

UNCLASSIFIED

AD NUMBER
AD836620
NEW LIMITATION CHANGE
TO Approved for public release, distribution unlimited
FROM Distribution authorized to U.S. Gov't. agencies and their contractors; Foreign Government Information; JUL 1964. Other requests shall be referred to Department of the Army, Fort Detrick, Attn: Technical Release Branch/TID, Frederick, MD 21701.
AUTHORITY
AMXFD ltr, 9 Feb 1972

THIS PAGE IS UNCLASSIFIED

AD 836620

TRANSLATION NO. 1130

DATE: 24 July 1964

DDC AVAILABILITY NOTICE

Reproduction of this publication in whole or in part is prohibited. However, DDC is authorized to reproduce the publication for United States Government purposes.

STATEMENT #2 UNCLASSIFIED
This document is subject to special export controls and each transmittal to foreign governments or foreign nationals may be made only with prior approval of Dept. of Army, Fort Detrick, ATTN: Technical Release Branch/TID, Frederick, Maryland 21701

R 11964

Best Available Copy

DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

RESEARCH ON LOCAL SENSITIZATION
GENERATED BY TUBERCULIN

[Following is a translation of an article by Marc Weiss, in the French-language journal Annales de Médecine (Medical Annals), Vol XVII, No 4, Paris, 1925, pages 408-435.]

The homeotopic repetition of the skin-test, cause of error in the study of energies.

Contrary to a quite well-spread opinion, tuberculin can behave as a sensitizing poison and the most striking characteristic of this sensitization is that it is limited to tissue and that it is local. The revivescence of old local tests under the influence of subcutaneous tuberculin injections is the most typical example available to us. It is also the most interesting one for the biologist. Between the revivescence of an old local test and the test of a tuberculous focus -- these two effects so different and yet so comparable of subcutaneous tuberculinization -- there is much more than a simple analogy and it may be concluded from it that tuberculin acts on the tissues in contact with which it had been introduced, in the same manner as the bacillus itself acts towards the tissues which it infects. To study the mechanism of sensitization caused by tuberculin, means, therefore, up to a certain point, the study of the mechanism of tuberculous allergy. Let us say, up to a certain point, for between the two things there is, as is known and as we shall see, quite an important difference.

Local sensitization caused by tuberculin never appeared more clearly than at the time when the ophthamoreaction was still in favor. Often times, one has to repeat the local tests several times, in order to be convinced of the results and since there are only two conjunctivae, clinicians had to recognize very early the danger of reinstillations: the reactions obtained on the already instilled eye had frequently an alarming character of intensity and contrasted in a peculiar way with the normal reactions obtained

on the opposite eye instilled for the first time. Due to this cause, among others, clinicians decided to abandon this diagnostic method, which was, moreover, less sensitive than the skin-test and also less easily accepted. Nevertheless, no matter how short the reign of the OR (ophthalmoreaction) was, it gave the opportunity of collecting enough facts, in order to establish suitably the principal laws of the phenomenon.

This sensitization was not of an anaphylactic nature. This is how it was possible to repeat the OR in a new-born baby (Roepke), in an animal free from tuberculosis (H. Vallée) without ever obtaining positive reactions. This is what differentiates essentially the action of tuberculin from that of the bacillus: the bacillus has the power of sensitizing a new organism; tuberculin can sensitize only an already infected and sensitive organism. "Not everything is capable of sensitization," wrote M. Pasteur-Vallery-Radot, expressing very well certain facts of anaphylaxy. The formula could be adapted to the case of tuberculin with this difference that here it is not a matter of area but of previous tuberculous infection.

This condition was neither recognized without difficulty nor admitted without arguments. Before Roepke's and H. Vallée's experiments which we have just quoted, it seemed difficult to admit its existence. In order to transform a negative OR into a positive OR, it was enough in fact to repeat the test two or three times: this result was obtained, so to speak, almost at will; at least, it seemed so. It is a paradox for which the reason became apparent later: hidden tuberculoses are much more frequent in the human species than it was believed and the OR, if not repeated, is not a very sensitive method. But by repeating it, its sensitivity is increased at the same time as that of the subject; the OR is made to agree with the pathological anatomy and with the C.R. (skin-test).

It was almost predictable that the skin-test also created a sensitizing action noticeable on homeotopic repetition of the tests for the revivescence of cutaneous tests under the influence of subcutaneous injections is not less clear than that of the ocular tests; but the effect of skin-tests repeated in series on the same point has been studied less than that of the ocular reinnervations: a note by Pirquet, another one by C. Mantoux, some confirming research by H. Koch and W. Schiller, a few lines devoted incidentally to this topic by Father Sahli (of Berne), to our knowledge, this is all that had been written about the question. Furthermore, the question was always viewed by these different authors under the same restricted angle: the angle of allergic tuberculosis. What happens with cases of anergic tuberculosis or of non-tuberculous instances?

For the latter, the answer was easy to guess: the homeotopic

reinoculation gives no result. At least, this is what we can conclude from the investigations we have just made and which will be published elsewhere.

The case of anergies was equally interesting: while studying the phenomena of anergies by a series of skin-tests, one risks, if care is not taken, inoculating the same area several times. Does one thus create a cause of error? This is the problem that we have tried to solve in the light of some experiments. This is also the topic of this article.

Nevertheless, the problem is not only interesting from a practical point of view. If the sensitization caused in the organism by the bacillus or its toxins is, above all, a tissue sensitization, the repeated failures of transmitted allergies and of antituberculous serotherapy can be explained better. It is possible that one day we will find amidst tissues antibodies of the tuberculous allergy for which we have searched until now in vain in humors. While waiting for this biological research, it seems important to get well acquainted, from a clinical point of view, with the phenomena of sensitization caused by tuberculin and this consideration leads us to consider the problem under its different aspects. We wanted, therefore, to check also, but under varied experimental conditions, the Pirquet-phenomenon: that is to say, the effect of homeotopic reinoculations in cases of allergic tuberculosis. According to this author, the reaction obtained by repetition on new areas is noticeably a normal reaction [See Note]: it develops after a certain incubation and completes its development in a few hours.

([Note:] Pirquet noticed, however, that in cases where the first reaction is of the belated type (incubation of three to four days) the next reaction is of the habitual type, i.e., quite premature. The sensitization, therefore, is not purely local.)

