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THE STANDING PROBLEM OF A VACCINE AGAINST HANSENIASIS: A NEW OPTION OFFERED IN TERMS OF IMMUNOPROPHYLAXIS AND IMMUNOTHERAPY

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1 — VACCINE FOR THE OVERT DISEASE

In terms of procedure in Preventive Medicine as in terms of logical reasoning, a vaccine should be devised that may be capable of giving full pre-pathogenic protection to the incidents and accidents that characterize the disease, as known from clinical and epidemiological points of view.

However, particularly on account of the features of Hansen's disease, it is useful to invert the order of factors for a moment, due to the profound alterations that have been obtained by the vaccination findings of Dr. Convit and his collaborators (Convit *et al.*, 1982).

Out of a total of 351 active cases of the Virchowian group and type (BL and LL in the British system, which we have not adopted) vaccinated three or more times, no less than 62% show clearly defined and striking clinical and histopathological changes which, with fever, general discomfort and arthralgia, represent well defined cases of the Souza Lima-Tajiri phenomenon — that is to say, forms of Tuberculoid Pseudo-exacerbations: so-called Reversal Reaction (RR).

Curiously, this whole syndrome of clinico-pathological reactivity, in the majority of cases requiring no less than 5 or more vaccinations, occurs in no more than 32.1% of positive responses to the intradermic test to a soluble antigen — leaving therefore 67.9% of the patients still immune negative, despite the intensity of phenomena provoked by the vaccination.

Everything that occurred in this material almost duplicates exactly what is classically seen in the clinical and histological syndromes typical of the pathergic responses usually seen in the forms of the immuno-negative L(V) group. After many repeated vaccinations, all the patients still remain distant from the quiet states of normal immuno-response.

Although one still cannot openly accept a "movement" outside type L(V), such responses represent, without a shadow of doubt, examples obtained for the first time through vaccinal provocation, of *immunological modulations* like those already known to fit the "cellular history" of the disease, in the words of Dr. Abulafia (1982).

This could possibly represent the immunogenic production of small clones of T cells capable of recognizing specific antigens and hence capable of explaining the phenomena, such as those that occur in different situations during the course of malignant Hansen's disease. The following situations are pertinent examples:

1 — the episodes of pseudoexacerbation (Souza Lima, 1955) — RR — after the regression of the forms of the malignant group with sulfone;

2 — the small foci of "Tuberculoid Contamination" described by Wade (1963) in the histoid form of L(V);

3 — the very rare cases, like Ag. Pupo's *princeps* patient, and the two referred by Souza Lima and Souza Campos (1947) of L(V) patients burnt out at the cost of large mutilations, showing at necropsy compact tuberculoid granulomas in the nerve trunks and in the skin;

4 — finally, in the light of the preceding cases, the equally rare patients studied by excellent observers of the so-called "nerve abscess" during the course of Virchowian Hansen's disease. This being an exception to the rule that makes these cases a *Colliquative T neuritis*, a typical form of Tuberculoid Hansen's disease. A designation as proposed by myself in 1935-1938, seeming better and simpler than the one proposed by Job *et al.* (1980) — "Segmental Necrotizing Granulomatous Neuritis of Leprosy".

I insist on the scrutiny of those microscopic aspects because it appears to me that it is very encouraging to discover in the old devastatingly malignant "monolith" of Virchowian Hansen's disease

— the sadly celebrated "Lepra lepromatosa", as proposed by myself in 1937 — *evident signs of a restricted but undeniable stronghold of cellular resistance*, even in these malignant cases.

This is surely a "breach" still to be explored, now that the work of Convit and his group proposes the use of a composition of *profound antigenic impact*, with this vaccine of M. Leprae + BCG complex.

II — Vaccine for subclinical infection ("infeckt")

Criteria for establishing the concept of infeckt in Hansen's disease.

It will obviously be a major advance when, in the epidemiological field, cases can be found in which we are certain of the installation of a subclinical infeckt state of the disease.

