E.O. 11-20(63)

CENTRE DE RECHERCHES CANCÉROLOGIQUES ET RADIOPATHOLOGIQUES
DE L'ASSOCIATION CLAUDE-BERNARD

Mathé Proposal

HOPITAL SAINT-LOUIS
PLACE DU DOCTEUR-FOURNIER, PARIS 10e • BOLIVAR 22-22

AIR1.941230.002e

DIRECTEUR : DOCTEUR GEORGES MATHÉ
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from Professor Georges MATHE
Director of the Center for Cancerological
and Radiopathological Research of the
Claude-Bernard Association
Hôpital Saint-Louis, PARIS X²

to EUROPEAN OFFICE, Aerospace Research
United States Air Force
Shell Building, 47, Centerstaan
BRUSSELS (Belgium)

A. GENERAL

1. PROJECT TITLE : Possibilities of control of the secondary syndrome complicating bone marrow transplantation for the treatment of whole-body irradiation.

2. NAME AND ADRESS OF ORGANIZATION : Claude-Bernard Association, Avenue Victoria, 3 PARIS IVe

3. PRINCIPAL INVESTIGATOR : Professor Georges MATHE, Director of the Center for Cancerological and Radiopathological Research of the Claude-Bernard Association, Hôpital Saint-Louis, PARIS X². Associate Professor of Cancerology of the Faculty of Medicine of Paris.

4. CONTRACTING REPRESENTATIVE : Monsieur GARDIE, Secretary General of the Claude Bernard Association, 3, avenue Victoria, PARIS IVe

5. PREFERRED STARTING DATE : January 1st, 1964

6. ESTIMATED DURATION : three years.

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B. TECHNICAL

1. BRIEF OF PROPOSED RESEARCH : Several teams of biologists have demonstrated in various animal species that the consequences of whole-body irradiation in a 100 % fatal dose can be treated with a transplantation of homologous bone marrow, but that this treatment is complicated by a secondary syndrome which sooner or later causes the death of a considerable proportion of the number of animals saved by the bone marrow transplantation from the immediate consequences of the irradiation.

We have shown that transplantation of homologous bone marrow after doses of irradiation of the order of 600-rad is also possible in man and prevents the aplasia brought about by the irradiation ; unfortunately, however, we have also observed in man secondary syndromes which have been fatal in more than 50 % of the cases.

The purpose of the proposed research is to carry out experiments in mice and in human patients with leukaemia, in an attempt to thrive more light on the secondary syndrome and its mechanism and to work out a curative or preventive treatment.

It has been demonstrated that this syndrome is largely due to the reaction of the immunologically competent cells of the transplanted bone marrow to the antigens of the recipient. Our attempts to develop a curative or preventive treatment will be directed in the first place at inhibition of this process.

We shall try to work out a curative treatment consisting of inhibition of the proliferation of the immunologically competent cells, in the first place with the chemical antimitotics that are being used or investigated in connection with cancer treatment.

Our experiments in the direction of preventive treatment will consist essentially in attemps to alter electively the immunologically competent cells of the bone marrow prior to their transplantation without at the same time altering the myeloic cells on which the medullary rehabilitation depends.

We plan to preserve the bone marrow for brief periods at different temperatures in the presence of substances known to affect electively the cells of the lymphoic series.

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2. REQUIREMENTS FOR PROPOSED RESEARCH : If a preventive or curative treatment of the secondary syndrome could be found, this would make it possible to apply bone-marrow transplantation without danger ; its application might be considered for four categories of cases : a) the treatment of persons exposed to radiation accidentally, either during a military bombardment or during an accident in the sphere of the civilian use of atomic energy ; b) the treatment of forms of anaemia and aplasia, of congenital nature such as the Mediterranean anaemia, on the worst scourges in the field of hereditary disease, or of acquired nature, in particular of iatrogenic nature : certain pharmacological substances, in particular, certain antibiotics and some products used in the chemotherapy of cancer have a strong toxic effect on the bone marrow ;
c) the treatment of patients with leukaemia and with certain forms of cancer with whole-body irradiation in a maximal dose followed by bone-marrow transplantation ; in such cases, the treatment has a twofold mechanism : radiotherapeutical, since the irradiation destroys a certain proportion of the cells, and immunotherapeutical, since the immunologically competent cells of the graft are immunized, as we have demonstrated in the mouse, against the leukaemic cells of the recipient on the one hand, and against a possible leukaemigenic or carcinogenic virus on the other ;
d) homologous organ transplantations : it has been shown that when a subject A is irradiated with a fatal dose and grafted with bone marrow from B, he is then able to tolerate any tissue or organ from B. The importance of this fact in connection with kidney transplantation is readily understandable.

