PONTIFICIAE ACADEMIAE SCIENTIARVM SCRIPTA VARIA
60

WORKING GROUP

ON

THE ARTIFICIAL PROLONGATION OF LIFE AND THE DETERMINATION OF THE EXACT MOMENT OF DEATH

October 19-21, 1985

EDITED BY

CARLOS CHAGAS

PONTIFICIA
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EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

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INDEX

SCIENTIFIC PAPERS

FOREWORD

« Sive vivimus sive morimur Domini sumus. »
(*Rom.* 14, 8)

The prolongation of life, which has been a constant preoccupation of humankind, has been a reality for a long time now. The average span of life has increased and will continue to do so. This is due to advances in medical knowledge, together with those obtained in immunization, sanitation, epidemiology, biostatistics, etc. The introduction of new technologies makes it possible to keep alive sick patients who formerly would have soon died. I would like to mention two examples of these technologies. The first one is the respirator, which has saved a large number of poliomyelitis patients at the time when this deadly infection was very frequent. The second one is the technique of renal dialysis, which is keeping many patients alive or has saved many of those affected by acute renal disorders, and has become of current usage.

The techniques for the artificial prolongation of life have become increasingly more perfect, and in fact one marvels at all the manual or automatic apparatuses, some of them programmed, which are today available in the centers of intensive therapy, in the wards, as also in the houses of affluent patients.

However, the current development of these techniques creates great and ever-increasing problems — moral, scientific, social and economic. From the economic point of view, it is known that the artificial prolongation of life weighs heavily on the budget of governments, as it does for the families in countries which do not have social security. Although we must state strongly that the value of life cannot in any way be measured in monetary terms, still we cannot deny that the economic problem exists. Thus, the question of curtailing the life of patients has the approval of many people.

The principal question that arises in such a poignant problem is to know at what moment the physician should or can discontinue the means which are maintaining his patient alive. It is one of the duties of a

physician to analyze all the factors that must weigh on his decision when he decides to stop the use of the artificial means employed. This is a decision difficult to arrive at; it involves the gift of life, which we must preserve with the greatest possible care. The physician must be guided by his conscience and his medical knowledge when, at the end of a fight for the survival of a patient, he has to decide if life is irreversibly lost. What a dramatic situation he confronts! What he can never do is to interrupt the therapeutic and spiritual care, as well as the material comfort, which have to be maintained to the end. What is inadmissible is to use any pharmacological or physical means to cause death. The care of a patient must be a constant preoccupation of the physician, and may lead him to the legitimate use of narcosis.

Pope Pius XII, on May 24, 1957 (*), in his address to a group of physicians and surgeons, gave us the guidelines to what should be done. He said that God only "obliges us to use ordinary means (according to the circumstances of the persons, the places, the times and the culture), that is, those means which do not impose any extraordinary obligation on oneself or on anyone else." Furthermore, he also answered positively the question: "Can a physician remove the respiratory apparatus before the definite cessation of the circulation?".

As a matter of fact, the decision concerning the treatment of the extremely sick brings to the physician a grave question of fact and of morals and rights — fact as regards the condition of the patient and the need or usefulness of any intervention; morals and rights as to the necessity of the intervention.

Another problem which has always existed, and has today become more important because of organ transplants, is that of the determination of the exact moment of death, as the organ to be transplanted must be utilized as soon as possible after the death of the donor. A very large number of medical associations have given thought to this question. General consensus was reached as to the fact that since human activity corresponds, from the biological point of view, to cerebral activity, it is the cessation of this activity that determines the state of death. A flat electroencephalogram taken at different times is considered in general as the sign that human life is ended. However, the number of electroencephalograms to be taken, as well as the interval between them, are still under debate.

(*) *Discorsi e Radiomessaggi di Sua Santità Pio XII*, Vol. XIX, p. 617.

The Working Group studied the two problems of the prolongation of life and the determination of the condition of death, under various aspects. A synthesis of its reflections has already been published. The reports, published under the responsibility of their authors, represent a welcome addition for their great scientific value and deserve to be known as a contribution to two problems which are among the most important in modern medicine.

It is my duty and my honor to thank heartily the participants in the Working Group for their efforts in preparing the manuscripts and taking part in the discussions, sometimes strenuous, which were held. I want also to thank Father Enrico di Rovasenda, Mrs. Michelle Porcelli, Mrs. Gilda Massa, and Mr. Silvio Devoto for the help they have given to assure the success in the publication of this volume.

CARLOS CHAGAS

President of the Pontifical Academy of Sciences

LIST OF PARTICIPANTS

CARLOS CHAGAS, President of the Pontifical Academy of Sciences, Vatican City.

JOHN COLLINS HARVEY, Georgetown University Hospital, 3800 Reservoir Rd. N.W., Washington D.C. 20007, U.S.A.

KONSTANTIN ALEXANDER HOSSMANN, Max-Planck Institut für Experimentelle Neurologie, Ostmerheimer Str. 200, 5000 Köln (Merheim) West Germany.

