REACTIONS PRODUCED IN PINTA, YAWS OR SYPHILIS PATIENTS ON INOCULATION WITH TREPONEMA PERTENUE CASTELLANI 1905

Its possible application to the test of cure of these treponematoses

by

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Introduction - Purpose of the experiments

There has for a long time been great interest in research on the relationship between syphilis, yaws and pinta. Because of their close etiological, clinico-serological and therapeutic relationships, particularly in syphilis and yaws, extensive controversy has arisen as to whether these diseases should be considered as a single entity or as two entirely separate diseases.

The present report gives the results of experimental inoculation with known strains of Treponema pertenue of different groups of patients suffering from pinta, yaws or syphilis in various stages of clinical evolution. In addition, another group of patients with the same diseases who had first received what was considered adequate treatment with arsenic and bismuth, penicillin alone, or a combination of these drugs, were also inoculated with T. pertenue. The purpose of these experiments was to make a careful study of the dermatological, serological and histological reactions to the inoculation and to determine the degree of defence or allergy which might have been developed as a result of these treponematoses. Subsequently, after a certain number of observations had been made, it was decided to apply the inoculation test to cases which were obscure from the clinical or serological viewpoint, in order to see if any light could be thrown on them.

1 Originally issued as WHO/VDT/251 (2 January 1958). The document has been revised and brought up to date by the author.

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Difficulty often arises in the diagnosis of patients with positive serological tests who, after thorough clinical and other examinations (X-ray of the heart and aorta, spinal fluid tests, eye-tests, etc.) appear normal. In some cases these are adults with an ill-defined venereal disease history, who have come from or lived in parts of the country where yaws or pinta are endemic. Sometimes they are children with craniofacial or dental deformities (some of which have been ascribed to congenital syphilis) and a suspected history of maternal syphilis. The question then arises as to whether these patients have late yaws, latent asymptomatic syphilis or are merely giving false positive serological reactions.

On other occasions the problem is that of patients who have previously received anti-syphilitic treatment but nevertheless continue to be seroreactive for months or years afterwards. The dilemma then arises of deciding whether this is a failure of therapy, calling for a new and more intensive treatment to counter the threat of future complications, or whether in reality the person is cured and the persistent seroreactivity is only of that obscure, unchangeable and residual type so frequently observed in venereal disease practice.

The fact that the three treponematoses coexist only in certain countries of the Americas (including Venezuela) and the possibility of applying the knowledge derived from the observations made to practical diagnosis, led us to undertake the investigations reported in this paper.

The experiments were carried out at the Research Department, National Institute of Venereology, attached to the Ministry of Public Health and Social Welfare, over a period of 12-1/2 years, during which 515 inoculations were made in patients suffering from treponematoses and in suspected cases, the validity of results being confirmed by comparison with 233 controls definitely known to be healthy.¹

¹ We take this opportunity of expressing our thanks to Drs A. Gil Izaquirre, P. M. Itriago, M. Vegas, Jacinto Convit, to Mr Eugenio del Vecchio, Mrs Graciela Russo and Mrs Esther de Gonzalez, who all in one way or another - in discussions and periodic analyses of the work, review of the histological and serological material, supervision of the patients - gave valuable assistance.
The work will be described in the following order:

I. Reactions in healthy controls

II. Reactions in pinta patients

III. Reactions in yaws patients

IV. Reactions in syphilitic patients

V. Application of the results obtained to the diagnosis of, and as a test for, the cure of, the treponematoses

VI. Summary and conclusions

I. REACTIONS IN HEALTHY CONTROLS

It was first made certain that no risk or disability was associated with the inoculation of Treponema pertenue. This was ensured by: (1) the careful selection of the test subjects; (2) the knowledge that T. pertenue causes no visceral complications nor any serious lesions when the patients are carefully watched and the course of the disease is halted by treatment at an early stage; (3) the certainty that, when desired, the disease could be rapidly cured with penicillin. There was but little risk of bringing about fixed sero-reactivity, since the longest period of observation, in a few cases, was one year.

