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THE REACTIVITY OF TUBERCULOUS SKIN AREAS TO TUBERCULIN

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The study of allergic reactions became greatly simplified since v. Pirquet has demonstrated that an evaluation of a change in the reactivity is possible not only by the general reaction, as thought previously, but also by the course of local reactions. According to his proposal, skin tests enable us to undertake the study of a whole range of problems of immunity processes in a detailed and reliable manner. The cutaneous reaction serves as a symptom by which an orientation on the reaction state of the entire organism is provided. In certain cases the cutaneous reaction is an indication of the course of localized, not generalized allergic processes as well. To these belong the investigations by v. Pirquet on the course of re-vaccination and tuberculin reactions on areas where a specific inflammation had already occurred. He was able to demonstrate that, by the exact observation of the reaction intensity and its time course, an insight into the mechanism of this phenomenon can be gained. He found quite regular relationships between tuberculin concentration and reaction intensity on one hand, and between antibody concentration and the course of the reaction in time on the other hand. The investigations were started by the observation that skin areas which have already been exposed to tuberculin show a different behavior following a repeated inoculation. The cause of this was thought by v. Pirquet to be a local concentration of antibodies. Romer was the first to indicate by his experiments with ricin and abrin that a localized antibody reaction, that is, one in a certain tissue or at a topographically defined area of the body, exists in addition to the general antibody production, for which the hemopoietic organs were made responsible at the time. By their experiments with typhoid bacilli, Wassermann and Citron also came to the conclusion that the tissue which is directly in contact with the toxin is primarily involved in the antibody production. The existence of local differences in the antibody production in tuberculosis is derived from the above mentioned findings of v. Pirquet. A series of other findings from clinical experiences, mainly with skin tb, also support this view. Nagelschmidt observed a different type and more pronounced reaction following intrafocal inoculation into lupus foci than when the vaccine was ad-

ministered to normal skin areas of the same individual. The experience of Bandler and Kreibich also belongs here; they observed that a cutaneous reaction between lichen nodes produced extraordinarily severe reactions. These cases indicate that on skin areas where acute, either manifest or clinically latent tb processes occur, the tissues respond to the local application of tuberculin with an increased reactivity.

These findings seem to be of great importance in the processes of a tuberculous inflammation. They provide no information, however, on individual details, for instance whether the increased reactivity is limited to the defined area of the inflammation only, or what influence the stage of the primary inflammation, at the time of the renewed introduction of the antigen, has on the course of the reaction.

Our investigations were intended to fill the existing gaps. Skin areas which reacted strongly to the previous administration of cutaneous or intracutaneous doses of old tuberculin (Alttuberkulin) were used as tuberculous tissue. The experimental use of this artificially produced skin tuberculosis instead of spontaneously developed tuberculous foci of the skin has the following reasons.

It enabled us to select, at any time, the area which seemed best suited for the application, and the exact observation of the development and course of the tuberculous process made it possible to initiate the second reaction always at a suitable moment. The secondary vaccinations which were made for purposes of the investigations were divided into two groups according to the stage of the primary processes; in the first group, the second vaccination was made during the acute inflammatory process, in the second group, it was made in skin areas where the inflammation has already subsided and clinical signs of it could no longer be observed. The first group received the intrafocal designation, for the second group the term scar reaction was used. A third series of investigations which were to provide information on the behavior of tissues surrounding the focus of infection were termed parafocal; in these cases the second vaccination was given into the clinically unchanged skin next to the acutely infected skin. Some of these cases truly belong in the group of scar reactions, namely those in which the second vaccination was administered to areas where the inflammatory process had been present but has already ceased clinically.

The second vaccination was mostly made according to Pirquet's method of cutaneous reaction; in some cases Mantoux's intracutaneous method was used. The determination of the reaction intensity was made by the customary measurement of two diameters perpendicular to each other (reported in mm; if both values were identical, only one number was given). As examples of the method used by us, the protocols of three cases are presented.

Stefanie Kendler, 6 years, scrofulosis.
10 Oct, Pirquet's (P.) test, undiluted old tuberculin.
11 Oct, dimensions of the reaction 20:14 mm.

