# The indeterminate group of hanseniasis, and its basic connotation: the polar concept. An evaluation and a refutation of the so-called "spectral" approach

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SUMMARY — The clinical, epidemiological and immunological importance of group I *has* been consistently ignored by English-speaking authors like Turk and Ridley ck Jopling, whose publications underestimate these inaugural, undifferentiated forms — the true matrix of the endemy.

The subtle use of the ambiguous word "indeterminate" — instead of the clear-cut undifferentiated, leads to the disregarding of a zone of instability between the groups and the polar types of the disease.

It happens that it is this very zone of instability (Orbaneja-Puchol 1961) that includes a wide range of pre-granulomatous lesions — exactly the undifferentiated forms together with a small rim (8-9%) of unstable granulomatous forms: B and TR.

In this paper it is demonstrated that the wide range of this endemic undifferentiated "matrix", amounting to 50-60% of all cases of hanseniasis, constitutes a precious tool of epidemiological investigation, contrasting with the comparatively small number of unstable forms at the granulous level (B and Til).

Termos índice: Indiferenciada. Indeterminada. Hanseníase incaracterística. Hanseníase maculosa. Classificação. Grupo I. Histotipos.

Key words: Undifferentiated. Indeterminate. Uncharacteristic Hanseniasis. Macular Hanseniasis. Classification. Group I. Histotypes.

The undifferentiated (so-called "indeterminate") group presents easily recognisable clinical features and a very well-defined immunological outcome. It is not necessary to include in its realm cases that are only clinically indeterminated, though microscopically advanced, presenting either discreet tuberculoid structure "in organization" or discreet leprocitary "leprous structures" (Buengeler, Souza Lima) .

These already differentiated I cases with its microscopically pre-T or pre-L (V) lesions can easily be classi- fied in the "fringe" that surrounds immutable polar types, i.e., they can be classified in the polar group as meant by Latapi (pre-T macular lesions being the "macular anaesthetic" cases of Dharmendra).

On the other hand, the group of undifferentiated cases can attain a marked degree of clinical regression

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while remaining *undifferentiated* even when submitted to prolonged and metic- ulous follow-up, with biopsies and serial sections for as long as 4-5 years. This is known to happen in up to 59.9% of cases submitted to a 5-year follow-up. The incidence of undifferentiated cases is, also elevated (60-80%) in "contacts" and in patients from private practice.

## I - THE INDETERMINATE ("UNCHARACTERISTIC") GROUP AS WORKED OUT BY SOUZA LIMA & ALAYON (1941), F. E. RABELLO (1943) AND AGUIAR PUPO (1939-1966)

I was surprised to hear such remarks about indeterminate "Leprosy" in the recent Bergen International Congress, a matter of utmost plainness to us Latin-american hansenologists. So confusing and complete misconception about "I" cases does have many explanations. Above all the total ignorance of fundamental Brazilian works on the subject, such as the basic monograph by Souza Lima & Alayon, dated of some 30 years ago.

I also consider that Ridley & Jopling's proposal of "five" histotypes will lead to a disastrous effect: the acceptance of LI, BI and TI, so-called "spectrum", will inevitably lead to the destruction of the I group, a great loss when seen from an epidemiological point of view. And thus, what since 1962-1966 appeared to be only a misconception turned out to be a great error: *Parvu,s error in initio magnus est in fine.* And little is done, regard- ing the histopathologic features of Hanseniasis by the English authors further from the classical three points of Felix Lewandowsky (1921): the simple inflammatory, the tuberculoid and the lepromatous basic histotypes.

It is no wonder that the English speaking hansenologists remain in trouble with the "I" group and even expressing having "problems with the Indeterminate Leprosy". They could admit instead their unfamiliarity with the concept of "Indeterminate Leprosy" itself.

For most Spanish, French (Languillon) and all Latin-american hansenologists there is no such a problem as to achieve a correct diagnosis of "I" cases. It seems quite easy to discern "I" cases with such elementary devices as the histamin-pilocarpin tests, and above all with a correct appraisal of Mit,suda reaction.