In the near future, in the field of epidemiological and immunological enquiry, the states of "Leprosy-infection" (Souza Campos 1956), or of subclinical infection (Godal 1974, Fliess *et al.* 1975) will emerge at the very biological root of what we call the HI-Immature group, the apparent clinical matrix of the disease.

Only recognized as a stage in the natural history of Hansen's disease, these subclinical states of Hansenic infection have recently been viewed in concrete terms.

In the past, J. Jadassohn (1913-1928) made clear reference to these phenomena in his masterly presentation of the general pathology of the disease (his "Allgemeine Pathologie" — in *Lepra* from the Handbuch of Kolle-Wassermann): "First of all I would like to stress the existence of pure invasions in which there are no reactions on the part of the organism and, on the other hand, "infections" that, clinically speaking, remain totally latent or that produce such tiny symptoms that they remain unnoticed by the carrier".

Jadassohn recalls Beurmann *et al.* (1906), and especially Gougerot (1906), who proposed that a distinction should be made between "latent microbism" in which the bacillus that is present and hibernating, as it were, causes no reaction in the tissues, and the "veritable incubation" which is restricted to just a few months, in other words, the "germination" phase that precedes the disease itself.

It happens that in the particular case of Hansen's disease, we experience a preliminary difficulty in view of the well-known

amplitude of the initial *Latency or Primary* inapparent stage (so-called "incubation"), beginning by circumscribing the "infeckt", before the inauguration of overt disease.

In this context, and unfortunately with necessary reservations, we would like to present some more complete data:

a — We can find a more exactly based assessment in the classic work of Rogers and Muir (1946), in which they sought to encompass the problem more closely, by using data on 84 reliable cases from the literature (average time of 2 years 2 months), followed by data obtained from the Indian Census of 1921, in 326 infantile cases, with the latency time from 0 to 3 years of age.

From this they produced the thesis, later denied by the work of Brazilians and Argentinian writers, of the extreme susceptibility of the child. When today we know, to the contrary, about the well-defined resistance of the small child of 0-4 years of age, with approximately 80% of the T (TT of British writers) forms, until the pubertal crisis, when the L(V) forms begin to intervene.

The data provided by the Japanese authors: Y. Hayashi (1941) are much more exact in 15 selected patients finding periods of 3-8 years in 12 out of those 15 cases; and even lower periods observed by Yajima (1942) in 993 patients: an average of 2-3 years.

b — At the end of this period of time, these people are on the brink of the overt disease, presumably ready to finally experience the habitual signs and symptoms characteristic of the disease. In this way, still healthy carriers of the specific pathogens already form a living part of the pathological process.

The chronological and biological correlations throughout these stages of the process are not, unfortunately in the case of Hansen's disease, as well demarcated as in tuberculosis. It is surmised that the human recipient invaded by *M. leprae*: "the immune compromised host", still negative to lepromin, can shelter a heavy load of bacilli, a wealth of germs still without any clinical expression (cf. the old findings on bacilli present in the lymph nodes of contacts in endemic areas).

Probably it can also be accepted that, by sheltering so many bacilli, these human recipients — even *before* the action of immune mechanisms — become an unexpected and potent source of contagion to the community, by far exceeding the cases of overt disease (cf. the well studied data of Indian authors).

On the other hand, we know of the epidemiology of so many infectocontagious conditions that, to maintain this subclinical "infeckt", both cellulo-mediated or humoral response mechanisms may come into action. In this sense there may occur the possible detection of antibodies in patients even without ever having shown any clinical evidence.

This leads us to question the pertinence of the criticisms that have been made of the value of the sero-reactions of the FLA-ABS type in a recent *mise au point* by Abe *et al.* (1973) — a criticism that was in fact raised by the results obtained also by Sritharan *et al.* (1981) showing high indices of positivity already in contacts, when confronted with the indices obtained in defined cases of the overt disease.