12 Oct, dimensions of the reaction 35:28 mm.
13 Oct, dimensions of the reaction 20:20 mm, lower reaction 23:17 mm.
On 13 Oct, the following three cutaneous reactions were made: P-test a) in an area where the reaction has already ceased (upper part), b) in the existing efflorescence (lower part), c) control in the left arm.
14 Jan, a) 30 mm (the diameter vertical to the two scratch marks measured), b) 8 mm, c) 20 mm.
15 Jan, a) 24 mm, b) 8 mm, c) 16:21 mm.

Ferdinand Pfeifer, 13 years, anemia.
1 Oct, P-test 15:20 mm.
14 Oct, the reaction from 1 Oct, ceased completely with some pigmentation remaining, 18:18 mm. Two cutaneous reactions at 11.30 A.M., a) in the old, pigmented area, b) control in the left arm.
14 Oct, a) control 5.00 A.M. 30:30 mm, b) control 5.00 A.M. 7:7 mm.
15 Oct, a) control 70:90 mm, b) control 11:12 mm.

Marie Primann, 14 years, latent tuberculosis.
8 Oct, P-test.
9 Oct, 10:13 mm.
17 Oct, 8:11 mm, upper part P-test in the old reaction site, 1 mm from the papilla but still in the area of the previous reaction; b) lower part P-test in the papilla; c) control.
18 Oct, a) 65:65 mm, b) 39:25 mm blister, c) control 32:22 mm.

The results of our experiments are summarized in the tables on the following two pages.

A summary of our experiments, classified in three groups in the manner described for purposes of a simplified review, follows.

1) The scar reaction was always more intense than the control reaction, that is much more pronounced in an interval of: 12 months (no 8), 4 months (no 6), 3 months (no 15), 5 weeks (no 27), 22 days (no 30), 18 days (no 39), 12 days (no 2), 9 days (no 38), 7 days (no 45); somewhat more pronounced in an interval of: 12 months (no 4), 4 months (no 3), 28 days (no 37), 12 days (no 9), 8 days (no 21), 8 days (no 47), 7 days (no 44), 5 days (no 51), 4 days (no 33).

2) The behavior of the intrafocal reaction as compared to the control reactions was: much more pronounced in an interval of: 1 day (no 16), 2 days (no 43), 9 days (no 29); somewhat more pronounced in an interval of: 9 days (no 5), 4 days (no 41), 7 days (no 32), 2 days (no 24); equal to in an interval of: 2 days (no 52), 2 days (no 22), 2 days (no 31), 7 days (no 23); weaker in an interval of: 3 days (no 1), 6 days (no 12), 1 day (no 42).

3) The behavior of the parafocal reaction in comparison to [illegible] control reactions was: more intense in an interval of: 2 days ([illegible],