ADIB D. JATENE, Instituto de Coraçao, Avenida Dr. Eneas Carvalho Aguira, 44 - 05403 São Paulo, S. P., Brazil.

DAVID H. INGVAR, Department of Clinical Neurophysiology, University Hospital, S-221 85 Lund, Sweden.

JÉRÔME LEJEUNE, Pontifical Academician, Institut de Progénèse, Faculté de Médecine, 45 rue des St. Pères, 75006 Paris.

JEAN-FRANÇOIS LEMAIRE, Journal « Le Point », 140 Rue de Rennes, 75006 Paris.

LUIGI LOMBARDI-VALLAURI, Università degli Studi di Firenze, Dipartimento di Teoria e Storia del Diritto, Piazza Indipendenza 9, 50129 Firenze.

GEORGES MATHÉ, Institut de Cancérologie et d'Immunogénétique, Hôpital Paul-Brousse, 14 Av. Paul-Vaillant-Couturier, 94800 Villejuif, France.

GÉRARD MILHAUD, Administration Générale de l'Assistance Publique, Service de Médecine Nucléaire, Hôpital Saint-Antoine, 184 rue du Faubourg St.-Antoine, 75571 Paris Cedex 12.

HANS WERNER PIA, Neurochirurgische Klinik der Justus-Liebig-Universität Giessen, Klinikstr. 29, D-6300 Giessen, Germany.

URBAN PONTÉN, Department of Neurosurgery, University Hospital, S-751 85 Uppsala, Sweden.

ELIO SGRECCIA, Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia « A. Gemelli », Largo F. Vito, 1 - 00168 Roma.

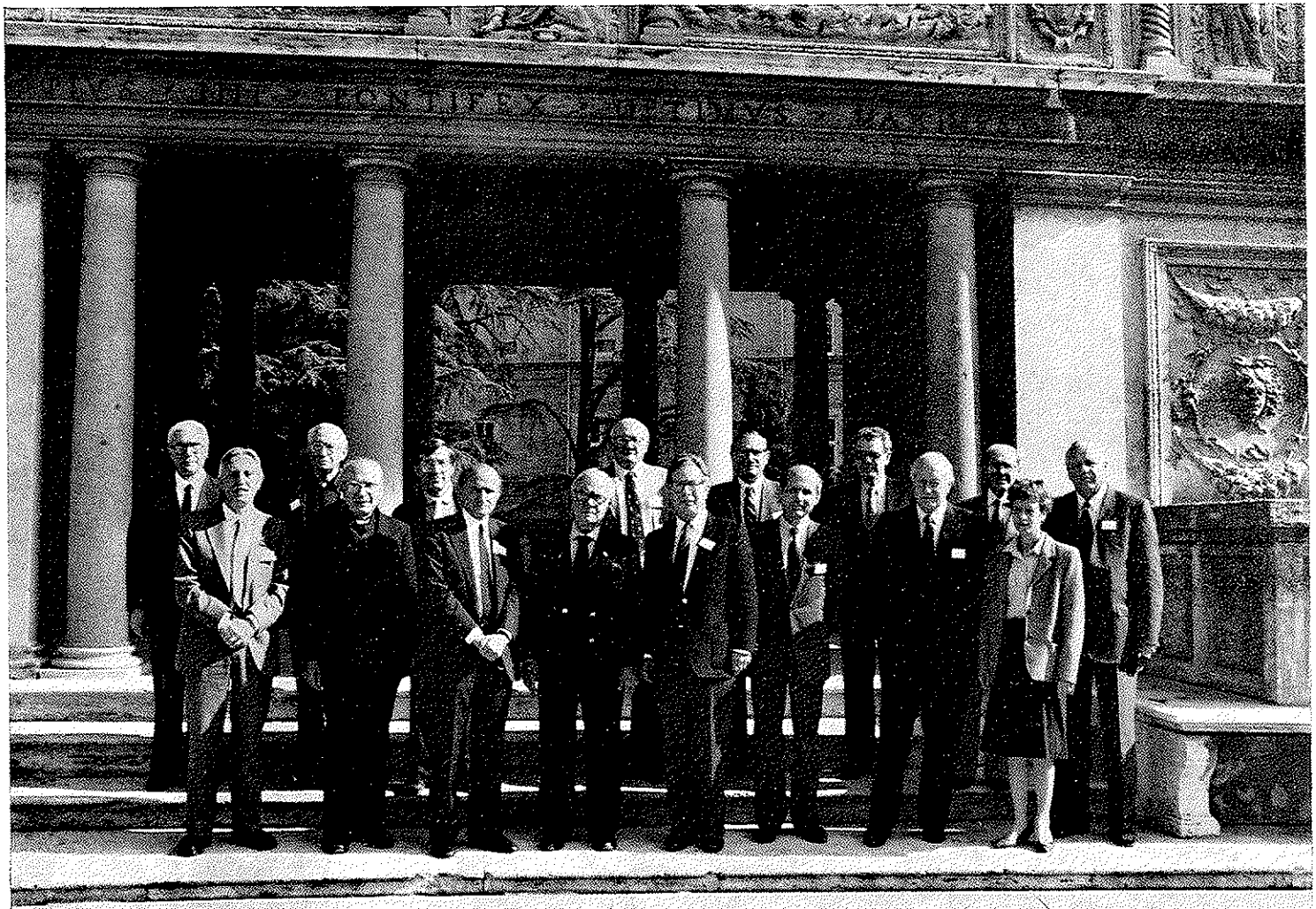
JAN VISSER, Pontificia Università Urbaniana, Via Urbano VIII, 16 - 00165 Roma.