A total of 233 controls was used; they were young people without any history of syphilis, yaws, or pinta, with negative serological tests, who agreed to collaborate in the experiments and accept the necessary discipline. The inoculation of each group of 10 patients with Treponema pertenue from a single source was accompanied by the simultaneous inoculation of three or more controls.

Strains

Five strains of T. pertenue were used: the first two came from boys with frambesides and the other three from young adults in the same stage of evolution. It was certain that none of these five cases was suffering from syphilis or pinta. The strains were maintained by monthly passages in healthy subjects. Although we had infected available rabbits and hamsters, we preferred to maintain the strain in human beings (infected controls) endeavouring in this way to obtain also reactions which would give a better and more accurate picture of the natural course of the disease.
Serological changes

Various types of serological test were used: Kahn, Wassermann, Mazzini, Rein-Bossak, "Sitolipina", Kline, Meinicke, Eagle, Hinton, VDRL and Kolmer. Most of the cases were studied by the VDRL and Kolmer tests, and during the last four years the RPCF was added. Many of the tests were made personally by Dr Eugenio Del Vecchio, PASB serological expert.

The serological tests started to be positive between 16 and 85 days after the inoculation. In most cases the Reiter test was the first to obtain reaction. It was noted that the Kolmer quantitative units and the VDRL dilutions remained low for a considerable period. After the subjects were treated (600,000-2,400,000 units of penicillin procaine G in oil with two per cent. aluminium monostearate) it was found that the Reiter test was the first to become negative.

Serological study of the controls revealed many interesting facts. One group of five individuals who had been treated with 600,000 units of pencillin when the Kahn and Wassermann tests were strongly positive were re-inoculated when the titres were as follows:

Case 1 Kahn 32 units, Wassermann 4+
Case 2 " 4 " " 4+
Case 3 " 0 " " 4+
Case 4 " 0 " " 4+
Case 5 " 0 " " 4+

The re-inoculation was carried out 17, 36, 44, 69 and 72 days respectively after penicillin treatment. In all cases the disease followed the same course as on the first occasion, which seems to show that there is no close relationship between positive blood tests and the degree of immunity of the individual. As regards yaws infections, this differs from the statement by Botreau-Roussel, who believes that a fall in seroreactivity is a sign of decreased immunity in the yaws patient.

Some controls treated 25-35 days after the infection had "taken", a period during which the Kahn and VDRL tests gave very low titres or were negative and the Wassermann test was weakly positive, became positive and about a month later reached
32 units for the Kahn test, 64 dilutions for the VDRL and 4+ for the Wassermann test, just as if the treatment had not interfered with the normal mechanism for the production of reagins.

Finally, some peculiarities observed in the course of the Kahn and Wassermann reactions should be mentioned. A small group of inoculated subjects gave Kahn reactions which were increasingly positive, reaching a titre of 128 units after an average period of 56 days; on the other hand, the Wassermann test remained completely negative throughout this time.

It was also interesting to note that in a few cases the Kahn and VDRL reactions first became positive and then spontaneously became negative for a certain time, some months after which these subjects again commenced to react and gradually to show the usual reagin titres.

II. REACTIONS IN PINTA PATIENTS

It was extremely interesting to observe the behaviour of pinta patients inoculated with *T. pertenue*, since no mention was found in the literature of this type of experiment. During inquiries in certain rural areas of Venezuela where pinta and yaws coexist epidemically, individuals were frequently met with a history of yaws and late lesions of pinta, but it could not be determined which of these complaints had been the first to develop.

With respect to syphilis and pinta, Léon Blanco, in an admirable paper describing clinical experiments, showed that syphilitics could be inoculated with *T. carateum* at various stages of the disease. In these patients the pinta infection developed independently of syphilis, as if there were no immunity of any kind.

Our pinta subjects consisted of 28 individuals, classified as follows:

In the early stage (the "pintids" of Léon Blanco) 7

In the late dyschromic stage, with uneven presence of treponemes 12

In the late stage, previously treated with various doses of bismuth or penicillin 9

28
It was found that untreated pinta patients in the early stage as well as those in the late stage were completely resistant to inoculation with *T. pertenue*, i.e. there was no change at the site of the inoculation.