Pirquet does not indicate in what radius from the point of inoculation local sensitization is effective. H. Koch and W. Schiller had tried to find it out but they did not give any explicit conclusion. It would be an interesting question but we have not approached it. In order to simplify the matter and to make all the experiments comparable, we always repeated the tests on the same point.

In the present article, we shall examine only one case: that of tuberculous patients (allergic or anergic) and we shall examine the question from a practical point of view. Is the homeotopic reinoculation a cause of error in the study of anergies?

Technique

Pirquet's skin-test is much more frequently used in practice than Mantoux's intradermal-test. Therefore, we used Pirquet's method for the successive inoculations. [See Note.] The tuberculin that we administered is unrefined tuberculin (called "veterinary") of the Pasteur Institute: it is generally used for skin-tests and in order to conform entirely to the habitual conditions we administered it in its pure form. By so doing, according to Pirquet, we placed ourselves in the most favorable conditions of experiment: it results from the research of this author that the reinoculation of sensitized zones and that of control zones always gives different reactions, but the difference becomes less clear when the tuberculin used for these reinoculations is diluted.

([Note:] We executed counter-experiments using Mantoux's method. We lack the opportunity in this article to give the results. We shall say simply that they were perceptibly identical with those of the skin-test.)

Each of the inoculations consisted of the following minor operation: single, linear, superficial and bloodless five-millimeter scarification. For the homeotopic reinoculations, the vaccinostyle passed over the trace, generally still visible, of the preceding scarification. The tuberculin drop, deposited on the scarification so as to coat the total length of the trace, on a five-minute contact was dried by capillarity with a piece of cotton; each of the homeotopic reinoculations carried the inoculation from a control point over a new skin which had carefully established in the symmetric region, at the same time and under the same conditions.

Each experiment consisted, therefore, of at least the two following successive operations:

1. First inoculation.
2. Simultaneous reinoculation of the previous point and of a control point.

In order to make the experiment more demonstrative, generally, we performed the experiment in duplicate: 1. two first inoculations; 2. two homeotopic inoculations and two control points.

It is important to note that in the thus regulated experiment the second operation consists of four (or two) inoculation points instead of two (or one) as in the first operation. This fact has no importance as long as we limit ourselves to the comparison between the test reaction (sensitive territory) and the

control reaction which was the usual goal of our experiments. But we wanted, in certain cases, to compare successive reactions. In such cases, we acted in a manner so that the inoculation points would be of equal number in each test, e.g., 1. four first CR (skin-tests); 2. two homeotopic reinoculations, two controls; 3. etc.

Generally, the first inoculations had been given in the outer part of the left arm, at intervals of five to six centimeters. At the time of the reinoculations, the controls were given in the outer part of the right arm with the same intervals. When we proceeded to several successive reinoculations on the first reaction, we acted in such a manner so that the successive controls would be placed at a certain distance from previous controls (e.g., at the deltoid region, or at the interior part of the arm) with a sufficient interval (seven to eight centimeters), in order to avoid being affected by them.

Finally, in order to avoid all errors the successive or simultaneous tests were always recorded with their proper dates and locations on a chart annexed to the observation of the subject.

The Graphic Method for the Study of Tests

In one particular case at least, the comparative study of the test and control reactions demands minutious care: when they both are positive. In such a case, it is only a matter of difference in speed and in size and these two elements can be studied with precision only with the aid of a graphic representation of tests, as, for instance, Pirquet did.

For clarity in what is going to follow, it seems to us indispensable to give here some indications on the evolution of the cutaneous tuberculin test: skin-test or intradermal-test, it makes no difference, since the evolution is the same in both cases.

The majority of skin-tests with tuberculin is composed, when they reach maturity, of two different elements concentric to each other: the papula which occupies the center of the reaction, and the areola. In this instance, the skin-test resembles exactly, but on a smaller scale, the local reaction of the subcutaneous tuberculin injection, such as had been described by Rist in 1913 in a communication to the Society of Scientific Studies on Tuberculosis. Besides, the existence of areolated skin-tests, called vacciniiform or urticarian by certain authors (J. Lemaire, Oppert, Hutinel, A. Jousset) is classic, but they seemed to us more frequent than they are said to be usually and mainly, more complex in their evolution. J. Lemaire admits that the areola (or halo) develops suddenly at the moment when the reaction proper, i.e., the papula, reaches its maximal intensity. Consequently, according to J. Lemaire, the areola is secondary. It can be drawn from our observations, repeated

many a time, that this description never corresponds to the reality of the facts. First, the skin-test is indifferntiated and then the two zones are formed by differentiation.

In short, the general curve of the areolaed reaction is, according to our findings, the following, similar in its general form to those of Porquet.

In this curve, point "i" marks the date of inoculation, "r" the appearance of the reaction, the broken line "r A P' P'" the variations of the total reactional surface.

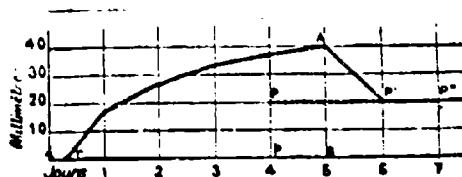


Figure 1: Cutaneous Reaction Curve (personal experiment) [Jours - days]

In the first phase of its development (period r p), the future "areolaed reaction" does not yet deserve this name. It is undifferentiated and presented under the aspect of an edematous elevation of a pale coloration, slightly pink which increases its radius progressively.

While it is developing thus in size, one can see its central area change in aspect and undergo an infiltration.

In "p", the differentiation is terminated. The central zone became a papula or a papular region of hardened consistency, of dark red or yellow-amber coloration. Its surface is smooth or bristling with small acuminate protruberances which seem to represent either pilous follicles that have become turgescnt or the rough shape of these miliary vesicles which, in certain cases, follow a more apparent development. Henceforth, a precise boundary separates the central region of the exterior parts of the reactions where the inflammation will never exceed the erythema state.

The central zone, once constituted, preserves exactly its primitive dimensions; it shows no tendency to grow which is expressed by the horizontal line P' P' P''. In this respect, our findings agree, once more, with those of Rist recorded for the local reaction of the injection. While the central zone completes its maturation (and, according to the clinical form, it will become papular, papulo-vesicular or papulo-bullous, the reaction continues its invasive progress (period p a). Thus the areola grows without changing aspect; the central zone changes aspect

without growing.