ALPHONSE D. WALDER, Academic Hospital St. Radboud, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

ROBERT J. WHITE, Case Western Reserve University at Cleveland Metropolitan General Hospital, 3395 Scranton Road, Cleveland, Ohio 44109, U.S.A.

SHELDON M. WOLFF, Department of Medecine, Tufts University School of Medicine, New England Medical Center, 171 Harrison Avenue, Boston, Massachusetts 02111, U.S.A.

E. J. ZERBINI, Hospital das Clinicas, Facultade de Medicina da Universidade de São Paulo, Caixa Postal 8091, São Paulo, Brazil.



Participants in the Working Group.

AUDIENCE OF THE HOLY FATHER

On October 21, 1985, His Holiness John Paul II granted an Audience in the "Sala del Concistoro" of the Apostolic Palace in the Vatican to the participants in the Working Group "The Artificial Prolongation of Life and the Exact Determination of the Moment of Death" and to some of the participants in the Study Week "The Interaction of Parasitic Diseases and Nutrition".

The group, introduced in the Apostolic Palace by the President of the Pontifical Academy of Sciences, His Excellency Prof. Carlos Chagas and accompained by the Director of the Chancellery, Rev. Father Enrico di Rovasenda and by the Co-Director, Ing. Renato Dardozzi, was paternally received by His Holiness, who at the end of the Audience wished to greet personally all the participants.

The President of the Academy, Prof. Carlos Chagas, delivered the following address:

Holy Father,

The honor which You confer on our Academy of Sciences in following the work which it carries on and in addressing to us words of encouragement which strengthen our dedication to our work, fills us all, Academicians and participants in our Working Groups, with a profound joy, gratitude and admiration.

We come again to report to You the results of our scientific reflections and to hear Your words of great wisdom and admirable depth. They seem the perfect words to all of us, Christian and non-Christian, who know the interest which You have in the improvement of the existential quality of man's condition.

Our first Working Group at this time has chosen as the subject of its discussions a theme which is at the limit of our scientific knowledge and at the same time has moral implications which are extremely important. The scientific progress of medicine and technology is so great that humanity

is endeavoring to solve the problem of conquering death, an illusion so attractive to many minds that it leads to a hope in certain pseudo-scientific and paramedical methods, which only produce passing states of illusion.

However, true medicine, especially in its preventive action, has succeeded in achieving a notable increase in the average life span and in improving the conditions of health of children, women and men of our time, although so far in a way that is unjustly unequal.

The cost of modern medical care has increased, but the expenditures which it requires, both in the rich countries and in the poor countries, unfortunately represent only a very small percentage of the military budgets.

On the other hand, we must not forget that scientific progress has given more pleasant conditions of survival to the sick and has made their agony less painful. My Christian education, with all that it implies of respect for life, my professional education and the Hippocratic Oath lead me to believe that the protection of life should be above all other considerations. However, I see growing around me currents of opinion which preach an intervention to end the life of a dying person or of a person whose life is reduced entirely to mere vegetative functions. The arguments in favor of a positive solution are evidence of the emotional and financial exhaustion of the family after long months of worry with only very brief moments of hope, and the unwillingness of the public relief systems or of the hospitals to support these sick people.

I believe that the scientific solution in this connection is to determine the exact moment when the irreversibility of the vital conditions has been reached. It is at that point, as Pius XII said, that a decision in which secondary interests must be put aside, can be arrived at with the participation of the family and its counsellors. At any rate, a positive intervention which can cause death is to be condemned and could never be admitted.

The scientific determination of the moment of death is an important problem today. We all know that the cells of the human body do not die all at once. However, anyone who has seen a person die, either due to a long or an acute illness, or due to an accident, recognizes the moment of death of a human being. For many of us it is the dramatic moment when the soul leaves the body and another life begins. For others, who are non-believers, it is the moment when existence ends for someone who for a certain time has enjoyed that invaluable gift of God which is life.

But how can we define the scientific parameters which determine the condition of death? This becomes urgent when we think of the great progress which transplantation techniques have finally been able to achieve

thanks to immunogenetics. Our report will give You, Holy Father, the conclusions we will have reached.

