CORRESPONDENCIA / CORRESPONDENCE

ABOUT BIORESISTANCE, COMPARATIVE CHEMORESISTANCE AND SULFONO RESISTANCE OF *M. leprae.*

While the emergence of-sulfone resistance in *M. leprae* was foreseen and known, for a long time, it is now presented as a tragedy jeopardizing leprosy control thorough monotherapy. This resistance mainly reported in the U.S.A. is not observed in all other parts of the world.

In our opinion, that observations result from an incorrect implementation of sulfone-therapy resulting in low sulfone blood levels, as a consequence of use complex disubstituted sulfones, insufficient daily dapsone dosages, irregular or noncompliance to treatment, premature interruption of treatment, etc. Chemotherapy must not be thoughtlessly used.

Underlining that microbial chemoresistance (as antibioresistance) is only a particular case of the general bioresistance this one directly bound to the life itself and, so often, an impediment to our present therapeutic actions, it is certainly enriching to remind us of the teachings given by insects (especially mosquitoes of the genera Anopheles and Aedes facing the "pesticides" so widely used through the world. Such are the exemplary difficulties of the antimalarial (and antiamarillic) campaigns led in French Guiana some years ago[2].

The utilisation of synthetic chemical products, in general biology and in pathology, of immense and indisputable practical interest, is able to induce, if we don't take care (and almost infaillibly if it is badly performed) to entanglements very troublesome or really catastrophic resistances. But there is no need to amplify the facts; some errors must be avoided, and others amended. Then, first, they have to be known and we have to look at in front of them.

We have to consider coldly the question of the "bioresistance" (=resistance of the being creatures or of the living tissues) of the various infectious agents, to therapeutics products, mainly of chemical origin, powerful, therefore, in fact, potentially toxic, perhaps dangerous and always of delicate utilisation. It is evident that resistance to the real chemical products (as to the antibiotics of mycological or bacterial origin) have already been multiplied, multiply just now and will be multiplied in the future. We have recognise these resistances to know, first, to avoid them, next to fight, or in case of need, to surpass them.

We doesn't know and regret the real importance (sometimes serious, in view of therapeutic action) of the bioresistance developped by numerous bacteria, from classical or substituted microscopic flora, such as *Mycobacterium tuberculosis,* the genera *Staphylococcus, Streptococcus, Neisseria, Pseudomonas,* and various patogenic fungi.

The bioresistance of our microbiologic agents has already, some decennies ago, transformed many aspects ,of our infectious (human as animal or vegetal) pathology. This is a phenomenon of an absolute generality, intimately bound with the life itself and dependent of it.

The sulfonoresistance of Hansen's bacillus is but a peculiar aspect of bioresistance (and of chemoresistance). To fight it with sucess it is necessary to understand the general mecanism of the appearance and of the development of chemoresistance after a bad application of a recognized chemoactivity.

That is why we think a typical example, well known and understood by its causes of appearance and expansion, its wretch consequences and the means of efficient fight used in that case, is able to be interesting and explicit

Our example reaching a zoologic scale greater than the microscopic one fixing more particulary our attention today, can be the resistance of numerous insects subdued to eradication campaigns by means of synthetic chemical compounds, that is to say of "pesticides", widely used through the whole world, especially for the fight against the great intertropical endemo-epidemics, at first range of which are malaria and yellow fever. An exemple of resistance, indeed, to remind and meditate usefully.

Thus, for our concern, in French Guiana, from 1948 (when we were just having brought with us, return of a fruitful leave in France, D.D.T. (Dichloro-diphenil-trichloroethane) and D.D.S. (Diamino-diphenyl-sulfone), each one in view of a broad practical applying on the field, we began our operation of systematic remnant intradomiciliary. dedetisation.

This was done according to the demonstration on the ground that Dr. A. Gabaldon had been pleased to make, at our personal intention, in Maracay, Venezuela, during the XIInd Panamerican Sanitary Conference (1947), against, with priority, at once, our great malarial vector-amid our 22 guianese species *of Anopheles* - *Anopheles darlings* and the classical vector of urban yellow fever, *Aedes aegypti*, which, facing the jungle yellow fever virus, permanently present in our guianese expansion of the huge amazonian forest, pullulated in all urban agglomerations of French Guiana.

This was indeed to grapple with a hard task, apparently a challenge, a wager, for a great majority, notably owing to the foreseenable difficulties of serious-and not seeming-practical aplications.

But on account of the expected excellent results we thought to be able to increase our understanding on the manners to approach generally chemoresistance, to avoid and, if necessary, in time, to transcend it.

Yes all this is far to be neglected, with regard to the sulfono-resistance of the Hansen's bacillus, now yielding gravely problems, as we know.

The fact remains that we clearly saw, after the use on a great scale and during many years of "pesticides", the errors of utilisation not to be done to acquire the pursued eradication, the "genocid", of the concerned insects.