No.	Name	Age	Diagnosis	Original Reaction: date	Original Reaction: appearance	Reaction on Further Investigations: interval since the original reaction	appearance of the area tested	Kind of Testing: Pirquet or Mantoux	scar reaction	intra focal	para focal	control reaction
52	W.A.	4 y	diphteria	25 Nov 13	12	2 days		M		17		21
51	R.F.	4 y	diptheria	14 Nov 13	0	5 d		M	6			3
49	C.M.	11 m	meningitis?	13 Nov 13	8	5 d		M		31		15
47	G.A.	14 y	epilepsy	10 Nov 13	+	8 d		M	6			4
45	N.N.	7 y	epilepsy	11 Nov 13	+	7 d		M	9			3
44	N.V.	11 y	epilepsy	11 Nov 13	+	7 d		M	7			4
7	M.M.	4 y	scrofulosis	22 Nov 13	22	22 d		P		0	0	0
48	K.R.	6 y		19 Nov 13	8	1 d		M		13	20	20
[illegible]	G.R.	6 y	hysteria	24 Jul 13	+	3 months		P	40			18
40	H.J.	6 y	spond. tb.				lupus areas	P	17,11[1]		20,29	32,23
33	P.F.	13 y	anemia	1 Oct 13	13	4 d		M	17,12			14,10
24	E.E.	12 y	epilepsy		18			P		12	10[2]	7
16	N.P.	10 y	neurasthenia	14 Oct 13	10	8 d		P		52	23	15
18	D.V.	11 y		20 Oct 13	9	1 d		P		15	12	8
1	K.S.	6 y	scrofulosis	10 Oct 13	17	3 d		P		8	30	20
21	K.M.	12.5y	ulcus ventr.	2 Oct 13	+	18 d		P	8			3
30	H.T.	12 y	icterus cat.	8 Oct 13	10	22 d		P	25			6
9	G.J.	13 y	anemia	5 Oct 13	8	12 d		P	11			7
8	T.M.	6.5y	spond. tb.	30 Oct 12	9	1 year		P	33			19
4	S.A.	6 y	tb. perit.	25 Oct 12	13	12 y		P	13			11
2	P.F.	13 y	anemia	2 Oct 12	17	12 d		P	80			11
36	H.J.	6 y	spnd. tb.				skin tb scar	M	23			12
43	F.E.	8 y	neurasthenia	11 Oct 13	6	2 d		M		25	19[3]	11
39	D.H.	5 y	hysteria	11 Oct 13	+	18 d		M	12			9
38	L.F.			22 Oct 13	0	9 d		M	12			5
35	K.S.	6 y	scrofulosis	4							9,7	12,9
37	W.T.	7 y	epilepsy	8 Oct 13	+	28 d		M	31			23
[illegible]	P.B.		diphtheria	28 Oct 13	8	2 d		M		20		18
[illegible]	[illegible].J.			3 Nov 13	17	9 d		M		32,13	37,19	20,31
[illegible]	A.H.	6 y	pulm. tb.	9 Dec 13	15	6 d		P			12	9
27	M.M.	4 y	scrofulosis	22 Sep 13	16	5 weeks		M		31		14
6	J.R.	4 y	gen. fungus	12 Jun 13	12	4 w		P		30[5]		15
3	S.H.	11 y	scrofulosis	9 Jun 13		4 m scar not pigm.		P		23		21

29	K.P.	12 y	asthma	21 Oct 13	20	9 d		M	33		10
11	M.J.	5 y	diphtheria	10 Oct 13	3	7 d		P	5		4
28	F.A.	12 y	epilepsy					M	8		4
10	G.M.	2.5y	diphtheria	15 Oct 13	3	2 d		P	6		4
17	S.M.	7 y	neurasth.	20 Oct 13	5	2 d		P	5		5
13	E.W.	10 m	diphtheria	13 Oct 13	2	4 d		P	5		6
12	E.J.	2.5y	diphtheria	11 Oct 13	7	6 d		P	14		13
23	W.M.	8 y	epilepsy		7			P	9	8	11
19	N.J.	13 y	neurasth.	18 Oct 13	0	4 d		P	21		10
32	U.V.	8 m	diphtheria	24 Oct 13	13	7 d		P	17		5
34	G.J.	12 y	anemia	29 Oct 13	10	1 d		M	25		22

Remarks: $\frac{1}{2}$ tumor characteristics,
$\frac{2}{2}$ small blisters,
$\frac{3}{4}$ small blisters,
$\frac{4}{4}$ two weeks beforehand, a scrofuloderma was present near the left ear; a reaction near this, a second reaction on another skin area corresponding to this site is reported,
$\frac{5}{5}$ small blisters.

9 days (no 41), 6 days (no 52); more than one week (no 24), 1 day (no 8), 8 days (no 16), 9 days (no 8), 3 days (no 1); equal to in an interval of: more than one week (no 23), 1 day (no 42).

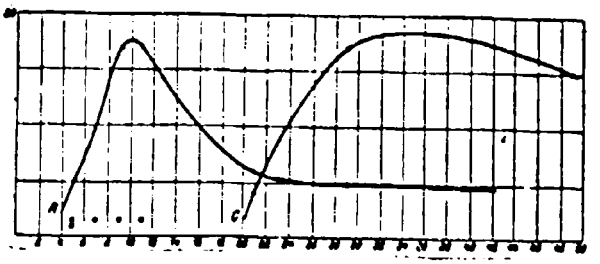
4) The behavior of the intrafocal reaction in comparison to the parafocal reaction is much more pronounced in the interval of: 8 days (no 16); moderately stronger in the interval of: 2 days (no 43), 1 day (no 18); equal in an interval of: more than one week (no 23), more than one week (no 24); weaker in an interval of: 9 days (no 41), 6 days (no 52), 1 day (no 42).