The inoculation "took" in four of the nine pinta subjects in the late stage who had previously been treated. The first, a girl of 15, who had been treated with adequate quantities of bismuth and arsenic about nine years previously, showed only some residual dyschromia and gave repeatedly negative serological tests. She developed a typical mother yaw after 36 days. The second was a young woman in whom the infection followed a very similar course. The third was a woman aged 50, who had suffered from pinta from about 15 years of age. She had been treated some two years previously with six million units of penicillin, followed by 20 doses of bismuth: her blood tests had become permanently negative. The course followed by the infection in this patient was very curious: the incubation period was lengthened to 32 days, during which a papule developed and very slowly increased in area, although never taking on the appearance of a frambesioma. After four months there was an erythematous hypochromic plaque some 6 cm in diameter, without infiltration but with treponemes in the lymph. This plaque commenced to clear up slowly from the centre outwards, healing being complete after six months and twenty days. The Kahn test became positive late with a very low titre - after seven months it was only two units. The whole course of the infection was very slow as if reflecting great resistance to the disease. The fourth case was a woman aged about 40 who, some 15 years before, had been treated with a considerable quantity of neosalvarsan and bismuth; although the incubation period was long - 30 days - a typical frambesioma subsequently developed.

Of the remaining five patients in this group, two were absolutely resistant and in the remaining three a hypochromic plaque 0.5-2 cm in diameter appeared at the site of inoculation, with very little infiltration. In the lymph from these plaques obtained by scarification, repeated examination failed to reveal the presence of treponemes.

The serological tests showed no changes and the patients continued to give the same reagin titres.

In conclusion, attempts to inoculate untreated pinta patients in the early or late stages with *T. pertenue* were unsuccessful.
III. REACTIONS IN YAWS PATIENTS

70 subjects were inoculated as follows:

In the early stage (secondary eruption)  
5

In the late stage (of these, eight had complications - osteoperiostitis or plantar hyperkeratosis)  
36

In the late stage, previously treated  
29

70

Of the five subjects in the early stage, whose ages ranged from 8 to 22 years, four responded to inoculation in 18-30 days, developing a framboesiform ulceration similar to that caused in them by the natural infection. One, a boy aged 17 with framboesomas of some ten months' duration, showed no change during 42 days' observation. We believe that this failure was due to his having entered the stage where cutaneous resistance develops, which, according to our observations, commences in most cases between the sixth and eighth months.

Of the 36 persons in the late stage, who had had the disease from 5 to 45 years and who had not received any treatment, 31 (86 per cent.), 15 to 25 days after inoculation, developed a group of small flat papules which then coalesced to form a plaque some 2 to 2.5 cm by 1 to 1.5 cm. The plaques were hypochromic, moderately infiltrated, not pruritic and slightly desquamative. After persisting for a considerable time with the same appearance and dimensions, they gradually regressed and disappeared in the course of four to six months, after which the infection came to a standstill in most cases. It was curious to note the great similarity between many of these cases and the hypochromic desquamative plaques (pianids) which some yaws patients show during the secondary stage and which are considered to be allergic in nature.

In one of the 31 patients who responded to the inoculation, the plaque continued to develop until at the end of 10 months and 24 days it was 9 cm by 5 cm. By this time the plaque had an extensive erythematous hypochromic base with a few central points of a delicate bluish or grey colour; the edges were formed by confluent, dry and desquamative papules. The circinate appearance of this latter lesion closely
resembled that of certain secondary pinta lesions, in particular that named by Léon Blanco "the erythematous-squamous variety of pinta".

Ten selected controls, who were inoculated with the lymph from these plaques, showed no cutaneous reaction during 50 to 60 days' observation. Some days later, the same controls all responded to inoculation with lymph containing treponemes.

For these reasons, it is considered that the lesions which appeared in the inoculated yaws patients are entirely allergic and non-infective.

