

Opinion on experimentation on patients in a chronic vegetative state. Report.

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Opinion

Requests for opinions have been made on the subject of therapeutic trials performed on patients in a chronic vegetative state.

One request bears on massive blood transfusion, by way of bone marrow, in view of a study on "palliatives for absolute and relative hypovolemic distress"

Another bears on a generalisation of such therapeutic trials.

The characteristics of these clinical conditions and how they differ from "irreversible coma" are worth a brief reminder.

Irreversible coma is the irreversible loss of all the functions of the brain, the brain stem, and the hemispheres, which is revealed and verified in particular by flat electro-encephalogram readings. In chronic or persistent vegetative states, however, patients retain vegetative functions if they are given excellent care.

In its Opinion on the Testing of New Treatments on Humans, the Committee stated clearly that a patient cannot be subjected to therapeutic trials which are not in any way connected to treatment of his own illness.

That statement could be considered sufficient to motivate the Committee's Opinion in the present case. However, the following comments are added with a view to responding more specifically to Professor Milhaud's questions :

1 - As regards the case submitted to us, after the experiment :

the protocol lacks sufficient scientific solidity ;

the patient, who was very emaciated, was given curare, and far from deriving any benefit from the experiment, ran some risks since in order to be able to administer massive

transfusion, it was necessary to start with very abundant blood depletion (performed in violation of regulations concerning blood collection);

the patient's consent was not, and could not, be obtained. Consent from next of kin was not given. The opinion of a committee of ethics was not sought beforehand. For all of these reasons, the Committee disapproves of the experiment carried out by Professor Milhaud.

2 - As regards therapeutic trials in general on patients in a confirmed and stable chronic vegetative state

, the Committee expresses its total opposition to the words pronounced by Professor Milhaud saying that these patients are "almost perfect human models and would constitute an intermediate state between animal and human". They are human beings, who should command all the more respect owed to a human person because they are particularly vulnerable. They must not be treated as a means of making scientific progress, through an experiment which, however useful or important it may be, does not aim to improve their condition.

Consequently, the National Consultative Ethics Committee's opinion on the two requests is unfavourable.

Report

The report we present is motivated by a request from Professor A. Milhaud, who is in charge of the department of anesthesia and resuscitation " A" in the regional university hospital centre of Amiens. The request was made in a letter dated 10th December 1985, sent to Professor Jean Bernard, President of the National Consultative Ethics Committee.

In his letter, Professor Milhaud states that "...this is a limited request for authorisation to continue on other patients in a chronic vegetative state, and possibly on healthy volunteers, therapeutic transfusion trials of potentially great value to relieve states of absolute or relative hypovolemic distress...".

This part of the letter of 10th December 1985 raises two initial issues :

firstly, the National Consultative Ethics Committee can only deliver opinions and is not empowered to give authorisations;

secondly, it is pointed out that Professor A. Milhaud had previously made the same request in a different formulation.

In an abstract of a presentation (in French and English) titled "Chronic vegetative states and human experimentation", made at the 10th conference on anesthesia, resuscitation, and oxyology, on Friday 11th October, 1985, Professor Milhaud and six co-authors wrote in the last paragraph : "...the medical team of the Amiens CHU are asking the National Consultative Ethics Committee, through Professor Jean Bernard, and the authorities, to now permit trials on subjects in confirmed and stable (more than a year) chronic vegetative states, and to initiate regulations to be adopted by international institutions".

In this case, the request is for generalised therapeutic trials, and there is no expression of any restriction. This intention was perceived by Professor Jean Bernard who wrote in a letter to Professor Milhaud on 17th October 1985 : "...it is clear that your general question concerns trials unrelated to the patient's condition".

The rapporteurs must therefore take into account the dual formulation of the request.

They should do so all the more because during an extensive discussion they had with Professor Milhaud on 2nd January, 1986, he made his hopes, if not his intentions, for the near future, perfectly clear. Professor Milhaud recalled that in 1963, in a symposium held in Barbizon, he was the first to encourage the practice of organ harvesting in brain dead patients for transplants. In 1985, Professor Milhaud reiterates with massive, rapid, intraosteal blood transfusion experiments on patients in a confirmed chronic vegetative state. He is using these experiments as a springboard to arrive at a much vaster field of experimental activity and is trying to convince the authorities to legalise experiments on "confirmed and stable" chronic vegetative patients.