One may easily understand our surprise, in this connection, when — in 1956 — i.e. exactly ten years after Rio de Janeiro Panamerican Conference, we read in the International Journal of Leprosy that Browne and Davey were deeply engaged in a discussion of so--called "macular series" and — worst of all, the alleged need of a name "that does not ignore the entirely unstable, dynamic character" of the I eases.

No less disappointing was the oblivion of the importance of this group of cases as a precious epidemiological tool, specially in field work. And this was the great merit of Aguiar Pupo (1946-66) and his disciples in showing how significant was the incidence of "I" cases among hansenie contacts, as high as in 70-80%. Along this line the 1939 paper of Aguiar Pupo was epochal in terms of the unexpected clinical and epidemiological stress on "uncharacteristic" (our present "indeterminate") group of cases. No less than 401

patients of a total of 583 hanseniasis cases of private practi,..e — i.e. 68.7%, the true "matrix" of the whole process.

In the same vein was much later the "rediscovery" of the impressive del Favero's figures on "I" cases found out by means of an *intensive survey* - no less than 53%, as was stressed by F. E. Rabello and L. M. Bechelli (3d Buenos Aires Panamerican Conference 1953).

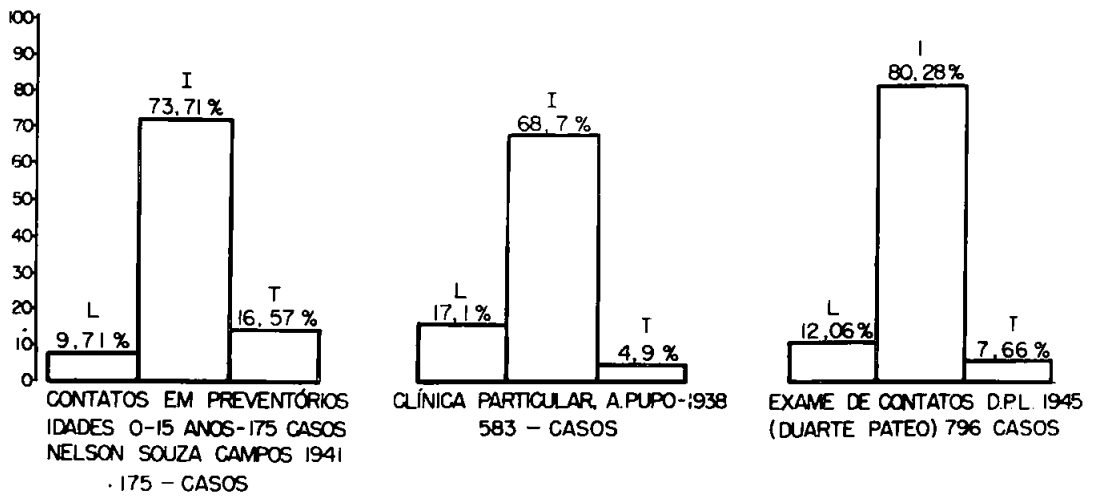
"Certain *macular* cases constitute at most a *variety* persisting for some time, but definitely not a fixed type" (F. E. Rabello 1937). And certainly not an "evanescent phase" of the disease, in the sense of Marchoux, Jeanselme.

Another text must be reproduced: "the scientific grounds of macular "forms" must be the same we use to define the two extreme forms", i.e., the clinical features, pathology, the response of the Mitsuda reaction and evolution : "a chronological evaluation of those three elements" (F. E. Babello 1943).

No less important in this field is the contention of Latin-american authorities that the "indeterminate" eases represent the basic line of instability, i.e. the pre-granulomatous "matrix" of the whole process.

A further step was attained by analysing Souza Lima & Alayon fundamental material, bringing to confirmation the differences that remained between "undifferentiated" cases and those already more or less "differentiated" into one of the polar directions, i.e., very slight or minor pre-L and pre-T lesions. Microscopic findings as a rule precede or more rarely follow in those advanced cases, clinical signs, if some time is given to completion of evolution.

