancing the escape of the tuberculin from the test site.
2. The local injection of adrenaline inhibits the Mantoux test, and this is attributed to the marked decrease in the cellular infiltration which was found on histological examination. It is suggested that the vasoconstriction produced by the adrenaline hampered access of antibody carrying lymphocytes into the test area.
3. The local injection of adrenaline enhances the tuberculin patch test and it is suggested that this is due to the retention of the tuberculin in the skin, as shown by the retaining action of adrenaline on fluorescein injected intradermally.
4. Blood vessels appear to participate in the production

of the tuberculin reaction by (a) bearing antibody-carrying cells to the test site and (b) by the influence of the circulation on the escape of the tuberculin from the test site.

5. The delayed nature of the tuberculin reaction may be due to the time required for the arrival and migration of antibody carrying cells into the test site, where, after combining with the antigen an inflammatory response is elicited.

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