The rapporteurs will first discuss rapid intraosseous infusion for the purpose of treating hypovolemic distress. Experimental observation of fast vascular filling by the intraosteal route, in a young patient in a chronic vegetative state, will be the subject of particular comment and analysis. Finally, the rapporteurs will consider for such patients, the more general issue of therapeutic trials.

Some points concerning intraosteal infusions

Studies carried out by J.A. Monzo in 1758, and J.M.F. Dubuisson-Christot in 1865, on the anatomy and physiology of the circulation of bone marrow; work done by E. Lexer in 1904, D.C. Doan in 1922, C.K. Drinker in 1922, and Josefson in 1934, on anatomical relations between medullar circulation and general circulation, have for a long time encouraged researchers and clinicians to use the intraosteal route. Researchers sought to gain insight on the effects of certain substances on hematopoiesis, and clinicians endeavoured to administer medication, plasma, or blood, when the usual venous access was unavailable.

We are therefore dealing with well known facts. To support that statement, we offer the following references :

- L.M. Totantins and colleagues, in 1941, (*in Annals of Surgery*, 114, Dec .) performed blood transfusion via the intrasternal route. The maximum flow of citrated blood was 25 ml/minute. They emphasised the painful nature of the procedure and that it should only be used if other means of access were unavailable, in the event of extensive burns for instance.

- R. Turkel, Transfusion by way of bone marrow, *Journal of Operations*, 10, 789 (Nov. 1959). This author wrote several other articles on the same subject. He reviewed the sternal, iliac, femoral, and tibial routes. He developed some instruments and considered the administration of blood, blood products, and various medications, but he repeatedly insisted on only using this technique on patients in a serious state of vascular collapse, as emergency aid outside a hospital environment when extreme urgency and circumstances prevent using the IV route.

- V.K. Kamerin, in 1976, in *Revue de Chirurgie d'URSS* considered the possibility of intraosteal blood or plasma infusion to make up blood loss on the site of an accident.

More recently, R.A. Berg in 1984, V.A. Rosseti and colleagues in 1985, suggested the intraosteal route for certain pediatric emergencies in children under the age of three, when medication cannot be given via the intravenous route.

The usefulness of this approach in the special circumstances of a medical emergency is therefore amply demonstrated, but it is no slur on that technique to consider that it takes second place after other resuscitation techniques such as the intravenous route which can be used in the great majority of cases.

Our colleagues in the resuscitation department of the Amiens C.H.U. (University Hospital) are no doubt well aware that they are not innovating. They wish to prove that it is possible

at no great risk to transfuse rapidly a large quantity of blood by the intraosteal route. But, as we have previously mentioned, it is not so much the expected outcome of the test which demands reflection, as the circumstances of the experiment and extension to a research programme on similar lines.

Irreversible coma and chronic vegetative states

We first considered the state of the patient subjected to the trial, and the experimental protocol which we were given.

It is extremely important to distinguish as a first step between the state of that patient and what has been designated as "irreversible coma" since P. Mollaret and M. Goulon first coined the expression.

"Irreversible coma" is the irreversible loss of all of the functions of the whole of the brain, the brain stem, and the hemispheres. Many methods for paraclinical confirmation of the diagnosis have been proposed, the oldest of which is the total flatness of the electroencephalogram.

The Jeanneney circular, dated April 1968, set out the legal characteristics of brain death to define the death of an individual. By this circular, organ harvesting on individuals in "irreversible coma" was authorised. Later on, the Caillavet law (1976) was passed to facilitate organ collection.

In this way, the death of the subject in "irreversible coma" is properly confirmed, and this state is compatible with organ harvesting in well defined legal circumstances.

"Chronic vegetative states" are a very different matter. Damage is confined mainly or even exclusively to the cerebral hemispheres, whereas the brain stem is largely unaffected. Such patients can survive for many years whilst retaining absolutely normal vegetative functions as long as they are given excellent nursing care.

It is difficult to say when such conditions become chronic, nor is it easy to predict the course of a prolonged vegetative state.

It is also very clear that patients vary very considerably in their ability to react to their environment significantly.

A. Milhaud and his co-workers, consider as do other authors, that after a twelve month persistence of the vegetative state, there is almost no likelihood of even slight improvement. In practice, this is equivalent to making an identical prognosis for vegetative states and "irreversible coma", and ignoring the anatomical, clinical, and biological differences between the two conditions.

However, A. Milhaud underlines a distinction which should be considered with the greatest attention since it conditions the significance of the experiment, which we are about to discuss.