Finally, the second Working Group, which is about to begin its work, is going to devote itself to one of the most serious aspects of our civilization in the countries of the Third World, but also in the patches of poverty in the rich countries. Malnutrition is one of the serious problems which defy humanity. Holy Father, You too have often reflected on the problem which threatens friendship and understanding among the countries of our planet. Various factors — among which I would cite only the lack of understanding on the part of the rich countries, and national and international interests — impede the full utilization of the agricultural production of the world. A part of the problem of malnutrition in its interaction with parasitic diseases will be studied.

Holy Father, tomorrow marks the seventh anniversary of the beginning of Your Pontificate. Not only the Church but the whole lay world rejoices on this occasion. Please accept the fervent and sincere good wishes of the Pontifical Academy of Sciences and of the scientists who have come to Rome to participate in our work.

In bringing You, Holy Father, the scientific findings on the subjects which have been the object of our discussion and thought, I express to You, in the name of my colleagues, our great admiration and the certainty that You will speak the good words which will shed the light constantly beaming from all Your actions on the subjects preoccupying a large part of humanity.

The Holy Father answered with the following discourse:

Ladies and Gentlemen,

1. *I extend a most cordial welcome to all of you. And I rejoice with the Pontifical Academy of Sciences and its illustrious President, Professor Carlos Chagas, for having succeeded in bringing together two groups of such distinguished scientists to reflect on the themes: "The Artificial Prolongation of Life and the Determination of the Exact Moment of Death", and "The Interaction of Parasitic Diseases and Nutrition".*

In the specialized areas encompassed by these themes, the men and women of science and medicine give yet another proof of their desire to work for the good of humanity. The Church is joined with you in this task, for she too seeks to be the servant of humanity. *As I said in my first Encyclical,* Redemptor Hominis: *"The Church cannot abandon man, for his 'destiny', that is to say, his election, calling, birth and death, salvation or perdition, is so closely and unbreakably linked with Christ"* (No. 14).

2. *Your presence reminds me of the Gospel parable of the Good Samaritan, the one who cared for an unnamed person who had been stripped of everything by robbers and left wounded at the side of the road.* The figure of that Good Samaritan I see reflected in each one of you, *who by means of science and medicine offer your care to nameless sufferers, both among peoples in full development and among the hosts of those individuals afflicted by diseases caused by malnutrition.*

For Christians, life and death, health and sickness, are given fresh meaning by the words of Saint Paul: "None of us lives to himself, and none of us dies to himself. If we live,

we live to the Lord, and if we die, we die to the Lord; so then, whether we live or whether we die, we are the Lord's" (Rom *14:7-8*).

These words offer great meaning and hope to us who believe in Christ; non-Christians, too, whom the Church esteems and with whom she wishes to collaborate, understand that within the mystery of life and death there are values which transcend all earthly treasures.

3. *When we approach the theme which you have dealt with in your first Group, "The Artificial Prolongation of Life and the Determination of the Exact Moment of Death", we do so with two fundamental convictions, namely: Life is a treasure; Death is a natural event.*

Since life is indeed a treasure, *it is appropriate that scientists promote research which can enhance and prolong human life and that physicians be well informed of the most advanced scientific means available to them in the field of medicine.*

Scientists and physicians are called to place their skill and energy at the service of life. They can never, for any reason or in any case, suppress it. For all who have a keen sense of the supreme value of the human person, believers and non-believers alike, euthanasia is a crime in which one must in no way cooperate or even consent to. Scientists and *physicians must not regard* themselves as the lords of life, but as its skilled and generous servants. *Only God who created the human person with an immortal soul and saved the human body with the gift of the Resurrection is the Lord of life.*

4. *It is the task of doctors and medical workers to give the sick the treatment which will help to cure them and which will aid them to bear their sufferings with dignity. Even when the sick are incurable they are never untreatable: whatever their condition, appropriate care should be provided for them.*

Among the useful and licit forms of treatment is the use of painkillers. *Although some people may be able to accept suffering without alleviation, for the majority pain*

diminishes their moral strength. Nevertheless, when considering the use of these, it is necessary to observe the teaching contained in the Declaration issued on 4 June 1980 by the Congregation for the Doctrine of the Faith: "Painkillers that cause unconsciousness need special consideration. For a person not only has to be able to satisfy his or her moral duties and family obligations; he or she also has to prepare himself or herself with full consciousness for meeting Christ".