It is important to notice that the line r A which represents the development of the total surface is regularly ascendent: a straight line, generally, or slightly approaching the horizontal toward the end. All curves obtained are alike, in this respect, though the reactional phase may be prolonged somewhat. In short, one sees the growth and the maturation progress simultaneously, at a more or less rapid, but always progressive, and regular pace.

At the moment when the areolated reaction reaches its extreme dimensions -- and completes its maturation -- for until the very end the center and the periphery obey a common impulse -- the areola disappears suddenly without leaving any trace, except, for a few hours, some irregular mottlings of a cyanotic tint [See Note]. The drop of the A P' curve results from this. As for the central zone, it can be seen sinking little by little; its coloration becomes dull; the vesicles, if there were any, become dry and the subjacent infiltration diminishes. A reddish spot -- later pigmented and squamous -- follows it, but the diameter remains equal to itself, from which the horizontal line P' P'', continuation of P P', originates.

([Note:] On the sudden and total disappearance of the areola we only confirm the findings of J. Lemaire for the CR, and of Rie for the injection test.)

In summary, one can distinguish three periods in the evolution: incubation (ir), reaction proper (ra) and involution. The comparison in Pirquet's experiment deals with the durations of ir and ra. It must also deal with the diameter of the tests. In this respect, it is useful to specify that the real diameter is that which is measured at moment a (maximal diameter): moment a, for two simultaneous experiments of unequal speed, may not be the same moment. These considerations are not purely theoretic; we shall see that the objective study of facts makes them necessary.

Preliminary Experiment Simultaneous Reactions on New Skin

Before comparing the speed of a test on sensitized skin and that of a test on new skin, it was useful to compare two tests on new skin and to assure ourselves that they would be synchronous.

We made this counter-test in every experiment since we made the inoculations always in duplicate. We always found a perfect synchronism between these tests on new skin. Likewise, also, the tests on sensitized skin were, on a different rhythm than the preceding ones, perfectly synchronous among themselves.

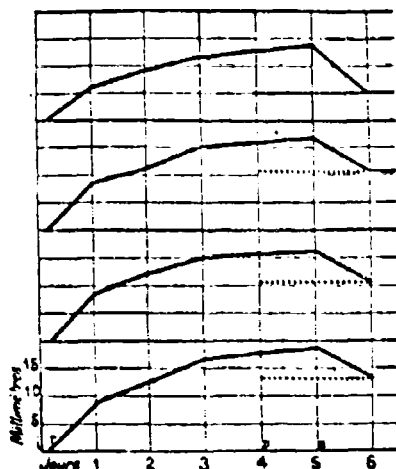


Figure 2: Simultaneous Cutaneous Reactions (new skin) [Jours = days]

In order to illustrate this general law which is also applied to first tests, we give the charts of four first tests executed simultaneously on the outer part of the arm. Their particularly slow evolution gives an opportunity to grasp well the different phases of the evolution, and also their isochronism.

Furthermore, we can establish that they are noticeably isometric. This means that the variations in size must be taken into consideration as well as the variations in rapidity.

Homeotopic Reinoculations

A tuberculous patient may have positive or negative reactions. In both cases, it was interesting to know the results of homeotopic reinoculation.

I. Reinoculation of Positive Reactions

Here again two eventualities can be presented: at the moment of reinoculation, the subject may be found in a state of allergy or he could have become anergic.

First Case -- The Control is Positive

These are the very conditions of Pirquet's experiment. According to him, homeotopic reinoculation gives a positive reaction which differs from the control reaction by its greater speed. In order to back his exposé, Pirquet gives the following chart where

two different experiments are represented.

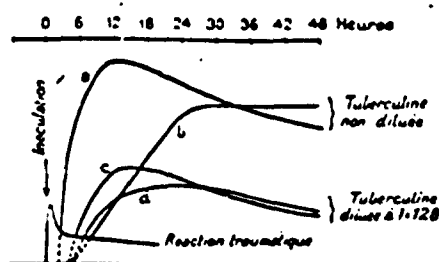


Figure 3: (Pirquet, L'Allergie [Allergy], 1910). [Legend: Heures = hours; Tuberculine non diluée = undiluted tuberculin; Tuberculine diluée à 1:128 = a 1:128 dilution of tuberculin; Réaction traumatique = traumatic reaction]

Curves a and b correspond to the concentrated tuberculin, c and d to a dilution at 1/128°. Each curve represents variations, in time, of the diameter of a reaction. Reactions a and c had been obtained on sensitized zones and b and d on control zones.

Experiment ab is definitely the most typical. Pirquet made us observe that reaction a is remarkable by its precociousness, its incubation being two hours, instead of five hours for the control. Furthermore, its development is rapid and almost sudden which illustrated in the curve by an abrupt ascension. Contrasting with the preceding curve, curve b of the control starts later, and rises very slowly. It is to be noticed, however, that finally, it reaches the same height as the preceding one. It is a point upon which Pirquet draws our attention. In fact, according to him, the difference between the two reactions is most a matter of schedule and not that of real magnitude (it is only natural that, in the first hours, the most prompt reaction seems also the greatest).

On reading Pirquet's description, one might think that it is necessary to multiply the successive inoculations on the studied territory so that the reactions would become precocious.

It can be deduced from our experiments that the phenomenon is produced always at the first reinoculation regardless of the subject, of the interval, of the time gone by since the preparatory inoculation. Therefore, in order to simplify the matter, we shall take as description type the reaction produced by a first reinoculation. But it is necessary to give more precise details.

According to Pirquet, the homeotopic test is simply more rapid than the control. As for its diameter D_h , it is equal to diameter D_t of the control. But H. Koch and W. Schiller think that the relation D_h/D_t can be superior to unity and that it is in direct proportion with growing age of the preparatory skin-test, as if the local sensitization would be strengthened with time.

Like Koch and Schiller, we have often seen a homeotopic reaction greater than the control and it seemed to us, as it had seemed to them, that the relation Dh/Dt increased with the interval of the two inoculations.

We shall take, therefore, as description type the case of a precocious (few days) reinoculation.

Control Reaction

The control reaction is presented noticeable as a normal reaction, that is to say, a first reaction. It is not useless to specify it, for it could be influenced by its progress in two ways:
1. by the first reaction (general sensitization of the tegument);
2. by its contemporary, the homeotopic reaction.