In this respect, we should make some comments on the ideas recently produced by reliable Brazilian observers. Among others, we would like to mention the following points which deserve further careful study, possibly in greater depth.

1 — The idea that the whole process should start from a single root, the Immature group, recalls, curiously enough, a similar scheme proposed by R. Cochrane in 1940: "basic lesions".

2 — However, I believe that, together with what we have learned since that time from the classic Brazilian, São Paulo masters among others, several reservations can be formulated as far as this idea is concerned.

3 — Not only as to the point of departure I, but also concerning some of its developments.

4 — I am quite aware that a broad spectrum scheme for everything that comes from Group I does not imply any "sequential" idea in the British authors' sense. On the contrary, what is now being proposed is a fixity (in my opinion, still rather premature perhaps) for what are known as "other types". This puts an end to the British sequential proposal in terms of microscopic findings. And it is already a definite advantage over them.

5 — I confess, on the other hand, that I am not so sure that there is a single root — Group I — at the basis of the whole process. And this reservation is proved to a certain extent by what we know of specific granulomatous diseases such as the "inapparent" forms in syphilis, for example, and the "sub- clinical forms" in tuberculosis as mentioned above.

On this point, I would refer to the well thought out ideas in Gomez Orbaneja and Garcia Perez's old paper (1953).

This — besides the lack of precision as to the true beginning of the process that the immuno-pathological findings of Myrvang and Godal (1973) perhaps present as a possible raising of the veil — still unfortunately hides, for us, *the biological onset* of the whole process.

In any case, I believe that, as the Spanish authors we have mentioned point out, this onset includes *more than one form of beginning.*

6 — This is exactly what is suggested by Noussitou (1979), an author who, although distant from us and always original in his concepts, interprets the Asiatic material in the same way as Argentinian and Brazilian Hansenologists.

Commenting on Ridley's scheme (Ridley, 1977), Noussitou does not accept that the "TT AND BT" cases result from untreated immature cases, but come directly from sub-clinical infections — just as Ridley imagines for the "LLp" cases, that is to say, in this rather complicated terminology, full-polar type L(V) cases.

As for infantile cases T and TR, Noussitou argues — and this we already know from Noussitou himself and Bechelli *et al.* (1974) — that they do not appear to come from the immature clinical matrix because, in Burma, I children "whiten" rapidly or soon become MAT or T (in 750 new infantile cases between 1965 and 1973 there were no more than 25% I, and already 64% T).

7 — This leads us to enquire into the display of certain definitely primary T forms of response of the tissues in Hansen's disease. This is particularly so in the following situations:

7.1 — As in primary tuberculosis of the skin and its cutaneous lymphnode complex (cf. Bruusgaard, 1926), the fundamental finding of Souza Lima and Souza Campos (1947) of the "infantile nodular T" forms did not imply the need for any I root. They were, though rare today, clearly primary, and data from 1947 and also more recently those given by Pessoa Mendes (1956) confirm, without a shadow of doubt, the primary nature of these "Early infantile T infiltrates", avoiding with this designation the word "leprosy".

In these cases, Pessoa Mendes observed 7 out of 12 with more than three lesions, three of these cases having 8, 17 and 23 lesions (the latter being found in two sisters, contacts who perhaps received infinitely large doses of infecting bacilli).

A spontaneous healing was observed in 8 of the 12 cases, the rest being in a clear state of involution. Mitsuda was strongly positive in all of them with + + +, and only one case with + +. It is important to notice that the follow-up was between 5 and 14 years — in Souza Campos' material it was between 15 and 21, as a rule with stable scars and definite "vermiculate" appearance.

The histological picture, for which P. Rath was responsible, revealed an almost equal number of *torpid structures* in 4 cases, reactional in 5. It is curious that this reactional aspect was only microscopic, *never clinical*, and it did not coincide in the case of the little sisters, one with 23 lesions, and found to be torpid, and one with 17 lesions, with reactional findings. Only these cases with numerous lesions were a hint to probable hematogenic origin, while in the majority of these infantile T cases, the solitary nature of the lesions or their very limited number recalls the discussions about the possible exogenous origin of certain cases of Lupus Vulgaris.