Accordingly, if we could control the secondary syndrome which is at present a stumbling-block in the use of bone-marrow grafting, we would be able to apply this method regularly, which would mean not only an important biological progress but in the first place a large step forward in the field of medical and surgical therapy.

3. APPROACH : a) Experiments will be carried out with bone-marrow grafting in mice and man which will make possible the clinical, hematological, histological and biochemical study of the secondary syndrome : an improvement of the symptomatic or preventive treatment will have to be based on a precise knowledge of these symptoms. An investigation will be pursued into the incidence of the secondary syndrome, the relationships of histocompatibility between donor and recipient, the number of cells transplanted and the interval between the transplantation and the irradiation.

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b) In the search for methods of curative treatment, we intend to test the adrenocortical steroids, the antibiotics, the chemical antimitotics and, in particular, the antimetabolites and the alkylating agents and ε-aminocaproic acid.

In the search for methods of preventive treatment, we [illegible] carry out tests with the use of several donors instead of one donor. We shall try to work out tests making possible a better selection of the donors and study the treatment of bone-marrow by preservation in the presence of various substances, adrenocortical steroids, chemical antimitotics and substances modifying cellular permeability.

4. HISTORICAL BACKGROUND : Several teams, that of VAN BEKKUM, that of FERREBEE, that of UPHOFF, that of LOUTIT and our own, have been working in this field for approx. 5 years. Of the more important results obtained, we may mention the decrease of the frequency of the secondary syndrome when the animals after the grafting are treated with amethopterine (UPHOFF, confirmed by us), or with cyclophosphamide (MATHE et al.) or with a small dose of irradiation (FERREBEE) or with penicillin (VAN BEKKUM) In the search for preventive treatment, it has been found possible to decrease the frequency of the secondary syndrome by using embryonal haematopoietic cells (LOUTIT), by using several donors (MATHE et al.) or by storing the bone marrow at 37° for 2 hours (MATHE et al.).

The best results that we have hitherto obtained in a human was seen in a person who suffered from acute leukaemia refractory to all forms of treatment : this patient was irradiated with a dose of 800 rad and subsequently was given bone marrow from 6 donors. His blood and bone marrow are now entirely restocked with the cells from one of these donors and the patient tolerates a skin graft from this donor. He has presented a very severe secondary syndrome which we had great difficulty in controlling but which could ultimately be supressed. For the last 5 months, this patient has presented only blood cells of the donor type and he is at present in perfect health.

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5. STATEMENT OF WORK : Aided by a grant for 3 years, we should like to carry out parallel experiments in the mouse and in man. The first experiments in the mouse will be concerned with the effect of preservation of the bone marrow in the presence of antimitotic or steroid substances.

The next experiments in man will consist in the use of more donors than one and in a symptomatic approach to the treatment of the secondary syndrome.

6 PERSONNEL : Principal Investigator : Professor Georges MATHE, born July 9, 1922, Associated Professor of Cancerology of the Faculty of Medicine.
Publications : see the bibliographical list above.

Other Investigators : Doctor J.L. AMIEL, Deputy Director of the Center for Cancerological and Radiopathological Research of the Claude-Bernard Association.

The following persons are also connected with the Center and may work on this project :

Mrs C. BREZIN, Doctor of Medicine
Mrs C. CHOQUET, B. Sc.
Dr L. SCHWARZENBERG, Doctor of Medicine
Dr A. CATTAN, Doctor of Medicine
Dr M. SCHNEIDER, Doctor of Medicine

7. UNSUPPORTED LEVEL OF EFFORT : Trials and experiments are now being carried out in this field, but in our opinion, the work is not sufficiently rewarding and progress is very slow because of a lack of funds (for operation costs in the first place).

8. FACILITIES

The Center possesses a stock of mice of pure strains equipment for biochemical investigations, for ordinary and fluorescence microscopy, autoradiography, tissue culture and irradiation.

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D. COST

Amount desired : Fr. 150.000, divided over three years :

1964 . Fr. 50.000.-
1965 : Fr. 50.000.-
1966 Fr. 50.000.-

1. PERSONNEL

1 Technical assistant	annual amount Fr.	19.000.-
1 Livestock assistant	annual amount Fr.	11.000.-
	Fr.	30.000.-

2. MATERIAL AND SUPPLIES

Chemical, glassware, etc..	annual amount Fr.	20.000.-
Total amount required per year	Fr.	50.000

PARIS, le 30 Octobre 1963

G. MATHE
Chef du Laboratoire de Recherches cancérologiques et radiobiologiques
Laboratoire du Docteur Georges
Hôpital de Malades
Fondation du Docteur Jaudin PARIS

- 6 NOV. 1963

Le Secrétaire Général