FREQUENCY OF L HANSENIASIS IN S. PAULO



Therefore, and of this I was already aware, I cases may exist in which histopathological findings may be conflictant — for a certain length of time, with clinical features — without necessarily implying in complete transformation to one or another of the polar shaped lesions. And this may account for Dharmendra's "maculo-anaesthetic forms", which thus remain in the borderline fringe *(group)* of the tuberculoid polar *type*.

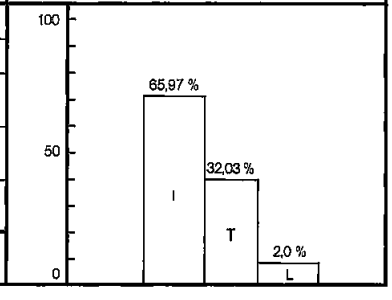
There are four capital issues in the natural history of group I.

— *1* Group I is quantitatively important in private practice (Aguiar Pupo 1939), specially among 5-15 teen-ages (Noussitou 1963).

— *2* Group I is largely predominant as the inaugural form of the disease among "contacts" (Aguiar Pupo *et al.* 1946-1966).

— *3* Group I as the presenting form of the disease is the very "matrix" of the endemy (F. E. Rabello, L. M. Bechelli 1953).

| ANÁLISE EPIDEMIOLÓGICA POR J. DE AGUIAR PUPO | | | | | | | PERCENTAGEM DE FORMAS CLÍNICAS |
|---|---|---|---|---|---|---|---|
| IDADES | FORMAS CLÍNICAS | | | | | | |
| | GRUPO INDETERMINADO | | TIPO TUBERCULÓIDE | | TIPO VIRCHOVIANO | | |
| 5-10 anos | 2.979 casos | | 1.016 casos | | 40 casos | | |
| 10-15 " | 1.773 " | | 1.012 " | | 58 " | | |
| 15-20 " | 153 " | | 211 " | | 48 " | | |
| total de 5 - 20 " | 4.905 " | 65,97 % | 2.239 " | 32,03 % | 146 " | 2.00 | |




Incidence of I cases among 5-15 teen-agers
(spud Noussitou, Burma 1963)

— 4 Group I gathers fairly homogeneous cases, presenting a nucleus of histologically undifferentiated features, bearing precise clinical, immunological and evolutive connotations.

.Since 1943, I have demonstrated that simple histological "residual" findings may not necessarily signify an actual "transformation" from L or T into the I group. On the contrary, cases sieged in the "core" of one of the polar types cannot be the subject of such "mutations".

In this connection, it is very important that even distinguished hansenologists, when confronted with such "residual" cases, based on purely conventional histological criteria, seem to forget the utmost importance of submitting their sections to *specific staining for lipids*.

# II- AN EVALUATION AND A REFUTATION OF THE SO-CALLED "SPECTRAL" APPROACH

The proposal of a "spectral concept" (Turk, 1970) will reestablish the original "chaos" as Latapi predicted in 1948, since this proposition does not account for the *immutability* of Latepi's *types* (so-called TT and LL).

The "interpolar" material (Languil-Ion 1969) composes a *zone of unstabil*-ity as postulated in 1961 by our Spanish colleagues Orbaneja and Puchol. Those "unstable forms", as Rebell° called them, gather first around a basic pre-granulomatous zone- group I, and then come to compose an advanced granulomatous zone-B and TR forms.

On the other hand, a disease presenting so stereotyped polar types would necessarily contain between them forms with ill-defined, cryptic and undeterminate polar "vocation" : the above mentioned zone of unstability. In fact, all or nearly all cases of hanseniasis should be LL or TT in *type,* were it not for our present inability to discern the real position of all "interpolar" cases, in terms of polarity. We are indeed in *urgent need of more refined* means of research, and conventional techniques must be abandoned in favor of newer ones, specially those offered by immunopathology and even immuno--genetics, in order to solve the problem of B and TR material.

What happens in the "zone of instability" (1)
Zone of instability (Orbaneja — Puchol, 1981)
Basic area (pre-granuloma)

Indeterminate group (Endemic matrix)

Modern active therapy is extremely successful in blocking the path leading both to L and to T groups and types.

Group / represents the more important phase of the disease adding up to 50-70% of all cases of the disease.