5. *The physician is not the lord of life, but neither is he the conqueror of death.* Death is an inevitable fact of human life, and the use of means for avoiding it must take into account the human condition. *With regard to the use of ordinary and extraordinary means, the Church expressed herself in the following terms in the Declaration which I have just mentioned: "If there are no other sufficient remedies, it is permitted, with the patient's consent, to have recourse to the means provided by the most advanced medical techniques, even if these means are still at the experimental stage and are not without a certain risk .... It is also permitted, with the patient's consent, to interrupt these means, where the results fall short of expectations. But for such a decision to be made, account will have to be taken of the reasonable wishes of the patient and the patient's family, as also of the advice of the doctors who are specially competent in the matter .... It is also permissible to make do with the normal means that medicine can offer. Therefore one cannot impose on anyone the obligation to have recourse to a technique which is already in use but which carries a risk or is burdensome .... When inevitable death is imminent in spite of the means used, it is permitted in conscience to take the decision to refuse forms of treatment that would only secure a precarious and burdensome prolongation of life, so long as the normal care due to the sick person in similar cases is not interrupted".*

6. *We are grateful to you, Ladies and Gentlemen, for having studied in detail the* scientific problems connected with attempting to define the moment of death. *A knowl-*

edge of these problems is essential for deciding with a sincere moral conscience the choice of ordinary or extraordinary forms of treatment, and for dealing with the important moral and legal aspects of transplants. It also helps us in the further consideration of whether the home or the hospital is the more suitable place for treatment of the sick and especially of the incurable.

The right to receive good treatment and the right to be able to die with dignity demand human and material resources, at home and in hospital, which ensure the comfort and dignity of the sick. Those who are sick and above all the dying must not lack the affection of their families, the care of doctors and nurses and the support of their friends.

Over and above all human comforts, no one can fail to see the enormous help given to the dying and their families by faith in God and by hope in eternal life. *I would therefore ask hospitals, doctors and above all relatives, especially in the present climate of secularization, to make it easy for the sick to come to God, since in their illness they experience new questions and anxieties which only in God can find an answer.*

7. In many areas of the world the matter which you have begun to study in your second Working Group has immense importance, namely the question of malnutrition. *Here the problem is not merely that of a scarcity of food but also the quality of food, whether it is suitable or not for the healthy development of the whole person. Malnutrition gives rise to diseases which hinder the development of the body and likewise impede the growth and maturity of intellect and will.*

The research which has been completed so far and which you are now examining in greater detail in this colloquium aims at identifying and treating the diseases associated with malnutrition. At the same time, it points to the need of adapting and improving methods of cultivation, methods which are capable of producing food with all the elements that can ensure proper human subsistence and the full physical and mental development of the person.

It is my fervent hope and prayer that your deliberations

will encourage the governments and peoples of the economically more advanced countries to help the populations more severely affected by malnutrition.

8. *Ladies and Gentlemen, the Catholic Church, which in the coming World Synod of Bishops will celebrate the twentieth anniversary of the Second Vatican Council, reconfirms the words which the Council Fathers addressed to the men and women of thought and science: "Our paths could not fail to cross. Your road is ours. Your paths are never foreign to ours. We are the friends of your vocation as searchers, companions in your labours, admirers of your successes, and, if necessary, consolers in your discouragement and your failures".*

It is with these sentiments that I invoke the blessings of God, the Lord of life, upon the Pontifical Academy of Sciences, upon all the members of the two present Working Groups and upon your families.

SCIENTIFIC PAPERS

CEREBRAL DEATH

« LIFE MEANS REGULATION AND MODULATION. DEATH MEANS IRREVERSIBLE LOSS OF REGULATION AND MODULATION »

HANS WERNER PIA
Department of Neurosurgery, Justus-Liebig-University
Giessen, F. R. Germany

The death of the organism is understood as complete and permanent cessation of every cell activity, both in aerobic and anaerobic conditions.

In the past, in overwhelming majority, the *death of the individuum* was due to the irreversible cessation of cardiac and respiratory function. Modern intensive care and therapy and especially artificial respiration starting with Mollaret and Goulon's report on coma dépassé in 1959 [8] permitted to establish the syndrome of *brain death,* which is considered equal to *the death of the human being.* The observation that under artificial respiration the autonomous function of the heart can maintain the circulation and thus the function of the other organs, including the spinal cord, and can continue for days or even much longer, has created a new dimension for man's process of dying and determination of the moment of death. The discussion about the determination of the moment of death due to irreversible loss of brain function or to irreversible loss of cardio-respiratory function is still going on, not only among physicians, but among philosophers, theologians and lawyers.

The decision to maintain artificially the respiratory function in case of irreversible loss of brain activity is an inhuman and needless manipulation of a dead human being. If cardiac asystole and apnoe are required as mandatory in order to declare the death, it follows that medical

therapy of a living organism with a dead brain is continued until cessation of cardiac function occurs.

For neurosurgeons — as well as for other medical specialties which deal with acute primary and early secondary severe brain injuries and brain diseases — an irreversibly damaged brain means the death of the man. Cardiac asystole will occur sooner or later, and the application of artificial respiration and other measures supporting the circulation cannot change the situation and cannot be considered as therapy. In spite of these measures, dead brain is subjected to the processes of autolysis and liquefaction. The time gained through these supportive measures is useless for the patient and is an enormous mental burden for the family whose suffering is unnecessarily prolonged. This is certainly not *humanitas* and *compassio* as understood by the physicians and the nursing staff.

In the past 20 years the principles of medical, ethical and juristic attitude toward determination of brain death have been laid down as far as aetiology, diagnosis of irreversibility, requirements and criteria are concerned. There is no doubt that brain death can be defined with the help of clinical methods [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13].