In a group of these patients who were given one or two doses of 600,000 units of penicillin, the hypochromic plaque disappeared very rapidly, in 5 to 10 days.

Of the 29 inoculated yaws patients who had been previously treated, only two "took" the inoculation.

From the serological viewpoint, no changes of any importance occurred. The majority continued to give high Kahn and Wassermann titres. In a few cases, where the period of observation was prolonged for about a year, the Kahn reaction decreased in titre or became negative, as seems to be the natural course of the response in certain types of patient.

In brief, yaws patients after the secondary stage, whether treated or untreated, were completely resistant to fresh infection with T. pertenue.

IV. REACTIONS IN SYPHILITIC PATIENTS

Many valuable experiments, both on human beings and on animals, have already been carried out to determine the immunological relationship between syphilis and yaws, whose close connexion as regards some of their clinical aspects and serological reactions as well as their causative agents - morphologically indistinguishable under the ultra microscope - has led some authorities (Hutchinson, Butler and Goodman among others) to put forward a unitary theory of these diseases.

Hoffmann, Iturbi and Manson-Bahr among others, suppose that the two diseases have a common origin, which idea they express as follows: "Under the more primitive conditions in the tropics, T. pertenue spreads from person to person as a result of close contact, whereas under more civilized conditions, in which such contact is not possible, T. pallidum came to be communicated venereally and, in this way, acquired a more virulent character".
Schobl concludes that *T. pallidum* is panblasto.tropic with a tendency to multiply in all the tissues and to produce lesions of the mesoblast in particular, whereas *T. pertenue* is epiblastotropi.c and invades specific tissues, especially the skin and bones.

At present, a dualist theory is in vogue, based on observational data, to which the work of Turner and Saunders has made a fundamental contribution. Nowadays, it is agreed that only syphilis can bring about visceral changes, particularly of the nervous system and the aorta, and can establish itself in the placenta, thus giving rise to congenital syphilis. Yaws can never bring about these pathological conditions.

Returning to the exclusively experimental field of inoculations, we may mention the early work of Charlouis who, in 1881, infected a negro suffering from yaws with the agent of syphilis, thus producing a syphilitic chancre at the site of inoculation.

Levaditi and Nattan Larrier obtained positive results by inoculating monkeys infected with yaws with syphilis, but failed when they endeavoured to inoculate syphilitic monkeys with *T. pertenue*.

Schobl demonstrated that monkeys with high yaws immunity, produced by repeated inoculation with *T. pertenue*, subsequently became resistant to syphilis.

Jahnel & Lange (1926 to 1928) inoculated a group of general paralytics with *T. pertenue* from rabbit passages (Nichols strain) and another group with the Pearce and Brown strain, without obtaining positive results.

In 1933, van der Shaar inoculated 40 patients suffering from progressive general paralysis with *T. pertenue*. The results were negative with one exception, a case whose cerebrospinal fluid gave a negative Wassermann reaction.

Finally, we may mention the valuable experimental work carried out on animals by Castellani, Nichols, Takahasi, and Ferris & Turner. However, their results or conclusions cannot be applied to man, in whom the clinical course of syphilis and yaws is very different from the course followed in monkeys and rabbits, the animals chosen for the experiments mentioned.
For the inoculation of *T. pertenue*, a group of syphilitics was selected which included patients in most stages of the disease, so as to determine as far as possible the extent of the immunity which could be developed. In the relevant literature consulted, no information relating to inoculation of patients suffering from early syphilis was found.

The syphilitic patients inoculated can be grouped as follows:

- Chancre in the pre-serological stage: 3
- Chancre in the serological stage: 5
- Secondary syphilis: 5
- Early latent: 20
- Late latent: 21
- Cardiovascular complications: 15
- Late, with cutaneous and mucous complications: 2
- Nervous, asymptomatic: 4
- General paralysis: 5
- Tabes dorsalis: 7
- Optic atrophy: 5
- Recent congenital: 3
- Late congenital: 38

In only one of these subjects was the result of the inoculation positive (chancre in serological stage); the rest were all negative.