Nevertheless, is it completely normal? In order to know it, it would be necessary to have compared systematically the control reaction to the first reaction, in conditions which make the two tests comparable (similar clinical circumstances, equal number of inoculations in each test). We have performed this experiment only very seldom, but it seemed to us that the control reaction itself was too rapid. In one of the subjects, the first reactions lasted five days; the second, allotopic reactions lasted only two days.

Besides, the problem presents only a secondary interest. What stands out from all our experiments is that the control reaction never exceeds a certain speed similar to that of the habitual first reactions. Its incubation is prolonged during several hours, its development is never completed before the end of the second day, and, finally, this development is perfectly progressive, indicated in the chart by a straight line: this is what is important to remember.

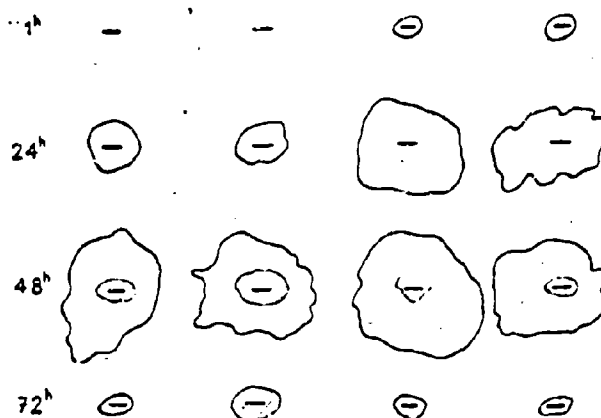


Figure 4: Homeotopic Reinoculation Experiment (personal). Right: 2 homeotopic reactions; left: 2 control reactions; successive counter-drawings of reactions (hours counted beginning with inoculation) Scale: 3/5.

The Homeotopic Test

It is more rapid than the control test, and here is, according to us, how the experiments take place:

Incubation is not completely suppressed, but it is shortened a great deal, reduced almost to none. Pirquet gives as indication 20 hours which already constitutes a definite advance on the control (five hours). In some of our experiments, we could see, even after thirty minutes, a papulous protruberance of inflammatory aspect which raised scarification on the side of the homeotopic reinoculation: the control, at the same time, did not differ in any manner from a scarification which might not have been coated with tuberculin.

A few hours pass, and the two reactions are in progress, but the probatory reaction is ahead by approximately 24 hours, according to its diameter.

It reaches, usually, from the end of the first day, its final dimensions and seems then to reach the control reaction which, generally, catches up with it at the end of the second day. It is also quite remarkable to see that the events take place almost always according to this schedule with a quasi mathematical exactitude: 24 hours for one reaction, 48 hours for the other. An even more peculiar thing is that we shall see that the conditions of the experiment can be almost indefinitely varied without modifying these two delays.

In a certain number of cases, however, the early reaction grows a little more during the second day. But what it gains in area is nothing compared to the gain of the first day, so that after 48 hours the control test may be able to equal it. (This is the case of Figure 3.)

The moment has arrived when the two tests near their end: we would like to give a few complementary details on the manner in which they end.

Their areolae disappear simultaneously, as is indicated in Figure 4. In short, the two tests which had been put into action by two different impulses, end exactly at the same time as if a common mechanism regulated their extinction. This fact seemed to us quite remarkable, but we would not dare to state that this is a constant phenomenon. In fact, it happens that the areola of the control is still clearly visible when that of the probatory test has already disappeared almost completely. The result is a curious oscillating movement between the two tests.

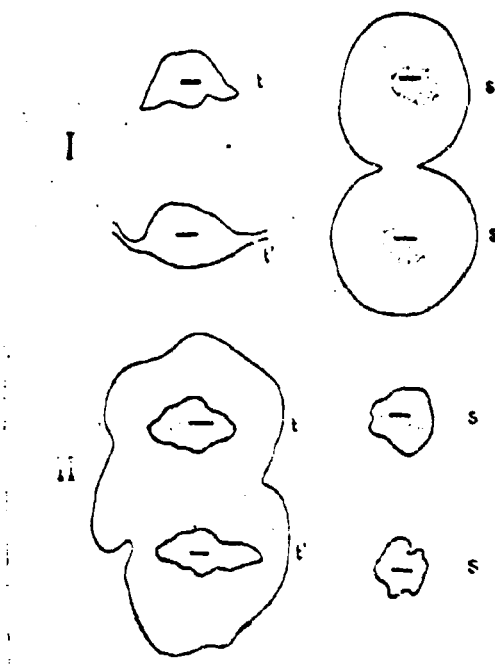


Figure 5: Homeotopic Reinoculation Experiments (personal). Right: 2 homeotopic reactions; left: 2 controls: I. counter-drawing, after 24 hours; II. counter-drawing, after 48 hours. Scale: 3/5.

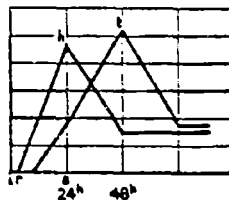


Figure 6: Homeotopic Reinoculation Experiment (personal). h = homeotopic reaction; t = control reaction.

On the first day, the probatory reaction is greater; the next day, the control reaction is greater (Figure 5). In such cases, point a of the probatory test is found carried toward the left, like its point r and the entire curve undergoes crowding toward that side.

In short, the homeotopic test is ahead of the control: ahead by approximately 48 hours.

We could characterize this special reactivity with one word: "proiergy".

Conditions of the Phenomenon

From the first homeotopic reinoculation on, the reaction assumes the proiergic type which we have just defined.

The interval which has taken place since the preparatory inoculation is a few days or several weeks. Compared with the control test (21 experiments have been summarized in Table 1).

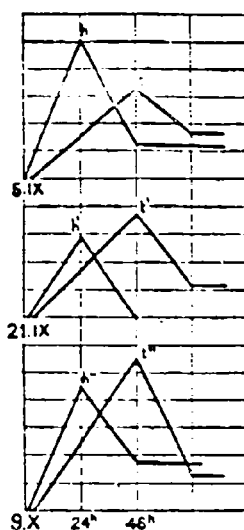


Figure 7: Successive reinoculations on the same point n, n', n'', homeotopic reactions; t, t', t'', control reactions.

It is curious that by varying this interval the relation of these two speeds is not changed; even their absolute value is not changed: 24 hours for the probatory test, 48 hours for the control test.