However, there are still discrepancies concerning the *interpretation of brain death.* So, for example, the Uniform Determinatoin of Death Act of the United States in 1981 defined brain death as:

1) irreversible cessation of circulatory and respiratory function and

2) *irreversible cessation of all functions of the entire brain, including the brain stem* [13].

In Great Britain the definition implies important difference because it is considered that: "Brain death means irreversible cessation of all brain stem functions" [9].

Thus, the question arises whether there are two types of death in general and of brain death in particular, and how is it possible to check all functions of the entire brain including that of the brain stem? The dilemma becomes even greater if the necessary distinction between *irreversible cessation of cortical function, i.e., the function of both hemispheres and that of the brain stem* is considered. The problem becomes even more complicated if, as the studies in my Department have shown, a distinction between different types of irreversible loss of function of

the hypothalamo-pituitary system and different levels of the brain stem is made [10].

Cortical failure means loss of higher brain functions: human consciousness and mind, awareness and cognition. In a person with cortical failure specific human attributes are missing, and what is left over is an organism with some biological functions preserved. Does the loss of personal identity equate death? Do we have to consider *cortical death* as a specific form of human brain death or, as I define it, of brain failure? Does this brain failure imply therapeutic consequences or not? These poor patients with some preserved brain stem function are in a so-called *apallic state or in persistent vegetative state* and remain so sometimes for years as exemplified by the Karen Quinlan tragedy. This condition demands serious considerations. It should be our aim to attempt to find medical, and even more, moral and ethical help for the responsible neurosurgeon or neurologist who has to decide about the future of such a patient at the early stage of the acute illness, trauma or hypoxic brain damage. This moral and legal help must be based on ascertained clinical and paraclinical findings and repeated investigations to exclude the slightest doubts concerning the nature, intensity and irreversibility of the lesion.

I will try to explain my point of view concerning brain death in more detail. These considerations are based upon my personal findings and those of my coworkers assembled over the last 30 years and laid down in 20 habilitation theses concerning primary and secondary lesions of the brain stem and hypothalamo-pituitary system [10].

Failure of the hypothalamo-pituitary system and of the brain stem

The aim of our clinical and experimental research has been, from the very beginning in the early fifties, to understand the mechanisms leading to integration and disintegration of the vegetative, metabolic and neuroendocrine functions of the hypothalamus, hypophysis and the brain stem and to acquire better knowlegde of factors responsible for compensation and decompensation of these complex neurogenic and humoral vital systems. Together with my neurosurgical coworkers and together with neuroradiologists, neuropathologists, neurophysiologists, neurochemists and mathematicians, we attempted to describe several syndromes of acute and chronic states or irritation and paralysis with result-

ing defects and death. These attempts led to the revised and integrated concept of *central disregulation.*

In human, as well as in experimental animals, lesions of the hypothalamo-hypophyseal system and the brain stem occur as a direct primary or indirect secondary involvement and are due to trauma, haemorrhage and space-occupying lesions, mostly associated with raised intracranial pressure.

The syndromes which I am going to describe concern acute lesions alone, as they are the reason of acute failure, decompensation and death. In chronic lesions complex mechanisms of compensation and adaptation, based on the plasticity of the involved structures, make the interpretation and understanding extremely difficult; furthermore, consideration of chronic involvement of these structures does not lead to the centre of our theme.

A general feature of all the types and sites of these lesions is the dynamic development of functional involvement and structural damage, beginning with signs of acute irritation and excitation of the function of these structures, progressing to the loss of compensation with partial and finally complete decompensation with brain death in case of irreversible structural deficit. With the exception of complete destruction of the brain stem, this functional disregulation syndrome is reversible at each stage, even in the phase of complete functional decompensation. Continuous clinical and paraclinical monitoring is mandatory.

Acute hypothalamo-pituitary paralysis syndrome

Due to the multiplicity of regulatory and interrelated factors influencing the hypothalamus and the pituitary gland, and because of diffuse acute involvement caused by severe trauma or haemorrhage, a complex and widespread symptomatology arises. This may be one of the reasons why acute lesions of this system were never mentioned in the context of cerebral death.

1) *Syndrome of polyuria, hypothermia and hypotension.* This syndrome has been described by my coworkers. In 15 patients with severe cranio-cerebral trauma and coma, polyuria or lowered urinary osmolality developed within a few hours after the injury and were followed by hypothermia and hypotension. After the first stage of increased secretion of antidiuretic hormone (ADH) a decrease of serum levels of this hormone occurs. The syndrome is characterized by a severe disturbance of the

hypothalamo-pituitary antidiuretic system. Normal stimulation via serum osmolality and blood pressure is absent. The vasopressin-test was negative in all cases, i.e., there was no increase of ACTH level following intravenous vasopressin administration in all cases. All patients died. In all these cases cardiac asystole preceded the cessation of respiration. These findings indicate a breakdown of the hypothalamic-anterior and posterior pituitary lobe connections.