These show reactions for easier to be observed than, for instance, those of Mycobacterium leprae (bacteria know for its particularly long time of multiplication - about twenty days - its impossibility to grow on our artificial mediums and also the difficulties - at least - which we have to inoculate it to laboratory animals) face to face with a chemical bacteriostatic molecule, how much powerful and active it can be, such as is Diamino-diphenyl-sulfone, also of course, potentially toxic for men.,

Then long attempts of pratical use on the field for the foremen and workers of our service of Antimalarial and Antiamarillic Fight had been necessary to learn how to set down, at a quick and regular rhythm, 2 gramms of pure D.D.T. by each square meter of treated mural surface, in solution in oil at 5% of active molecule for non absorbing (painted) walls

and in suspension in water, also at 5% (from a wettable powder at 50% of active D.D.T.) for the more or less porous and absorbing walls. So we obtained a remnant insecticide activity during about five months, necessary and sufficient to annihilate several sucessive generations of mosquistoes and without the risk of engender D.D.T. resistant varieties of these mosquitoes (as a result of a transient and noxious repellent effect).

All houses, barring none, had been treated with the sufficiently swift rhymth so it was not talk for mosquitoes to take advantage of the repellent first action of the insecticide to find refuge into neighbouring "healthy" (for having been no, or insufficiently, "treated") dwellings.

A local resolution passing obligatory the antimosquito campaigns allowed to overcome the scare cases where persuasion appeared insufficient.

Therefore very strict application, in agglomerations as well as into habitations scattered the banks of the streams furrowing our guianese equatorial forest (itself otherwise, practically empty), had been carried on.

Among our 180 species of mosquitoes, evidently, have been first hit the two great anthropophile vectors *Anopheles darlingi* and *Aedes aegypti*, once again at the astonishment and misunderstanding of several.

The *Stegomyia* completely disappeared during about ten years from whole French Guiana, as officially recognized himself Dr. Fred Soper, Director of the Panamerican Sanitary Bureau (XIInd Panamerican Sanitary Conference, Ciudad Trujillo, October 1950) eradication verified, on the premises, by two P.A.S.B. missions, each during three weeks (MM.D. Raush and Duret).

But, alas, the urban yellow fever vector reappeared and quickly invaded anew our French Equatorial Department, by 1963, being this time resistant to dot and also cross - resistant to all other chlorinated insecticides such as Actidrine, Dieldrine, Gammexane, Chlordane, Lindane,...

The situation was that time, really serious. What had been happened? What errors might have been committed? How to react?

During the execution of our campaigns we always kept direct and useful contacts with the managers of the siilar actions led in our neighbouring countries, following up their evolutions on the ground and, this, particularly in British Guiana (Dr. Giclioli and Dr. De Caires and mainly, in Dutch Guiana, Surinam, (Drs. Wolff and Van der Kuyp), on account of our long common frontier.

Rapidly we understood that the campaigns in Surinam, for several causes and various difficulties, of political, administrative or social origins, could not be led with the necessary rigor and, so, we looked ahead the apparition of D.D.T. - resistance in *Aedes aegypt*[2].

And, effectively, as Cleary foreseen, we were the first foreign sufferers of a neighbourhood become dangerous. Our own efforts for many years were reduced to ashes. In a few months, during 1963, French Guiana, was completely invaded by an *Aedes aegypti* chemoresistant to all chlorinated "pesticides", then generally advised and used all over the world for antimosquitoes campaigns.

We say again: this is not without analogy with the present problem of hanseniasis in front of the sulfono-resistance of some strains *of Mycobacterium leprae.*

But to come back to our antimosquito fight is was out of question, for us, to give in. Facing the new cronstraints we bent upon the organo-phosphorousated insecticides already known. These had bad press, being expensive (important for systematic and wide spread campaigns), hard to 'be applied by intradomiciliary pulverisations, of short remnant abilities and, above all, renowned toxic for men and warm blooded animals.

Biologically that toxicity was evidently and naturally bound to their insecticide properties, what is to be logically expected of every really active chemical product: "the dark side of the picture". After appropriate trials, first in the laboratory and afterwards on the field we resolved to use a deo dorized Malathihon which could be considered as less toxic and endowed with a certain remnance.

We applied it by intradomiciliary projections, in solution in oil at 5% of active product and also, for the porous surfaces, at 5% in suspension in water, so obtaining an insecticide remnance of several months, which was proved sufficient to resume with success, from 1964, an efficient antimosquito-campaigns against our two great anthropophile vector.

We regard obvious that to have valid results in general biology, as in pathology, by the utilization of a chemoactivity it is, first, capital to dispose of powerful molecules in the considered scope and secondly to utilize them wich shrewdness, determination, tenacity and, evidently, intelligence and commun sense, to avoid or to palliate errors and failures, modifying eventually certain first data.

Then remembering and retailing the difficulties of our long antimosquito fight in French Guiana, as an example of chemoresis tance, we conclued that two measures are required in order to prevent the emergence of primary or secondary resistance to dapsone in M. Ieprae.

First, it is necessary to go back to the previous regimen of 200 mg dapsone daily in adults. It yields the maximum-toleraded-effective-dosage. It should never have been rejected in favor of 100 mg daily, as currently recommended at the moment. The second measure is the implementation of triple drug therapy (MDT), using concurrently D.D.S. in association with Rifampicine and Clofazimine or Ethionamide. This is a logical and rational approach, at least from a theoretical point of view. However, MDT is most unfortunately ,quite expensive and therefore inapplicable in most countries with high prevalence, since they are poor and underdeveloped. Implementation of MDT also raises great problems in these countries, since dosages have to be strictly adhered to in order to prevent a potentially catastrophic emergence of multiple drug resistance in *M. leprae.*

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