The successive reinoculations, repeated at short intervals, do not modify any more this relation, as it is proven by the following experiment.

One would expect that the proiergic reaction becomes faster and faster upon each one of the successive inoculations. One can see that this is not at all the case. The displacement of the curve toward the left is produced between the preparatory inoculation and the first reinoculation. Then, the successive tests do

nothing else but reproduce in a monotonous way the curve of the first proiergic test.

For the controls, we had occasion to make the same remark. In one of our experiments, the first reactions lasted five days. At the first experiment of homeotopic reinoculation, the tests (control) on new skin lasted only two days: but at the time of ulterior reinoculations this same two-day delay is reproduced in a monotonous way. We had the right to take into account this experiment of a diabetic patient, was found clinically in the same state throughout the different stages of the experiment. Furthermore, the successive test had involved an equal number of inoculation points (four for the first inoculations, then, four second inoculations, i.e., two homeotopic, two allotopic, etc.).

In summary, the events take place as if the first skin-test gave the maximum possible sensitization and ulterior tests add nothing to it. We consider this formula as certainly true in the case of homeotopic reinoculations [See Note], a practical lesson is deduced from it, which can be summarized in the following manner: in the method of serial skin-tests, one should not account for a growth of rapidity or of size which is produced as a result of the skin-test between the first and the second tests as due to an intrinsic cause (favorable morbid evolution), for this change can be blamed on the sensitization. The variations become interesting for the clinician only after the second test.

([Note:] On this point, our impressions, moreover, agree with Pirquet's observations: according to him, when a normal subject has a first delayed reaction, the second reaction is early, but subsequent reinoculations do not increase this precocity.)

But this question is only a parenthesis in our article, and in order to come back to the homeotopic reinoculations, we shall conclude this subject: no matter what the conditions of the experiment are, the homeotopic reinoculation gives an earlier reaction than the control.

Therefore, we can say that Pirquet's phenomenon is constant.

Modalities of the Phenomenon

According to the conditions of the experiment and perhaps also according to individual predispositions, what varies is the extent and the intensity of the proiergic reaction. We mean by this the relation of this extent and intensity to the extent and to the intensity of the control.

But we also mean it in the absolute sense for we have seen sometimes that the proiergic reactions reach truly unusual dimensions

and intensity, and, moreover, they are accompanied by ganglionic reactions, or even, in some very exceptional cases, by general phenomena which are never seen with the skin-test. In short, the pro-
ergergic test is often, at the same time, a hyperergergic test.

1. Variations in Extent

Since the homeotopic reaction is the more precocious, it is necessarily greater during the hours which follow inoculation. Until the end of the first day, it maintains, in all cases, its superiority. But, at the end of 24 hours, it stops growing, while the control reaction continues its progress and will not stop before the end of the second day.

In the example that we have chosen, and which is in agreement with Pirquet's description, the two reactions were equal between themselves: we mean by this, that the height of the two curves is the same.

But our findings, similar, in this respect, to those of H. Koch and W. Schiller, have shown to us that the Oh relation of the two diameters is subject to variations.

The proergergic reaction may be smaller than the control reaction (see the second curve of Figure 7). It suggests quite well the idea of an incomplete local immunity to which a real hypersensitivity would be associated closely.

The homeotopic reaction may be equal to the control reaction, and this is the case that we have chosen for description type (Figures 4, 5, and 6).

Finally, it can be greater than the control reaction, and here is, according to our observations, how the events take place in such a case.

After a short incubation, the homeotopic reaction assures for itself immediately a great superiority over the control. Toward the end of the first day, it slows down its advance, or even stops growing, but the surface it occupies henceforth, is large enough to prevent the control, which progresses, however, without slowing down, from equalling it.

When the term of the second day arrives and the reactions approach their end, they are of every unequal dimensions.

In which cases is the proergergic reaction greater than the control? It seemed difficult to us to determine this with certainty.

The individual predispositions have, maybe, their role in it.

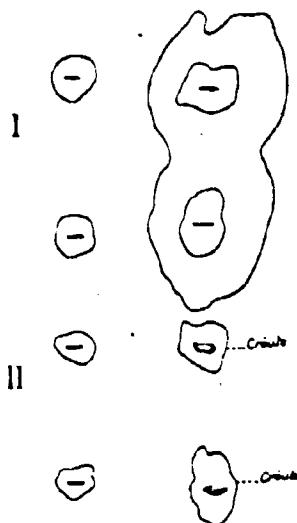


Figure 8: Homeotopic Reinoculation Experiments (personal). Hyperergic form of the homeotopic reaction; right: homeotopic reactions; left: control reactions. I. Counter-drawing at the end of 24 hours; II. Counter-drawings at the end of 48 hours. Scale: 3/5. [croûte = crust].

But, on the other hand, it is probable that the conditions of the experiment are not indifferent.

Like H. Koch and W. Schiller, we are tempted to think that the interval elapsed since the preparatory inoculation is an important factor.

In order to estimate its role, it was essential to gather similar cases: the simplest was to choose subjects which had been subjected to only one preparatory inoculation. Table 1 summarizes the result of this experiment (21 subjects).

In short, the relation Dh/Dt becomes greater than unity, beginning with approximately the tenth day.

One can wonder what the reason for this change is. The first idea which comes to mind is that the local sensitization becomes stronger with passing time. In fact, such is the opinion which seems to emanate from the study of H. Koch and W. Schiller (opinion clearly formulated by G. Bessau according to the facts of H. Koch and W. Schiller). But this is a complex problem. Is it really the probatory reactions which become effectively greater, or is it rather the control reaction which become normal again, after having been too

great during a period of time?

TABLE 1
Homeostopic Reinoculations
 (All reinoculations mentioned in this table carried out in the same manner with Pirquet's skin-test)

Time elapsed since 1st inoculation (days)	Effect of the homeostopic reinoculation in relation to the control reaction	
	Precocity	Size
5	---	---
6	---	---
6	---	---
7	---	---
10	---	---
10	---	---
10	---	---
10	---	---
13	---	---
14	---	---
15	---	---
19	---	---
20	---	---
20	---	---
22	---	---
24	---	---
26	---	---
26	---	---
48	---	---
50	---	---
240	---	---

(Under "Precocity", + and - indicate greater or lesser precocity than control; under "Size", + indicates a more precocious reaction than control)

Certain experiments which we have undertaken but would take too long to explain here, make us think that the question deserves at least to be examined, and as a conclusion, we shall only say that the local character of the sensitization becomes accentuated in time.

