Bruno DURIEUX →

The Minister of Health

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Paris, June 6, 1991

Dear Minister,

You asked me in a letter dated April 8 for a scientific opinion on the experiments on humans in active immunotherapy and particularly those carried out at SaintAntoine. This opinion would address:

1 - The scientific value of this type of experiments and the importance of pursuing them.

2 - If yes, the conditions under which they should be pursued.

Without taking up again an inquiry which had already been made, in any case, I have limited myself to the scientific aspects of the problem and to the conditions under which therapeutic tests should be conducted. I endeavored thus to gather together the available information, to listen to the various scientists and doctors who have carried out experiments of this type in France, and to consult undisputed experts in matters of vaccinal virology and therapeutic tests of SIDA. In particular I consulted several times the scientific Advisor in charge of therapeutic tests at l'ANRS, under the presidency of Professor Jean Dormont.

Please find attached a detailed note. I regret its length but the problem was complex and it seemed to me necessary to bring together for you all of the elements of information. You will also find attached annexes giving you certain necesseary technical information.

I am available to you, Monsieur le Ministre, to give you any additional explications, and I beg you to believe in the expression of my highest consideration (i.e.,sincerely).

Pr. Jean-Paul Levy

NOTE CONCERNING ACTIVE IMMUNOTHERAPY IN VIH INFECTED SUBJECTS

(heading for next page) →

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The first question concerns: the scientific value of this type of experiment.

Active immunotherapy, which one must distinguish from vaccination destined to protect those who are seronegative from infection, has as a therapeutic goal the reinforcement and reactivation of anti-viral defenses, supposing that their collapse plays an important role in the passage from the asymptomatic state to declared illness, in the course of VIH infection. This therapy should, thus, be applied principaly to subjects whose defenses are on the decline and whose CD4 cells are in the process of diminishing rapidly. Its use at an earlier stage would, in theory, be to stimulate the defenses before they are too much altered, but the eventual proof of efficacy would be extremely difficult to establish and would necessitate very long comparitive studies using hundreds of subjects.

1) <u>At the experimental level the bases for these approaches are tenuous.</u> To my knowledge it has never been possible to demonstrate the protection of an animal already infected by a "lentivirus" or an other "retrovirus", thanks to an active immunotherapy. This, however, does not prove that such a protection is impossible in the case of VIH. We can call upon, moreover, certain arguments against active immunotherapy, but their real value remains to be demonstrated. I would cite notably:

a) the existence at a relatively early stage of a spontaneous and frank reaction, at least as far as certain killer T cells are concerned, such that the usefulness of reinforcement can be contested.

b) in every stage, the possible noxious effects of the killer T reaction, which are probable in certain cases, outside even of any immunotherapy, but whose amplitude is uncertain.

c) the possible danger to these subjects of a transitory stimulation of the T cells, which can be followed by a greater viral production.

2) <u>the tests done up to the present time on humans:</u>

Experiments done on humains are of small number. The best known are those of J. Salk with an inactived and incomplete VIH virus, and those of D. Zagury which were carried out in association with either French or Zairan clinicians. The method used by D. Zagury is more complex than that of J. Salk, with notable variations in time. Zagury's method uses, among other things, injection of cells of the patient "surinfectees" in vitro to render them "antigeniques". I only have information about the work done in France and thus can't take into account those done in Zaire.

The American work of J. Salk is the object of considerable reserve as to.....(This is the end of the page. Is there a page missing?)

The second question concerned "the conditions under which these experiments should be carried out."

1) <u>The use of "virus vaccinaux recombinants" must be formally proscribed for seropositive patients:</u>

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The experiments at Saint-Antoire were realised using as immunogen cells of the patient, "surinfectees" in vitro by "des virus vaccinaux recombinants." These viruses permitted the expression of "des antigenes d'enveloppe du virus VIH-1 (recombinant on a Lister stock)" and antigens of the proteins GAG and POL (WR de Moss stocks). These preparations didn't cause any apparent complication in the subjects who were not profoundly immunodepressed. On the other hand, it is extremely likely that the three deceased subjects who belonged to an additional protocol, called "compassionnel", among the very immunodeficient patients having at the beginning of the treatment less than 80 lymphocytes CD4/mm3, carried lesions of "vaccine necrotique" with loco-regional diffusion. In at least one case the death seems to have been directly tied to this necrosis.

The virus of the vaccine is known, long before Sida, as dangerous in subjects carrying a deficit of cellular immunity. The one used in the experiments at Saint-Antoine was theoretically inactivated to avoid this danger which the authors were not unaware of. In fact inactivation of virus vaccinal is particularly difficult, especially when it is intracellular. The conditions used in these experiments (concentration of elevated cells, short time of incubation in paraformaldehyde, low temperature) were according to all appearances insufficient for a complete inactivation and the tests in vitro that were used could not detect with certainty a low rate of risidual virulent virus. It should be noted that the WR de Moss stock, which has never been used as a vaccine in humans, is particularly pathogenic in animals; it was not used in the first experiments of D. Zagury.