Subsequently, 214 syphilitics who had previously received what was regarded as adequate treatment (6-10 million units PAM) were inoculated. The group comprised 148 subjects treated for acquired syphilis, 4 treated for early congenital syphilis and 63 for late congenital syphilis. Of the first 148, 41 "took", most of them treated in the early phase. Of the 63 "late congenitals", 17 were positive, and of the 63 "early congenitals", 3 were positive.
The syphilitics with cardiovascular complications, those with nervous system lesions, and three patients with congenital syphilis, were re-inoculated with *T. pertenue*; they had all previously received large doses of penicillin, and in three general paralytics, this treatment had been supplemented by malaria therapy. The results were all negative, except for a very interesting case of a person aged 33 with asymptomatic neurosyphilis, in whom the inoculation did not at first "take"; after he had received 20 million units of penicillin, 30 doses of mapharside and 40 of bismuth subsalicylate, he became infected and the infection coincided with return to normal of the cerebrospinal fluid.

Some subjects responded with plaques in which no treponemes were found on dark-field examination; the plaques regressed spontaneously and rapidly, in the same way as described in the chapter relating to yaws.

Summing up: of 133 subjects suffering from syphilis in various stages, it was only possible to infect with *T. pertenue* one individual with recent symptoms of syphilis, which leads to the conclusion that syphilitics are protected against yaws.

V. APPLICATION OF THE RESULTS OBTAINED TO THE DIAGNOSIS OF, AND AS A TEST FOR THE CURE OF, THE TREPONEMATOSES

In the light of the results obtained in the experiments described above, which indicated that it was impossible to inoculate *T. pertenue* in patients, particularly those with syphilis, who had not been cured of their treponematosis, test inoculations were carried out on a number of persons whose diagnosis was doubtful.

The results so far obtained seem most promising and continue to confirm the value of this test. As it would be too lengthy to give all the details of each case, they are summarized as follows:

(1) A group of 45 children from the Child Syphilis Service of the National Institute of Venereology was tested. Some of those (with positive serological reactions) who were negative to inoculation, had been brought to the Service by outside persons or referred to it by Welfare Institutes, and no epidemiological information could be supplied. Later the parents, when interrogated, confirmed that the children had previously suffered from yaws. Others, apparently healthy and with weak positive serological reactions, were also negative to inoculation with *T. pertenue*. 
Extensive inquiries revealed that during pregnancy the mothers had been infected and thus the children were actually latent (congenital) syphilis. On the other hand, in a group which reacted positively to T. pertenue inoculation, close supervision by periodic examinations appeared to leave no doubt that they were really free from infection. In this connexion, an interesting case is that of a girl of six whose father was suffering from aortic insufficiency caused by dilatation and gave a persistently positive reaction, despite massive treatment. The child had a curious appearance, a "bird face" with delay in the eruption of some of the teeth, which were malerupted; the mother had not been treated during pregnancy. The appearance mentioned, in conjunction with the family history, indicated congenital syphilis, but the child was seronegative. The inoculation rapidly "took" and her blood became reactive just as if she were a healthy subject. This was surprising and we examined the mother (a fairly young woman): she was clinically and serologically healthy. When she was inoculated, the disease developed as in a first infection. On the contrary, the inoculation of the father was negative on three occasions. It was therefore concluded that the mother and daughter were free from syphilis because the union of the parents had taken place after the syphilis in the husband had become non-infectious.

(2) Seven adults who had been treated three or four years previously for late asymptomatic syphilis continued to give positive Wassermann and VDRL reactions, the latter ranging from 16 to 64 dilutions. Inoculation with T. pertenue was positive in all seven cases and when some time later they developed syphilitic chancre, this was fortunate and sufficient proof that the first infection had been really cured.

(3) Two women who, as in the above cases, had been treated with large quantities of penicillin, were negative to inoculation with T. pertenue; 18 months and two years afterwards respectively aortitis appeared, which was diagnosed clinically and confirmed by radiological examination.