CT-examinations showed in all these patients complete obstruction of the chiasmatic and lamina terminalis cisterns. The post mortem examinations showed uniform *morphological changes*: haemorrhages and ischaemic-hypoxic changes in the hypothalamus, the pituitary stalk, neurohypophysis and in the adenohypophysis. In contrast the morphological changes in the brain stem were missing or were minimal.

2) *Isolated involvement of the antidiuretic hypothalamo-pituitary system* was connected with survival in all cases. In these patients the vasopressin-test was positive: the vasopressin injection was followed by normal increase of ACTH level, indicating that the hypothalamo-adeno-pituitary axis was intact at least for the adrenocorticotropic hormone. In summary: The syndrome of polyuria, hypothermia and hypotension may be described as a special form of brain death: so-called *hypothalamo-pituitary death.*

The accompanying *vegetative symptoms* are governed by vasodepression and vasoparalysis with attacks of cardiac arrest, ECG-changes and episodes of frequent circulatory failure; however, a systematic analysis of these symptoms is still missing.

3) *Central hypothalamic hyperglycaemia* constitutes another specific syndrome. It is characterized by extreme levels of hyperglycaemia associated with hyperinsulinaemia, hyperglucagonaemia, complete resistance to insulin, lack of ketonuria and low levels of cortisol and human growth hormone (HGH). In cases of central hypothalamic hyperglycaemia *the glucose level sensors* within the hypothalamus are blocked by destruction or oedema and react as in intracellular glucopenia in spite of extreme high levels of blood sugar. This syndrome may be associated with *hyperthermia, diabetes insipidus, and secondary aldosteronism.*

All patients with the described syndrome died because of circulatory insufficiency. I am convinced that several forms of *hypothalamo-pituitary failures* will be defined in the near future and thus the problem of cerebral

death may become even more complicated from the medical, scientific point of view.

From the practical point of view there are and there will be no noteworthy problems concerning the exact estimation of the moment of death, which will occur with cardiac arrest followed by apnoe. The hypothalamic influence upon the autonomous function of the heart explains the early heart failure and excludes such patients as potential organ donors [11].

Brain stem failure

The diagnosis of primary and secondary lesions of the brain stem has been improved by special CT-techniques, magnetic resonance imaging (MRI), application of multimodality evoked potentials (MEP) and examination of brain stem reflexes. Clinical examinations supported by special animal experiments, morphological studies and mathematical correlations permit exact evaluation of the site, extent, aetiology and with a certain degree of probability permit to predict the course and prognosis of patients with vegetative and metabolic disturbances due to brain stem failure.

Mesencephalic failure

Clinical syndromes due to mesencephalic disturbances have been known for a long time. Our own studies contributed to the understanding of vegetative, metabolic, neurophysiological and circulatory mechanisms, connected with these syndromes and their relation to a compression of the midbrain and intracranial pressure.

Acute mesencephalic or hypothalamo-mesencephalic compression syndromes are characterized by extreme ergotropic reaction with peripheral vasoconstriction, increase in all vegetative and metabolic parameters and their modulation, disinhibition of respiration areas against CO_2 and a failure of evaporative heat loss. Upper and lower decerebration and synchronous reactions and frequent rhythmic phenomena occur.

Excessive neuronal activation with increased modulation, synchronization and rhythmicity is explained by the loss of inhibitory influences of cortical and subcortical structures. It is the result of specific reaction of the isolated mesencephalon in the acute stage of disinhibition.

In acute paralysis syndrome the irritation and excitation are ag-

gravated. Blood pressure, heart rate, respiration, temperature are increased to extreme values. Body temperature may rise up to 43° Celsius and the heart rate to above 180/min. The normal pulse rate modulation of 5-30 beats/min. may increase to 50-80/min. and sometimes short variations of the range approaching 100 beats/min. may be observed. This irritation phase becomes life-threatening and the decompensation may occur rapidly with breakdown of arterial blood pressure and a machine-like respiration without any modulation. The latter are signs of *mesencephalic failure* and reflect the specific form of central death, so-called *mesencephalic death.*

Thanks to modern successful treatment of this irritation syndrome, this form of cerebral death is only rarely observed nowadays. Several specific blocking agents are now available and permit a fairly easy control of the vegetative storm. It has to be remembered, however, that with such treatment only symptoms are controlled and the manifestations of the syndrome are masked. The control of these symptoms is extremely important for preventing further secondary damage, but the nature of the mesencephalic failure is not influenced by this treatment.

Pontine and bulbar failure

Among pontine and bulbar paralysis syndromes the *bulbar failure* is the most important and is the main cause of central death — *so-called bulbar death.* The characteristic sign is the decrease and loss of activity of the respiration areas to CO_2 with arrest of respiration, followed by cardiac arrest within a few minutes if respiration is not continued artificially. With artificial respiration cardiac function continues thanks to the autonomous innervation system. The vegetative parameters decrease and there is a complete lack of normal modulation. The monitored curves of heart beat and blood pressure become straight, and only unmodulated 0.15/min. *pressure waves* are observed. Their presence indicates complete loss of central regulation and they are probably of spinal origin. The body temperature decreases continuously, resulting in deep hypothermia and complete *poikilothermia,* which expresses the total cessation of temperature regulation.