Indeed, in written material which we have examined, our colleague compares "the poor experimental models", i.e. patients in "irreversible coma" (which he considers to be "too fragile"), and patients in a vegetative state of over a year's duration, which he describes as "almost perfect human models".

Descriptive analysis of the experimental observation of 23rd May, 1985

The trial was conducted in order to appreciate the effectiveness and possible side effects of abundant transfusion, performed rapidly by the intraosteal route, after blood depletion.

The subject of the experiment was a twenty-nine year old man, injured in a road accident three years previously, in a persistent vegetative state. The patient who was in a hospital in Berck, was transferred to Amiens at the end of April 1985 (or early May) "...because he appeared to be suffering from lower limb phlebitis complicated by pulmonary embolism". The family was told that the move was required so that he could undergo necessary tests.

When asked about the patient's symptoms (during our meeting on 2nd January, 1986) Professor Milhaud did not supply a great deal of information. The diagnosis of pulmonary embolism was not confirmed, but the patient's file does not include any pulmonary scintigraphic data, nor any indication of prothrombin levels or of prothrombin complex factors. There is no mention of heparin IV therapy. However, according to Professor Milhaud, subcutaneous heparin was given (but there is no mention of doses or duration of treatment).

It seems likely however that any coagulation anomaly, which might have persisted during the patient's transfer, was absent on the day of the experiment, since the authors took the risk of inserting a Swan Ganz catheter in the right atrium and such a decision would not have been compatible with a continuing hypercoagulating tendency.

In the pre-experimental work-up, it is said that cortical activity was nil, but that the brain stem was perfectly functional. The EEG was slow on the whole, non reactive, with signs of greater distress in the left temporal and posterior areas.

The experiment began with administration of curare and an analgesic (Ketamine). Unfortunately, vascular collapse occurred when phlebotomy began, and led to infusion of two litres of Plasmion (we will return to this very high dose and to what Professor Milhaud replied when we asked for this to be explained).

A litre of blood was removed from the right subclavian vein, using two roller pumps (SARNS). The procedure lasted nine and a half minutes.

Intrailliac transfusion of that blood was performed immediately after, and lasted two minutes (a Liévain trocar was used).

Arterial blood pressure dropped progressively during phlebotomy, but regained initial value once the volume removed had been restituted.

Pressure in the right atrium was only slightly modified.

The heart rate remained perfectly stable.

Biological tests which were to take place immediately after the experiment (differential blood count, ionogramme, bilirubin, serum iron level, etc.) so as to discover in particular possible hemolysis, could not be done because all the samples had been frozen.

Clinical and biological developments were normal. Apprehension concerning fat embolism was fortunately not justified.

The patient returned to Berck during June: he died there in September.

Comments

Scientific

We asked whether a local ethics committee had been consulted before the experiment. We were told that none existed in Amiens in May 1985.

We asked whether a transfusion specialist participated in the experiment. Professor Milhaud's team did not include one.

The question is important because although blood depletion was corrected immediately by reinjection of the blood, for a patient weighing about forty kilograms, a litre is a considerable amount.

We are quoting here from 2 sub-paragraphs of article 2 of a ruling dated 22nd December 1982 on the subject of phlebotomy.

"...The quantity of blood removed at any one time must take into account the weight of the donor.

Maximum authorised quantities are limited to seven millilitres per kilogram of donor's weight, and must never be more in total than four hundred and fifty millilitres, exclusive of samples required for tests.

Even if one takes account of the special method used in the observation we are discussing, it is undeniable that removal of a litre of blood from a cachectic and hypotensive patient, in less than ten minutes, was far too much. Professor Milhaud agreed.

We also remarked that prescribing Ketamine indicated a highly legitimate intention, i.e. making the experiment painless, but that this suggested that the patient was not spontaneously insensitive to pain.

As we had difficulty in understanding the indication for prescribing curare, we asked Professor Milhaud to explain. He could not remember that particular experimental detail and allowed that it was not entirely necessary.

Here again, the question is not futile since our colleagues were confronted with vascular collapse before phlebotomy. They incriminate hyperventilation, which is not impossible, but can curare be definitely excluded ?

Then there was the very high dose of Plasmion infused to overcome vascular collapse.

Any clinician would be startled by the fact that two litres of Plasmion were injected. With such a dose, acute pulmonary oedema is a distinct possibility. We apprised Professor Milhaud of our astonishment, which he shared immediately, and said that he thought that the quantity was surely a misprint and that the quantity actually infused must have been two bottles.