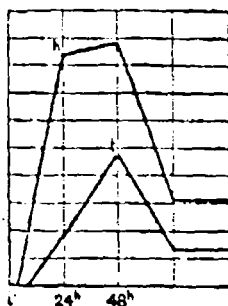


Figure 9: Homeotopic Reinoculation Experiment (personal). Hyperergic form of the homeotopic reaction. h = homeotopic reaction; t = control reaction.

2. Variations in Intensity

What we have said about the relative extent of the two reactions can be repeated about their intensity. The homeotopic reaction being the more precocious appears to be also the more intense during the hours following inoculation. For example, if the reactions are of the vesicular type, one can see that the vesicles of the proergic reaction are formed distinctly on the first day, while the control reaction had not passed yet the papular state.

In many a case, the control reaction progressing at its proper pace which is slow, completes its maturation during the second day; thus, the two reactions are then similar in all respects.

But the experiment has shown to us that the I_h/I_t relation of intensities was, like the D_h/D_t relation, subject to variations.

Rarely, it is below unity. Much more often the proergic reaction is really the more intense of the two.

It is thus that in the group of the proergic reactions, the vesicular and phlyctenular forms are much more frequent than in the control group.

We shall add even that the proergic reaction can produce aspects that the skin-test, performed under the usual conditions, practically never produces. We have often been stricken by the fluxionary character of the second homeotopic reactions. A voluminous edema, very hard and somewhat painful, develops during the hours which follow inoculation and increases until the end of the first or the second day. At that moment, it occupies a rather larger space (diameter of seven to eight centimeters). In some subjects which we have observed, it presented an almost worrying pseudo-

phlegmonous aspect. But the fluctuation was missing and in a few hours, everything returned to order. This rapid appearance followed by an even more rapid disappearance, seemed to underline the anaphylactic origin, or more exactly perhaps, the hyperergic origin of these phenomena.

3. Ganglionic Reactions

A particular character of the homeotopic reaction is, according to us, the existence of a painful adenopathy in the corresponding ganglionic region.

The normal skin-test had almost never any effect on the ganglions. The fact, however, had been noticed by Mr. Rist, in 1913, and by Mr. Blechmann, in 1914.

But the adeno-reaction (term used by Blechmann) seems relatively rare; Rist thinks that it is limited to children and he even adds: to children who have intense skin-reactions. Mr. A. Jousset, concerning Mr. Blechmann's report, declared that he has never encountered the adeno-reaction in adults. This opinion seemed always correct to us, except in the case of homeotopic reinoculations.

In fact, a ganglionic reaction follows, in a certain number of cases, the homeotopic reinoculation in adults and since the phenomenon has never been called to our attention, we think it useful to give a few more precise indications about it.

According to our observations, there exists a quite clear relation between the intensity of the cutaneous reaction and the existence of the ganglionic reaction. A hyperergic, vesicular, phlyctenar and a fortiori fluxionary reaction is accompanied almost always by a satellite adenopathy. When the cutaneous reaction is more discrete, the adenopathy is missing.

The subjects perceive themselves the existence of the ganglionic engorgement which is somewhat painful spontaneously. The tumefied ganglions are rounded, of a renitent consistency and perfectly mobile; they can have the volume of an almond. The ganglions may be painful without having increased the volume.

The progress of the adenopathy is exactly parallel to that of the proergic cutaneous reaction: it is precocious and transient.

The ganglionic reaction is strictly localized to the lymphatic region of the homeotopic reinoculation. If it had been administered in the left arm and the control in the right arm, there would be ganglions only in the left arm-pit.

4. Revivescence of Previous Skin-tests

We have observed in one of our subjects the following fact:

Four first inoculations had been administered in the left arm, at about five cm from one another. They were positive. A few days later, two of these tests (the two lowest) were subjected to homeotopic reinoculation. The two new tests were of the fluxionary hyperergic type. During their development, the other two also entered revivescence.

It seemed to us that this fact is worth mentioning for the skin-test administered in normal skin never produces the revivescence of previous skin-tests; at least, we have never seen it doing so.

5. General Reactions (?)

We believe that we have to mention, for the sake of reference, the following facts without drawing any conclusion from them except that it is necessary to avoid homeotopic reinoculations in subjects very sensitive to tuberculin.

(1) In a 50-year old woman, stricken with aortitis and arterial hypertension, who was found in the state of total cardiac insufficiency, we witnessed the production, on homeotopic reinoculation, of a rather violent crisis of asthmaticiform dyspnea.

A bleeding, followed by an intravenous injection of ouabain, put an end to accidents, but it seems difficult for us to consider it as a simple coincidence.

The hyperergic reaction was very intense, of a fluxionary type, just as happens often when the first skin-test itself has been very intense, which was the case, and crisis of dyspnea broke out at the precise moment when the fluxion arrived at the peak of its curve.

(2) In a pulmonary tuberculous patient subject to asthma crises, the reinoculation of two very old positive skin-tests (several months) was followed by an asthma attack and the temperature, which was near normal during the preceding days, became feverous for several days.

In other cases (more than 80 experiments), we have not noticed that the homeotopic reinoculation would influence the temperature, the tuberculous foci or the disease in progress.

In summary, the homeotopic reaction is always faster than the control reaction (proergy). Furthermore, it may be greater

and more intense, it may act on the corresponding ganglions, old skin-tests and perhaps on the entire economy (hyperergy). These modalities are useful to know for the practice of repeated skin-tests.

Second Case -- The Control is Negative

In the preceding experiments, the control was positive. We were, therefore, under the very conditions of Pirquet's experiment: successive reinoculations with a constantly allergic tuberculous patient. We saw what was in such a case the constant result of homeotopic reinoculations: positive reactions, always proiergic, sometimes hyperergic. But a subject whose first reaction was positive may, due to different known causes (acute infectious diseases, hepatic insufficiency, cachexy...) become anergic: we mean by this that reinoculations in new skin will give a negative result, for what would the homeotopic reinoculation of a previous positive reaction give in such a case?

The problem, to our knowledge, has never been faced and we do not pretend to solve it, but the case that we are going to relate here gives at least an interesting indication.

The observation was gathered and summarized in the service of our professor, Dr. Dalché.