The alleged "five points of the spectrum" as proposed by Ridley & Jopling has been presented as confessedly "arbitrary" and contain admittedly "intermediary points between the five marker points" (why five and not fifteen?). This proposal is in fact no more than an interesting "vue d'ésprit", *hardly acceptable in terms of practice.*

What happens in the "zone of instability" (2)
Zone of instability (Orbaneja — Puchol, 1961)
Advanced area (granuloma)

B, TE, Reversal T and other baffling forms

Modern active therapy often unsuccessful in blocking the path leading to L and T groups and types brings up the question of possible genotypes (LL — T1 — Lt — TI Alonzo, 1966) explaining induced conflictant forms.

Ridley & Jopling's position is untenable:

*1* because it works on the obvious and does not add up to any *new* contribution at the immunobiological level;

*2* because it renders the present diagnosis of two types and two groups still more difficult, in the sense that it introduces *subjective* instead of objective grading criteria (evocative of L1, L2 and L3 of the old classification) ;

*3* because it presupposes between polar types a continuous flow *which does not exist* as even "indeterminate" cases may stay long as I;

4 because it implies with LI, BI, TI sub-groups the destruction of group I, a most precious tool in field-work for the recognition of the "matrix" of the whole process as well as of the endemy;



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5 because it does not account for what is possibly going to happen in the future, i.e., the reduction of all or nearly all "unstable" forms to L (V) and T polar groups and types;

6 finally, because it is based in an error of method, calling for so-called "Occam's razor" ("entities need not be multiplied if unnecessary" — J. Stuart Mill).

Returning to the B — TR material, it must be stressed that it is a very small lot of the whole problem, summing up in terms of B forms to no.more than 3.2% (Convit in Venezuela, Browne in Belgian Congo) — its known maximum being 6.8% (Alonso 1966).

Moreover, with these *unstable* forms we have to face a *reality* — the so- - called "dimorphous leprosy" and a *fiction* — the "dimorphous group". As a matter of fact, cases and forms B do not constitute a "group", as they are actually "forms" of a group in Latapi's sense — the L (V) group, at the immune-negative pole. Notation recommended of these forms being: *B forms of group L(V).* On the other hands, cases and forms TR — "tuberculoid reactional" (Souza Campos 1940), curiously ignored by some English- - speaking hansenologists, do not constitute any "group", as they belong' already to a group — the T group at the immune-positive pole. Notation of these cases will be *TR forms of group T.*

On behalf of the polarity concept, Latin-american hansenologists must strongly object to Dr. Turk's contention of a constant "swing" between the poles. Along this line, it must be said that it is not true that the disease only "seldom" remains in the "indeterminate" pre-granulomatous group. On the contrary, in their classical findings on the subject, Souza Lima and Alayon (1941) and F. E. Rabello (1943) could make sure of *the long persistant character* of a lot of "indeterminate" cases as such, by using serial sections and repeated biopsies along 3 to 5 years.

There is no such a thing like a movable spectrum between the poles. For instance, the T *type* cases (so-called TT) do not share any kind of "movement", as they are absolutely immutable ("citadel of resistance") being Mitsuda +++ plus (sometimes necrotic) and absolutely benign, healing with little or limited defect:

The *"citadel of resistance"*

1. The early tuberculoid infiltrates (Souza Campos (1937).

2. Micro-papuloid hansenid (leprid) figurate and *torpid.*

3. Colliquative tuberculoid neuritis ("nerve abscess").

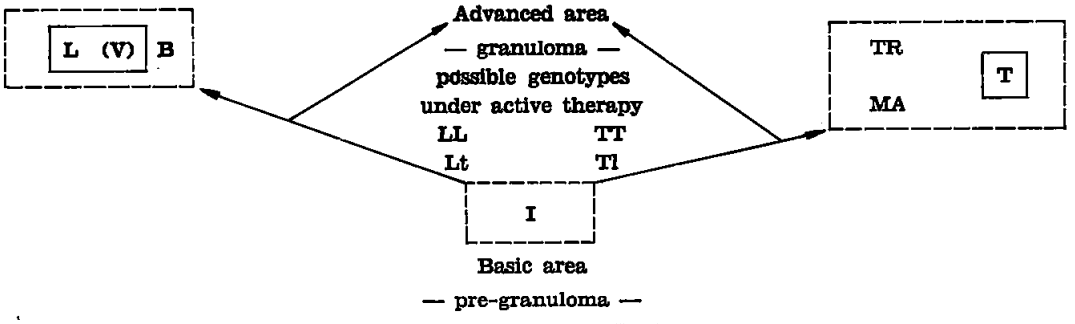
4. Primary and single TR forms (F. E. Rabello 1940, R. D. Azulay 1960).

Finally, immunopathological findings while providing a spectacular confirmation of the polar concept, cannot be expressed in terms of a "spectrum". In fact, the difference between immune-positive and immune- - negative poles may be not so deep, for instance in values of antithyro-globulin factor as 11 versus 48% or of antimycobacterial antibodies as 28 versus 55%, or of amyloid nephropathy as 8 versus 26%.

These figures present only average values, some of them have been recent- ly reevaluated and all in all confirmed : for example Terencio de Las Aguas *et al.* 1974, on quite similar findings.

**HANSENIASI: DYNAMICS OP THE PROCESS**

**Zone of Instability**
**(Orbaneja — Puehol 1961)**




[ ] = types (immutable)
L(V) = type virchowian
T = type tuberculoid
I = group indeterminate
LL — TT = homozygous (Alonso 1966)
Lt — Tl = heterozygous (Alonso 1966)

[ ] = groups (unstable)
B = forms of the group L(V)
TR = forms of the group T
MA = maculo-anesthaetic (Dharmendra)

**(hence unstable often baffling forms and often induced by modern active therapy and/or by associated non-hanseniasis pathologies).**

A recent consideration of the "zone of instability" as defined by Orbaneja and Puchol in 1961 leads to the understanding of the development of "forms" of difficult classification amongst the small number of unstable granulomatous forms of the advanced zone. These amount to 5-7% for B cases of group L (V) and 8-9% for TR. cases of group T, formerly thought to be submitted to "lepromatous conversion" (Souza Lima — Souza Campos 1947). But it is precisely this assumed "transformation" (no more than 4.7% of total T forms) that was aptly denounced by Abuso (1966) who preferred them classified in the doubtful "interpolar" situation.

The influence of multiple factors of instability at the granuloma level must be taken in account:

1. Active drugs that may possibly influence the bacilli metabolism and even invert morphological indexes. Actually it has been noticed that cases of difficult interpretation began to be recognized since 1951-54, i.e. some 8-10 years after the introduction of sulphone therapy.

2. Certain diseases like diabetes mellitus or visceral malignancy may contribute to provoke unstable TR and B forms (Opromolla).

3. Finally, genotypes LL and TT (homozygous) and Lt Ti (heterozygous) can be hypothesized (Alonso) as one more factor of instability.

In short, we can presuppose at least three factors of instability active therapy, associated non-hansenic pathology, working on predisposing genomes, and engendering occasional unforeseen responses.

**RESUMO**

*Neste trabalho faz-se uma revisão de textos antigos, brasileiros, alguns de mais de 30 anos - todos lamentavelmente ignorados por alguns autores estrangeiros, mas que entretanto ainda hoje fazem autoridade, sempre que se deseje uma correta concepção do Grupo Indeterminado da Hanseníase.*

*A tônica desses textos, hoje clássicos, cai na necessidade de acabar, de uma vez por todas, com as incertezas e ambigüidades geradas pela agora inaceitável palavra "Indeterminado".*

*justamente d sombra dessa equivoca palavra, que alguns autores de língua inglesa pretendem atacar e, se possível, destruir a nossa brasileira, argentina, mexicana - e hoje latina concepção da Hanseníase, em especial quanto às luzes que traz para a dinâmica do processo.*

*Retomando a alternativa - já proposta no Congresso de Havana 1948, é vivamente recomendada a expressão Indiferenciado para bem definir este grupo, fundamental também como instrumento, preciosa no campo epidemiológico.*

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