A number of people with an obscure diagnosis are now being kept under observation, some of them being negative and others positive to inoculation with T. pertenue. At some future time it will be possible to give a definite decision on these cases.
In conclusion, it is believed that the experiments reported have opened up an extensive field of investigation in relation to diagnosis and cure of human treponematoses, based on the correct interpretation of the dermatological response to, and perhaps also on a histological study of the lesions caused by *T. pertenue*.

Many more cases must be very carefully analysed before a final verdict on the value of these tests can be given.

**VI. SUMMARY AND CONCLUSIONS**

The present report describes the dermatological, histopathological and serological results obtained by the inoculation of various groups of subjects suffering from yaws, pinta or syphilis with *T. pertenue* Castellani 1905. The purpose of this was to determine the degree of immunity or allergy which they might have developed to this organism.

Five hundred and fifteen inoculations were carried out on patients, and the results compared with those from 233 controls, known to be healthy. Subsequently, when the results were available, the procedure was applied to a group of subjects with obscure clinical and serological diagnoses: it was also tried out as a test of cure of syphilis, yaws or pinta. This is the true practical application of the experiments, above all as concerns syphilis, since physicians often cannot decide whether cure has been obtained, or not.

The work is set out in the following order:

I. Reactions in healthy controls

II. Reactions in pinta patients

III. Reactions in yaws patients

IV. Reactions in syphilitic patients

V. Application of the results obtained to the diagnosis of, and as a test for the cure of, the treponematoses

I. The controls consisted of young subjects, completely free from syphilis, yaws and pinta. For every 10 patients inoculated, four controls were also inoculated. The reactions given by them, from the clinical as well as the histological and serological viewpoint, were completely uniform. This aspect of the work is illustrated by a series of photographs.
II. The experiments on pinta patients were considered to be the most interesting, since as far as is known, they had not been attempted by any other workers. As concerns syphilis and pinta, the excellent work by Léon Blanco has shown that *T. carateum* can be inoculated into syphilitics at any phase of the disease.

Nineteen pinta patients were inoculated (four in the early stage and 11 in the late stage). The inoculation was negative in all cases. Four pinta patients who had previously received intensive treatment were successfully infected. Nevertheless, the course of the infection was slowed up, giving the impression of a certain resistance to the disease.

III. Seventy yaws patients were inoculated, five in the early period - with trachomas - 36 in the late stage and 29 in the late stage who had previously been treated. Four of the five in the early stage were successfully infected; this was because the defence mechanism had not yet been established. All the others - whether treated or not - were completely resistant to the new infection.

IV. A group of 133 syphilitic patients in the most divergent stages of the disease was inoculated; they included chancres in the pre-serological and serological stage, secondary syphilides, early latent, late latent, late with cardiovascular complications, asymptomatic nervous and congenital syphilis, with ocular and bone symptoms.

In only one case (chancre at serological stage) was it possible to infect with *T. pertenue*.

V. In view of the above facts, which seem to indicate the definite impossibility of inoculating with *T. pertenue* patients who have not been cured of their treponematosis, it was decided to apply the test to the following subjects:

(a) A group of children, in whom the diagnosis could not be established clinically or by blood tests: the results here fully agreed with findings obtained by careful periodical examinations.

(b) Seven adults treated for latent late syphilis who had continued to give positive blood reactions for months afterwards, ranging between 32 and 64 dilutions (VDRL): these gave positive responses to the inoculation and some time afterwards developed primary syphilitic infections (chancres) which indicated beyond any doubt that the first infection had been cured.
(c) Two subjects - previously treated for asymptomatic late syphilis - who were considered to be cured because the blood tests were permanently negative: inoculation with *T. pertenue* gave negative results. Two and three years afterwards respectively there were symptoms of aortitis which were confirmed radiologically.

The impressive results obtained in these experiments lead us to conclude that: Inoculation with *T. pertenue* - a sensitive and safe test - constitutes a valuable aid to the elucidation of obscure cases of yaws, pinta or syphilis.
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Fig. 1. Small papules appearing 12 days after inoculation. This is the earliest and mildest modification of the skin obtained. Few treponemes.