Observation. -- Mr. Mi..., Claude, 63 years old, suffering from an atrophic cirrhosis of the liver, caused by alcohol, had a positive reaction to the skin-test, as is normal, according to Mr. N. Fiessinger and Mr. Brodin, when the hepatic cell is still sufficient, which seemed to have been his case: a very discrete conjunctival subicterus, the presence of urobilin in the urine were, in fact, the sole clinical symptoms of hepatic insufficiency detectable in this subject. The syndrome of portal hypertension was dominating in him: the otherwise moderately abundant ascitis, supplementary abdominal, venous circulation and volume increase of the spleen. As we have already indicated, the liver was small and hard

After a first stay of a week in the hospital, the patient believed himself to be in shape to return to his usual occupations, and, in spite of the advice given him, he left the hospital. He returned to his work and we have reason to think that he continued his drinking habits. It is not surprising that his state became worse and that after a month he returned to the hospital.

The ascitis increased in volume and the existence of a soft, white edema was noticed in the inferior limbs, which did not exist during his first stay. Moreover, the yellowish coloration of the conjunctivae turned to a darker shade: the face was more emaciated the complexion became more ashen. In the urine, less frequent and

darker, the urobilin increased. In short, the symptoms of hepatic insufficiency, while remaining quite discrete, were more evident than before, and it is to this particularity, without a doubt, that one must attribute the change in the results of the skin-test. And it was completely negative.

In summary, this patient whose skin-test was positive had been stricken by anergy during an episode of hepatic insufficiency: this is a case which is now classic since the fine research of Messinger and Brodin.

The trace of the old positive reactions was still, in spite of the elapsed time (50-61 days) clearly visible in forms of pigmented maculae. Even the small linear scar of the scarifications was distinguishable.

Instructed by our preceding research, we knew that a positive reaction leaves a local sensitization and it seemed interesting to us to know if the homeotopic reinoculation of these maculae could give, in spite of the cause which made the other parts of the cutaneous coating anergic, a positive result.

We were able to perform this experiment under very precise conditions for conforming to the rule which we had observed during all our research, we recorded exactly all dates of successive tests and, in order to avoid all possible errors, we noted the exact location of the tests on joint charts at the observation clinics.

First, here are the tests previous to the experiment, with their results:

23 August 1923: two positive (first CR (two well-hardened papulae with a real diameter of 8 mm.)

3 September 1923: two positive CR (new skin) (two papulae with a real diameter of 6 mm.)

17 October 1923: two negative CR (new skin)

The homeotopic reinoculation experiment was undertaken on 17 October 1923 and the reinoculated scars were those of the oldest positive reactions, those of 23 August (61-day interval). At the same time as these two old points, two new points had been inoculated symmetrically with the preceding ones.

Result of the homeotopic reinoculation: two red, papular reactions which had at the 17th hour diameters of 22 and 15 mm. They persisted until the third day: therefore, they were positive and quite intense.

This result contrasted with the negative result of the immediately preceding experiment (17 October). Nevertheless, in order to explain this change, it was impossible to invoke different conditions of experiment (four simultaneous inoculation points instead of two) or a change in the reactivity of the subject. It is the result of the controls that proves it:

Results of the controls (repeated controls) two completely negative reactions.

Thus, in a patient whose tegument has become anergic the location of old positive reactions, exceptional to the rule, had conserved its reactivity. One can even observe that it had become more intense (22 and 15 mm instead of 8 and 8 mm).

This fact could be summarized by saying that the local sensitization developed during the allergy period has been stronger in our patient than the anergy.

We would not like to draw any general conclusion from this single experiment. It is well to observe that conditions were quite favorable for the production of the phenomenon: a rather long interval (61 days) elapsed since the preparatory inoculation of 23 August and we have seen that the local sensitization becomes more evident as the interval becomes longer.

On the other hand, it can be suspected that the different causes of anergy are all equally powerful. By repeating the experiment with different patients, maybe, one could realize that it is possible to distinguish two degrees of anergy in the region of old positive reactions. This hypothesis is to be verified.

While waiting for more complete research the observation which we have reported gives a first indication and it would be permitted for us to conclude that during the course of a disease becoming anergic, the homeotopic reinoculation of an old positive reaction can give a positive reaction while, everywhere else, the reactions are negative. The word "perergy" would seem to us capable of defining this very tenacious reaction.

Conclusions Relative to the Reinoculation of Positive Skin-tests

While studying the effects of the homeotopic reinoculation on the region of old positive reactions, we proposed to verify Pirquet's opinion, according to which the obtained reactions are too premature. We noticed this character in a constant manner. But we have established, moreover, that the reactions were often too intense; finally, that they can remain positive in spite of the subject's anergy.

Proiergy, hyperergy, perergy: these are the characters in three words of the cutaneous reactivity on the region of old positive reactions.

II. Reinoculation of Negative Reactions

A tuberculous patient whose skin-test was negative can at the moment of reinoculation, be still anergic or have regained the allergic reactivity.

This gives two cases to be considered:

First Case. -- The Control is Negative

This circumstance was produced in the following observation:

Observation: Miss Sach..., 31 years old, Saint-Marie Warc,
No 15.

Bilateral pulmonary tuberculosis, cavitary to the left, three months old; hectic fever, diarrhea, progressive loss of weight, cachexia.

Subjected to a series of successive skin-tests, first, she gave positive but progressively weakening reactions and finally negative reactions (new skin).

Dates and results of successive tests: 29 August (+), 3 September (+), 11 September (+), 26 October (+), 1 November (-).

8 December, homeotopic reinoculation on the two negative skin-tests of the previous test (37-day interval); inoculation, simultaneous, of two new points.

Negative results everywhere.

This observation seems to indicate that a negative reaction does not produce any effect of sensitization. It is true that we had to deal with a particularly severe anergy as is the usual case in pulmonary thises with subacute evolution having reached the ultimate period of their evolution. Admitting that the negative reactions had produced a certain degree of local sensitization, the latter could be insufficient to counter-balance effectively, at the moment of reinoculation, the general cause leading to anergy. We had, therefore, to undertake a counter-experiment: reinoculation of a negative skin-test of a subject having become again allergic.