Since we must give an opinion on the scientific nature of the experiment, we have to admit that it does give us an impression of improvisation which is not entirely explained by the fumbling which is inevitable in any novel research. The lack of control is undeniable. This was true for the administration of curare (which was perhaps unnecessary, said the author), for the quantity of blood removed, then infused, and for the imprecision regarding the Plasmion dose.

Finally, although we note with satisfaction that massive and rapid intraosteal infusion did not induce local complications, nor pulmonary complications, we find it regrettable that

defective conservation of samples at the end of the experiment deprived it of significant biological data.

Ethical and legal

The various components of the problem, as they have just been described in the area of medical technique, may be summarised as regards ethics and legality in the following way. The patient concerned was in a chronic vegetative state. A purely cognitive experiment was conducted which could not be of any help to him. His state of health did not permit him to consent. The family's consent was neither obtained nor requested. The opinion of an ethics committee was not sought before the experiment.

Before formulating a considered opinion, these various points must be reviewed.

The subject's condition :

Essential functions subsisted - circulation, heart, respiration - but he no longer responded to external stimuli. He can neither communicate nor relate. Therefore, he had to submit to interventions on his body to keep him alive or even improve his condition, without any imaginable perceptible response.

Could he still feel pain ?

Experimenters did not neglect this point since they gave a sedative (Ketamine).

The experiment :

A certain amount of blood was removed and reinjected into the iliac crest.

There was never any pretence that these procedures were of use to the patient. Professor Milhaud describes the experiment as of interest in the study of absolute and relative hypovolemic distress. Possible benefit therefore was only likely for the community generally. In fact, the National Consultative Committee, in its Opinion on the Testing of New Treatments, considered the question of a sick subject, and excluded any experiment of a treatment for some other disease. In such a situation, the risk-benefit evaluation must be strictly uncompromising. The case submitted to us does not permit such an evaluation. No advantage is expected for the patient. Furthermore, reinjection was only conceivable if it could be performed on a partially blood-deprived subject. It was therefore necessary, albeit for a limited period, to place the subject in a state of fragility induced by this need and remove some of his blood. If, in the final analysis, the patient did benefit from the experiment, that was because he was endangered during the first phase of that experiment. He was used twice over. It was necessary to bring him down to begin with, in order to see in a later phase whether he could be brought back to his previous state of health in a satisfactory manner with the chosen technique.

The subject's consent :

Legal texts and jurisprudence have defined the notion of a patient's informed consent to therapy. Thus, the power that science confers on one man over another is controlled and moderated by knowledge imparted to the patient about the action to be undertaken and consent obtained from him for it to be done. The patient treated by Professor Milhaud and his medical team was incapable of giving informed consent or even any consent at all. The loss of all capacity to relate with others prevented anyone from even attempting to gain consent. For that matter, if we tried to transpose the situation to a sick but conscious subject, the following questions could be asked :

would a doctor contemplate removing a litre of blood and reinjecting it immediately to the patient ?

would the patient accept in the knowledge that it would not improve in any way the course of his illness ?

Without doubt, replies would be negative.

The consent of next of kin :

We know, from the documents supplied, that the patient's parents were not consulted. Had they been, their consent could not have conferred legitimacy on an experiment which, as we have seen, did not benefit their son in any way. For that reason, the reasoning used by Professor Milhaud's letter of 27th November 1985 to Doctor Roux, based on article 11 of Annex 4 to the Helsinki Declaration, is unacceptable, because the possibilities offered by that text are only applicable to patients in therapy to whom medication is given to improve their therapy. It is also the reason why, the conviction expressed by Professor Milhaud in his transcription of a telephone conversation with the patient's father, to the effect that the father had agreed, has no validity in these circumstances.

Indeed, it goes without saying that the obligation of benefit to the patient is a way of preventing careless consent in the patient's name, or consent for reasons alien to the patient's interests.

Consultation of an ethics committee:

It cannot be said that this was totally neglected since it is precisely why this Committee is now considering the subject. However, the request was made after the experiment took place. This method of proceeding will naturally have no effect on the Opinion formulated by the Committee, but it does create problems:

- a) if the Opinion is unfavourable, the person conducting the experiment will have irremediably failed to be ethical;
- b) in any event, a precedent will have been created in the direction of a *fait accompli* policy.

Some legal considerations must be added to these ethical points.