We must therefore accept that there are primary forms, such as cases I, Infantile T, and TR, that dispense *before or after* any kind of lesions. We should notice that in Souza Campos' infantile cases, this careful observer has already pointed out that they were strongly

immunopositive — i.e., Mitsuda-positive long before the nodular T lesions, judging from the children who, living in the same conditions, clearly showed that they were suffering from sub-clinical infections, without any overt evidence of disease.

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Knowing already the *main potentialities of persistently* immunonegative contacts, it is now the *lieu et place* to examine them in the light of the findings of Dr. Convit and his group.

Small children 0-4 years of age will not be included, with an option limited almost only to the group and type T (BT or TT according to British authors); as well as school children between 6-10 years of age with options still limited to the forms T and to the group I — "Immature" Hansen's disease.

It is precisely the groups of young contacts between 12 and 19 years of age, vaccinated with the proposed Vaccine of *M. Leprae* + BCG, that are of interest, because there one can find human recipients who, as is known, still have a chance of displaying resistance.

It is well known that in endemic countries, individuals who remain immunonegative to the Mitsuda test, from 16 to 20 years of age, are already considered as potentially dangerous and of high risk.

This situation is now being challenged by the vaccination efforts of the Convit proposal, with *results* still limited by the as yet small number of people vaccinated: 25 to 357 vaccinated between the ages of 12 to 14, and 15 to 19.

These are, however, promising results, as besides the immunological reversal, respectively from 89.8 to 92.9%, there did not occur *any apparent disruption* in the *statu quo ante*, i.e., without clinical sign of progression towards any form, even T, of the overt disease. As to the immunological level, Rotberg, who repeatedly studied this subject in 1934 and between 1937 and 1944, provided observations about the immunological root of the overt disease. As is well-known, Rotberg (1937) established that Mitsuda anergy results from a congenital incapacity to respond to lepromin, due to the lack of a congenital protection factor — Factor N (or better called, perhaps, NR for native resistance).

Hence, the corollary idea of the existence of an "anergic margin" at the root of L(V) forms a circumstance fortunately limited to only some 20% — which has now been corrected in a more precise estimate by Convit's figures to *no more that 8-10%* — of vaccinated contacts.

There would then be a "ceiling" for the appearance of L(V) forms as was suggested, on the epidemiological level, by Kajpoor in India (1963). Another piece of evidence in favour of this limit of the anergic margin is shown by the well-known fact that even for those in very close contact (husband and wife) a persistent negative Mitsuda does not necessarily mean an ominous future because it is quite possible, especially for the woman, to stay "healthy" indefinitely, although immuno-negative: living in a condition of subclinical infection, enjoying a native and/or acquired resistance, which I have proposed to call resistance with a small *r*.

This is ideal material for future enquiries which, in terms of sub-clinical infections, may help us to discover the *biological matrix* of the disease, and in the near future a possible field of choice for immuno-prophylactic attempts on the lines of Dr. Convit's *M. leprae* + BCG vaccination.

Access to discovery in the field of scientific research lies, as in other areas of thinking, in achieving "new forms to new contents".

The work being elaborated by Dr. Convit and his group had been following a careful Pastorian methodology.

The irreversibility, still always claimed, of the immuno-negative status vis-à-vis *M. leprae*, although fortunately limited in compromised hosts, shows more than one vulnerable point whether in spontaneous conditions or, as has now been demonstrated by Dr. Convit's findings, with the use of a powerful immuno-therapeutic challenge.

For this reason, all of us Hansenologists in Latin America are following with enormous interest the efforts of our Venezuelan colleagues to launch an attack on the hitherto inaccessible set of states that may lead to Virchow's leprosy, now finally vulnerable at its very roots.

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