Second Case. -- The Control is Positive

This circumstance was produced in one of the female patients

with the following observation:

Fig. observation (summary): Miss Bo..., Germaine, 18 years old, suffering from blennorrhagic rheumatism of which the cause was a metrorrhagia of the same nature. Beginning marked by multiple skin-tests and a high temperature. After a few days, the affection took the form of a monoarthritis of the left knee with a hydarthrosis. This lesion seemed resistant to sodium salicylate which is active only after several weeks on the action of antigonococcic vaccination. The patient entered the hospital at the very beginning of her rheumatism and we witnessed the acute phase of the infection. The skin-test was, at this moment, completely negative. But after a few days the simultaneous reinoculation of these two negative reactions and of the two controls revealed to us the characteristic phenomenon of local sensitization: the homeotopic reactions were proergic and hyperergic. The following is the detailed account of the experiment:

22 August: two completely negative skin-tests (they had been controlled for several consecutive days).

5 September: (fourteen-day interval). Homeotopic reinoculation. The controls were positive but they completed their development only after 48 hours; they remained in the papular state and their diameters did not exceed 10 and 16 mm. The homeotopic reactions were premature (complete development in 24 hours), their central zone was covered with confluent vesicles and their diameters reached 25 and 24 mm.

The aspect of the reactions after 24 hours was the following: (counter-drawings)

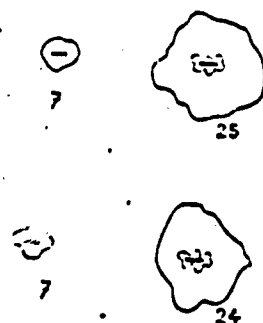


Figure 10: Homeotopic Reinoculation of a Negative Skin-test after Return of the Allergy. Right: homeotopic reactions; Left: control reactions; aspect after 24 hours. Scale 3/1.

Therefore, the negative reaction is not less sensitizing

than the positive reaction. What is the reason, then, for the discordant observation that we have recorded precedingly? The observation we are going to give now seems to indicate clearly the reason for it: While the general cause leading to anergy remains very powerful, local sensitization cannot be proved evident.

Second observation: Mrs. M.I.L..., 42 years old, Sainte Marie Ward No 1, serious typhoid fever with an anaxo-dynamic form; relapse appearance of a psycho-polyneurotic syndrome during convalescence; cure.

The skin-tests which should have subsequently become positive were constantly negative until the moment of definite defervescence.

At the time of the first skin test, 23 August 1923, the disease was in its third week; fever with great descending oscillations; prostration; inflamed tongue; distended and painful abdomen; generalized bronchitis. Two simultaneous inoculations. Negative reactions.

11 September 1923, during the relapse (fever, subdelirium, cyanosis, parched tongue, diffused bronchitis, bed sore, homeotopic reinoculation of the two negative reactions of 23 August (19-day interval), inoculation of the two control points.

The two controls are negative, the two test inoculations are also negative.

In summary, the observation is up to now similar to that of Miss Bach... and can be summarized as follows: severe and persistent anergy, negative homeotopic reinoculation.

But the events are modified in the sequence. It was not a question of a terminal anergy as in the case of Miss Bach. The patient, after a painful convalescence (bed sore, psycho-polyneurotic syndrome of toxi-infectious origin) recovered completely and one day the reactivity reappeared. Nevertheless, the homeotopic reinoculation of all negative reactions gave at that moment the characteristic phenomenon of local sensitization (prolergy and hyperergy). In order to be more certain we verified the following reactions: first, the reactions of 11 September (27-day interval) and those of 23 August (48-day interval). In both cases, the result was demonstrative.

All told, the negative reactions behave exactly in the same manner as the positive reaction and we could give to this study of the homeotopic reinoculation of tuberculous patients a general conclusion, valid for the practice of repeated skin tests in the study of anergies.

General Conclusions

In the study of anergies using the method of serial skin tests, the reinoculation of a cutaneous zone previously inoculated always becomes a cause of error; whether the reaction was negative or positive or the subject is energetic or allergic at the moment of reinoculation. The reactions obtained by homeotopic reinoculation give an inexact picture of the subject's reactivity: the sensitization created locally by tuberculin makes them too premature, too gross, too strong and even, in certain cases of energy, unduly positive. On the other hand, it seems that the homeotopic reinoculation is sometimes able to supply some interesting information. A negative reaction obtained at the location of an old skin test seems to indicate a state of particularly severe energy.

BIBLIOGRAPHY

PIRQUET, C., "Quantitative Experiments with the Cutaneous Tuberculin Reaction," Journ. of Pharm. and Exper. Therap., Vol I, 151.

----, Allergie (Allergy), Berlin: Julius Springer, 1910.

HANTOUX, C., "La voie intradermique en tuberculinothérapie" (The Intradermal Way in Tuberculin Therapy), Presse Médicale, No 14, 17 Feb 1912, 146.

RIST, E., "La réaction locale, consécutive à l'injection probatoire de tuberculine" (Local Reaction Following a Test Injection of Tuberculin), Soc. d'Et. Scientif. de la Tuberculose, Feb 1913.

KOCH, H. and SCHILLER, W., "Über die Reaktionsfähigkeit tuberkulöser Hautstellen auf Tuberkulin" (On the Ability of Tuberculous Cutaneous Inoculations to React to Tuberculin), Zeitschr. f. Kinderheilk., Vol XI, 1914, 133.

BEISSAU, G., "Die Tuberkulinüberempfindlichkeit und die durch Tuberkulin Darreichung zu erzielende Tuberkulinunempfindlichkeit" (Sensitivity to Tuberculin and Tuberculin Insensitivity Achieved by means of Tuberculin Therapy), Jahrb. f. Kinderheilk., 1915, 371-432 and 482-545.

PAGNIEZ, P., "L'anaphylaxie" (Anaphylaxia), Nouveau Traité de Médecine (New Treatise on Medicine), Vol VII, Masson, 1921.

SAHLI, La tuberculinothérapie et le traitement intradermique (Tuberculin Therapy and Intradermal Treatment), Paris: Maloine, 1922.

CALMETTE, L'infection bacillaire et la tuberculose chez l'homme et

Chez les animaux (Bacillary Infection and Tuberculosis in Man and in Animals), Masson, 1922.

COULAUD, E., "Cuti-réaction avec une paratuberculine (fléoline) chez l'homme" (Skin Test with a Paratuberculin (Fleolin) in Man), International Tuberculosis Congress, Lausanne, August 1924.

- END -