During the experiment conducted by Professor Milhaud, there was voluntary injury to the physical integrity of the patient. Without any doubt, this action comes under the provisions of article 309, or those of article R. 40 of the *Code Pénal*, depending on the outcome of the intervention. It is in fact voluntary violence, committed at the time of phlebotomy and of accompanying actions which were its follow-up. It is true that the stated intention did not aim to harm, but in law, the motive does not enter into the consideration of an offence.

Nor could the argument be put forward that a medical or surgical act was involved. A practitioner's actions are executed with the consent of the patient and the intention is therapeutic. This analysis would not have differed if the parents' consent had been obtained since it would not have sufficed to legitimise an illicit act.

If the incriminated act had harmed the patient, the author's liability could have been incurred in civil law and led to reparation for the damage.

It was observed that Professor Milhaud had made two requests of unequal scope to the Committee. The first of these is more restrictive and directly linked to the experiment described above. It seeks authorisation to continue therapeutic transfusion trials on other subjects in a chronic vegetative state or on healthy volunteers.

The observations formulated regarding the protocol submitted to us, guide in an obvious direction any response from us on generalising the experiment. The arguments are already laid out in the Committee's Opinion on testing new medications. Individuals selected for

therapeutic transfusion trials would not be, in view of their condition, capable of giving informed consent.

As for healthy volunteers whose possible inclusion in such experiments was suggested, the rules in the above Opinion would apply.

The second request broadens the scope. It is directed at therapeutic trials in general (and not just limited to transfusion) on subjects in a chronic vegetative state.

It is obvious that a position adopted for a specific therapy would not be modified for therapies in general. However, an added dimension to the issue is given by the suggested notion of an "intermediary between animal and human being" being a good research medium, or, to use another form of words used by Professor Milhaud and his medical team, "an almost perfect model".

In this way, a new form of life would appear : neither altogether human nor altogether animal which, due to its physical and mental regression, would be put at the mercy of experimentation. This being, for which perhaps a name would have to be found, would serve to improve the well being of his fellows and thus escape from threatened euthanasia. This seems to be saying that a body could be mutilated so as to preclude destruction.

In this way, the author of this request for an Opinion does not uphold his theory solely on the basis of scientific and therapeutic progress. He introduces philosophical arguments. Beyond practical justification, we are in the presence of doctrinal precepts.

The dangers which we have pointed out of experimenting on patients in a chronic vegetative state, however beneficial to the community at large, would be grossly increased if it was stated as a guiding principle that it would apply to infra-human beings treated as mere instruments. Such a concept would lead to an abolition of every ethical rampart.

Conclusion

At the end of this analysis, the following comments are emphasised :

- clinical and biological safeguards which must be demanded before such therapeutic experimentation, are not apparent in the documentation given to the rapporteurs;
- the experiment lacks scientific solidity. Existing medical literature throws sufficient light on the question for an opinion to be formed on the indications and techniques of intraosteal blood infusion. Our colleagues from Amiens are not innovating and furthermore, freezing the blood samples at the end of the experiment deprives it of significant biological data.
- curare was given to this chronic vegetative patient, and massive blood depletion was performed (in much greater quantities than is allowed for collection of blood). Risks incurred were far from trivial;
- the authors of the trial did not ask for prior consent from the family, nor for a prior opinion from an ethics committee.

For all of the above reasons, the rapporteurs suggest that the National Consultative Ethics Committee may wish to issue an unfavourable opinion regarding the therapeutic trial presented to them, and in general on attempts to perform intraosteal blood transfusion on patients in a "chronic vegetative state" if their clinical status does not require it.

The Opinion would be incomplete if it was limited to the above expression. As it is put to us, it concerns experimentation on human beings generally and raises the essential problem of reconciling individual and collective interests which the Committee has encountered on several previous occasions. On this point, we have stated as a principle that the individual

must never be sacrificed to society. It is true that we have accepted the idea that, exceptionally, the subject might suffer minor and temporary discomfort in the name of the common good. But we insisted that such a situation could be tolerated only if the trial contributed to treating the subject. It is clear that this principle bears no connection to the experiment conducted by Professor Milhaud whose only claim to possible results is in the name of collective benefits.

With such intentions, a human being has no more value than laboratory material used for an experiment which in this case, furthermore, is of questionable scientific interest. These final thoughts lead us to suggest also an unfavourable Opinion on the subject of any experimentation on patients in confirmed and stable (more than a year) chronic vegetative states.