Fig. 2. After 21 days the papules become infiltrated and erythematous, tending to coalesce.
Fig. 3. After 25 days the papules are confluent, and have formed a plaque. More treponemes are visible in the dark field.

Fig. 4. After 31 days the lesion, which is erythematous and very infiltrated, is about to become eroded. Treponemes are plentiful.
Fig. 5. After 38 days superficial erosion is commencing in the lesion.

Fig. 6. After 46 days the typical "mother yaw" has developed. It is a papilloma, readily bleeding, very exudative, causing little pain, whose surface becomes covered with a thick scab.
Fig. 7. Small satellite papules (daughter yaws) start to appear around the mother yaw; they are more easily detected by touch than by sight.

Fig. 8. After 58 days a group of infiltrated papules can be seen around the circumference of the lesion. The daughter papules contain large numbers of treponemes.
Fig. 9. After 62 days healing starts in the centre and a clear halo appears around the lesion. The number of treponemes begins to diminish.

Fig. 10. The lesion is regressing. The surrounding area becomes hypochromic and finally desquamative. The daughter papules have partly disappeared. There are very few treponemes.
Fig. 11. Lesion after 28 days. Epidermis: irregularly alternating areas of acanthosis and atrophy. Dermis: vascular dilatation and hyperplasia. Lympho-histiocytic infiltration in the upper dermis.

Fig. 12. Initial lesion after 39 days. Epidermis: erosion partially involving the mucous layer; in the deeper part of the latter spongiosis can be seen. Dermis: extensive oedema of the collagen. Moderate oedema of the vascular walls with swelling of the intima. Perivascular lymphoplasmoctic infiltration. Presence of pigment in certain sites.
Fig. 13. Eroded initial lesion after 54 days. Epidermis: pseudo-tumoral hyperplasia of the epithelium and acute inflammation, which in certain places forms small abscesses and in others is diffuse. Dermis: granuloma very rich in vessels, formed by histiocytes and round cells.
Fig. 14. Hypochromic plaque with slight infiltration following inoculation with *T. pertenue* of a patient with late pinta. There are no treponemes in the lymph. Photograph taken very close to the skin.

Fig. 15. Cross-section of a plaque in a pinta patient 35 days after inoculation. Epidermis: irregular, atrophied in places. Areas of hyperkeratosis, predominantly follicular. Dermis: perivascular infiltration consisting of round cells. Increase in the connective tissue cells and in the density of the collagen.
Fig. 16. Section of a plaque (32 days) in a patient with late pinta 32 days after inoculation. Epidermis: irregular with areas of spongiosis; mild hyperkeratosis. Dermis: cellular proliferation and perivascular infiltration in the upper dermis.
Fig. 17. Hypochromic-desquamative plaque following inoculation of a yaws patient. It shows great clinical similarity to the "planids" sometimes seen in the secondary stage of the natural infection. There were no treponemes.

Fig. 18. Section of the plaque in the previous figure. Epidermis: areas of hyperkeratosis; discreet parakeratosis. Dermis: cellular proliferation and perivascular infiltration in the upper dermis. The resemblance to Fig. 16 is obvious.
Fig. 19. Infiltrated plaque following inoculation of a patient with tabes. There were no treponemes in the lymph.

Fig. 20. Section of the plaque in the previous photograph. Epidermis: slight acanthosis in certain sites invaded by dermal cells. Dermis: slight oedema, vascular dilatation. Perivascular infiltration of round cells and histiocytes.
Fig. 21. Curious skin reaction obtained on inoculation of a subject previously treated for asymptomatic neurosyphilis; although the inoculation was positive the course followed was very irregular.

Fig. 22. Section of the lesion shown in the previous figure. Epidermis: irregular with slight follicular hyperkeratosis. Dermis: thickening of the walls of the fine vessels; chronic perivascular infiltration of round cells.