It is evident that the use of any "virus vaccine recombinant" must be proscribed in all active immunotherapy experiments in seropositive subjects, whatever the means of inoculation. All injections of preparations including "des virus vaccinaux" have, in any case, been stopped as of several weeks ago at Saint-Antoine: subcutanous or intramuscular injections when the necroses at the point of inoculation were noticed and the venous injections since April 4 , 1991, at which time those responsible for the tests judged that the vaccine could have been responsible for the necroses.

Such tests could only be begun again (in subjects not having great immunitary deficits) if sure processes of inactivation were put in place, or if non pathogenic recombinants (for example thermosensitive) could be isolated, and on condition that proof be made of a particular interest in the use of these viruses for the preparation of immunogens.

2) The conditions under which active immunotherapy test should be persued are those that one would like to see generalised for therapeutic test where SIDA is concerned:

Maybe it is suitable to remember two basic principles:

1) There exists in the domain of SIDA a veritable duty to do research. Therapeutic tests in particular are necessary and the participation of clinicians in these tests must be as broad and as by the consent of the parties as possible.

2) This research must be carried out under rigorous conditions, for "that which is not scientific, is not ethical", according to the terms of the National Committee on Ethics.

The problem presented here surpasses considerably the question of the tests carried out at Saint-Antoine and immunotherapy, and it (the problem) joins the problem presented, in a general way, by the therapeutic tests in the area of SIDA. It seems to me, as it does to all the experts consulted, that the following recommendations must be made:

1) One cannot insist too much on the necessity of an evaluation prior to each test by specialised scientific authorities. In a general way, the methodology of therapeutic tests is difficult and its teaching in the course of medical studies does not permit most doctors to acquire true competence. Parallel teaching exists, but many hospital authorities have not benefited from it. The methodological support that should exist in hospitals is practically nonexistent. In fact the test has only recently come into practice. It is in some way a new form of medicine-patient relationship and this will probably be the biggest part of clinical research in the coming decades. It is urgent that we take into consideration this historic turning point in the practice of medicine.

2) the idea of "compassionnel" treatment must be explained. The therapeutic accidents observed at Saint-Antoine come out of tests made in this area. In spite of the understandable and always growing pressure of patients, the administration called "compassionnelle" should be confined to precise cases with:

a) a certain already shown efficacy,

b) a well defined toxicity,

c) a real impossibility of including the patient in rigorously controled tests, even in very advanced phases of evolution.

3) It would be desirable that a guiding athority evaluate experiments using biological substances in humans beginning with the earliest stages of the tests. This authority could be located at the Management of Pharmacy and Medicines, and protocols concerning SIDA should be submited to this authority, when such substances are involved, so that the conditions of use could be appraised. Such an authority, according to all appearances, would have drawn attention to the conditions of inactivation of the vaccinal virus in the case of the questionned tests.

4) the role of ethical committees, from now on replaced by the committees for the protection of afflicted people of the Hurlet law, is evidently essential. It may be good to remember, with respect to this, that the requests of J-J. Pocidalo to the national committee or those of D. Zagury and the clinicians at Saint-Antoine to the local ethical committee were voluntary and in no way obligatory. The situation has been different since January of 1991.

In light of the accidents which occured, reflexion on their methods of work seem desirable. These committees would often need of additional

scientific knowledge, especially in very specialised areas such as SIDA. The multiplication of committees only increases this problem, and expertise is not easy to find. One recalls the recommendation of scientific authorities on which the committees should be advised to lean, a limited expertise not being sufficient in this area.

One must finally remember the regulations that are imposed in the carrying out of a test:

a) Follow through of toxicity: Immediate declatation to the minister of serious or unforseen side effects imposed by the Huriet law (article L 209-12).

b) Follow through on important decisions on the continuing or stopping of a test or on any modification of a protocol. Here again the law provides for, in the same article, the informing of the Minister. In practice two recommendations are important:

- The "independent committees" which alone can stop or give authorisation to continue a test in the face of a new event should be obligatory for any test that is delicate or of long duration.

- The promoters and principal experimenters should be clearly reminded that any modification of a protocol, in particular modification of the site of the study, of those in charge of an experiment, or of the nature of the inoculated substances requires a new opinion of the ethical committee and of the technical authorities, as stated in the law. In the experiments at St-Antoine the reference to the decision of the national committee makes scarcely any sense, in 1990, to the extent that experimenters and hospitals have changed and where "recombinants vaccines" (at least those of WR stock) have been introduced into protocols since the request of 1987.

c) For report let us remember the follow through on the quality of the gathered data. It is necessary that everything be put in order so that respect for "good clinical practices" is assured during the duration of the test and not afterwords.