From the 15 experiments (paragraph 2), no regularity could be derived in the intensity of the intrafocal reaction. This may have been caused by the fact that the time interval between the primary and secondary infection was not uniform. It was apparent that in five of the eight cases in which a more pronounced intrafocal reaction developed, the time interval was over a week or more. In the cases, however, in which a less pronounced or equal reaction was produced by the superinfection, the time interval was 6 days in only one case, in another case it was 3 days, in five cases 1-2 days. This leads to the presumption that the extent of the intrafocal reaction is, in general, dependent on the interval between the two infections in such a manner that the reaction becomes more pronounced with the increase of the interval. This interval enables us to estimate the stage of the primary inflammation. We can assume, namely, that the peak of the reaction is reached already in the first 24 hours and this is followed by the stage of regression of the inflammation. Of course, the interval does not provide us with a fully precise measure since we know that the individual tuberculin reactions may differ in their duration.

In paragraphs 3 and 4, the results of our investigations of the parafocal reaction are summarized. The parafocal reaction was much more pronounced than the controls in 8 cases and it was equal to them in 2 cases. In the 8 cases of stronger reaction, the superinfection was introduced in the area near the still visible, inflamed site. It has to be noted that this area was affected by the inflammation of the earlier reaction but no more sign of inflammation was clinically apparent at the time of the second vaccination. In the 2 cases which were equal to the controls, the primary reaction was very small and the secondary vaccination, although made in the neighborhood, was introduced in a skin area which was not affected previously. This indicated that the parafocal secondary vaccination results in a more intensive reaction only when it is introduced into an area in which a specific, tuberculous inflammation had previously occurred, as in the scar reaction.

In the previous discussion only the reaction intensity has been considered. In the following graph, (Fig. 1), the reaction course in time is presented.

mm diameter



hours

Fig. 1.

1. Preismann, R=reaction, C=control (Fig. 1).
2. Pfeifer, intrafocal, beginning of the specific reaction less than 4 hours, peak = 16 mm after 21 hours,
   control, beginning of the specific reaction at about 10 hours, peak = 5 mm after 21 hours,
3. Goberitz, beginning of the specific reaction at about 4.5 hours, rapid increase up to 7 hours, peak up to 30 hours,
   beginning of the control reaction about 10 hours, slow increase up to a maximum of 30 hours.

Common to all three cases is the early appearance and rapid increase of the intensity of the scar reaction in comparison to the reaction in a normal skin area. These observations are in good agreement with the view of v. Pirquet, already discussed, that a secondary vaccination in areas of an earlier, specific inflammation results in a more rapid and more intensive reaction.

The cases discussed so far represented primary tuberculous inflammations which followed a cutaneous application of old tuberculin according to the Pirquet method. In some cases a secondary testing was made in areas which received a previous percutaneous treatment with a 30 per cent old tuberculin ointment (Moro's method).

For instance: Hermine Steindl. 9 Jan, concentrated old tuberculin was massaged into the inner side of the right lower arm. Next day five lichen-like nodes were visible. After 12 days, a P-test was made on the area previously exposed to the ointment, with a control reaction on the corresponding area of the left arm. The following day the extent of the reaction on the right arm was 35 mm, on the control arm was 25 mm.

Similar results were obtained in four other cases; the control reaction was greater in only one case. The results of these investigations are also in complete agreement with those obtained in scar reactions. Here too, the previously treated areas give more extensive reactions than the controls.

In four cases the opportunity has arisen to make secondary vaccinations in spontaneous tuberculous inflammations of the skin instead of the artificial infections. These cases are described in the following.

1) 6 year old girl, scrofulosis.
3 Oct, a scrofuloderm appeared near the left ear 2 weeks previously. A reaction was introduced in the immediate vicinity of the inflamed area (parafocal) with a control at the corresponding site behind the right ear.
4 Oct, parafocal 10:12,
5 Oct, focal 7, control 9.

2) 6 year old boy, spondylitis tuberculosa and skin tb (disseminated lupus of the skin).
5 Nov, an intracutaneous injection was given into the scar of one of the lupus foci with controls on a corresponding area.
6 Nov, scar reaction 23, control 17,
10 Nov, a P-test was made, in a similar manner, in a previous efflorescence next to an active one with a control on a corresponding skin area,
11 Nov, scar reaction 17, parafocal 20, tumor like, control 32.

3) 6 month old girl with a primary tuberculous site on the left cheek. The P reaction was very strongly positive.
18 Mar, one tenth of a mg old tuberculin was injected into the primary site,
19 Mar, no reaction could be observed.

4) 2 year old child, scrofulosis. On the right side of the neck several healed fistulae were seen. One fistula was surrounded by a square, infiltrated area of 35:10 mm size.
12 May, one fifth of a mg old tuberculin injected into this infiltrated tissue and the same amount given in the left lower arm,
13 May, the infiltrative tissue was somewhat more red, its size remained unchanged, control about 70 with a small blister in the middle.

The results indicate that noted differences from the controls are apparent also after secondary vaccination of the site of spontaneous inflammatory processes of a tuberculous origin on the skin, namely, the inflamed areas give a less pronounced reaction than the controls. Cases 3 and 4 could also be classified as intrafocal reactions. In case 2, the secondary vaccinations were placed into previous lupus areas; the reactions, however, were different. This could be due to the fact that the inflammations in the lupus areas were not in the same stage in both cases. The two parafocal reactions, cases 1 and 2, were each smaller than the controls. In the literature, two different results of similar experiments can be found. Intrafocal vaccinations in lupus foci of adults are reported by Nagelschmied. This resulted in the development of tumors with a wide range of variation in their depth, duration and area. These cases differed from ours by the fact that Nagelschmied used undiluted tuberculin and a diluted one (1/5 mg) was used by us. In this manner tissue destruction was produced by Nagelschmied while we were unsuccessful in the production of more extensive inflammation reactions. The above-mentioned experiments

by Bandler and Kreibich with vaccination between lichen nodes show some analogies with our percutaneous application of old tuberculin, the resultant extensive reactions in the surrounding, clinically unchanged skin areas were the same.

The results of our investigations are as follows: 1. Cutaneous or intracutaneous secondary vaccinations with old tuberculin in a tuberculous tissue give different results, even when applied similarly, which are dependent on the site of the administration and on the stage of the original inflammation.

2. Intrafocal secondary vaccinations, that is those administered into clinically inflamed areas, did not behave uniformly in a comparison with the controls. Yet, a more distinct dependence is evident on the time interval between the original and later vaccination in such a way that the reaction following the second vaccination increases in its intensity directly with the increase of the time interval, that is, with the progress of the course of the original inflammation.

3. The parafocal secondary vaccinations, that is those which are placed between areas still inflamed clinically, gave increased reactions only if the site of application was within the previous area of the primary reaction. In other cases, the reactions were equal to or weaker than the controls.

4. The scar reactions, that is those where secondary vaccination is placed into areas of inflammations which are completely healed clinically, gave uniformly stronger reactions than the controls.

5. The following may provide an explanation for these observations. The specific tuberculous inflammation is developed by an allergic process, according to v. Pirquet, as a result of apotoxin which is formed from the antigen and antibody (origin). Differences in the intensity of the reaction can arise by a variation of the quantitative relationship between the antigen and the antibody. We can assume that, in freshly inflamed areas, no free antibody is present which could react with the new supply of antigen to form apotoxin, the cause of the inflammation (ad 2). Following the decline of the inflammation, a local accumulation of antibodies remains (also according to v. Pirquet). On this area of the skin, more antibody is present than in other, clinically normal, skin areas. This is the reason for the strong reaction of these areas to the introduced antigen (ad 4). Furthermore, transitions between such extreme cases are also in existence where the primary inflammation is no longer at its peak but is already in a state of regression (ad 2 and 3).

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One graph.