Temperature regulation is a basal and vital function of normothermic organisms and is responsible for the balance between heat production and heat loss and the normal function of all metabolic and enzymatic activities. The integration of thermal information and activation of regu-

latory mechanisms is a major and "primitive" function of the central nervous system, especially of the hypothalamus, brain stem and spinal cord with graded control mechanism organized in cranio-caudal direction from narrow-band to wide-band control. Overriding the latter produces incomplete and complete poikilothermia, which was already mentioned as a feature of hypothalamic, mesencephalic and bulbar failure.

The progression in terms of deterioration from acute primary midbrain syndrome into pontine and finally into a bulbar syndrome is very frequent in patients which we discussed above. This oro-caudal involvement and deterioration of the function at different levels of the brain stem can be recognized and monitored by clinical and neurophysiological examinations. In patients with *bulbar death* or *brain stem death all evoked potentials and brain stem reflexes* are abolished. This includes acoustic brain stem potentials, blink reflex, trigeminal facial and masseter reflex, visual evoked potential and cortical somato-sensory evoked potentials whereas the medullary potentials can still be recorded. Generally, clinical examination is sufficient for the diagnosis of death, but the evaluation of the evoked potentials can be of decisive help and permits to establish the site, extent, course and prognosis of the lesion of the brain stem. I will not discuss here the relatively limited value of the scalp-EEG.

Computerized tomography is of great help for the diagnosis of the damage, its extent, and the progression of secondary disturbances, such as oedema, haemorrhages and herniations of brain. An irreversible lesion is proved and confirmed by isodense or hypodense structureless scan in slices of the whole brain or of the brain stem alone. In adults, this is supplemented by the evidence of complete obliteration of all the cisterns around the hypothalamus and the brain stem. It has to be stressed that these findings alone are insufficient to declare death; however, they are of great importance for the decision concerning artificial respiration and continuation of treatment.

The examination of the cerebral circulation by total angiography, recording of intracranial pressure and cerebral perfusion pressure, and starting recently, evaluation of the presence of blood flow by transcranial Doppler-sonography and study of the blood flow by dynamic CT are sometimes considered as helpful supplementary methods but in fact seem to be unnecessary for the purpose of declaration of death.

For the near future our therapeutic strategy in terms of continuation or abandonment may be influenced by the mentioned noninvasive procedures.

Localized lesions of the brain stem

Localized lesions of the brain stem must be separated strictly from acute generalized brain lesions with primary or secondary involvement of the hypothalamo-pituitary system and/or the brain stem. It is one of the great achievements of the surgical and nonsurgical therapy in the last decades, that such lesions — neoplastic, vascular and even traumatic — are not invariably connected with death. Such lesions can be survived sometimes with spectacular results and minor deficits, but more often with permanent severe defect syndromes.

Modern diagnostic procedures are extremely helpful for the decision concerning the therapy of these patients and render it less difficult than in patients with diffuse damage.

Conclusions

I have tried to demonstrate that cerebral death connected with acute severe cerebral damage is not a uniform syndrome, but consists of several, well characterized syndromes of irreversible hypothalamic-pituitary, mesencephalic and bulbar failure. Loss of consciousness — coma — is common to all these forms. The diagnosis is based on establishing complete irreversible damage of specific vital basal functions such as hypothalamo-pituitary transmission, water and electrolyte metabolism, temperature regulation, circulation and respiration. This is no primary apnoeic coma alone, but there is a primary asystolic coma as one of the signs of hypothalamo-pituitary and hypothalamo-mesencephalic failure. The common feature of all types of this failure is the irreversible break-down of central neurogenous and/or neurohumoral regulatory systems with specific main signs which depend on the site of the acute irreversible damage. Our examinations can be summarized as follows in a brief statement: "Life means regulation and modulation and death means loss of regulation and modulation".

The break-down of the central regulation system means the break-down of the specific human cortical function at the same time. Without hypothalamo-pituitary system and without brain stem, cortical and subcortical functions are abolished. Thus hypothalamo-pituitary and brain stem death means the death of the whole brain. The demand for complete loss of function of the whole brain, including the brain stem as criterion for definition of death, seems therefore to be irrelevant. It has to be

mentioned, however, that in few patients with irreversible brain stem or bulbar failure and with complete loss of cerebral circulation, partial hypothalamo-pituitary function with preserved hormone excretion and positive reactions to stimulation was found. This was probably due to the blood supply to these structures from extracranial circulation and was of no relevance for the survival.

In patients with bulbar death, irreversible cessation of respiration and complete loss of brain stem functions, artificial respiration should be started and maintained only if organ explantation is considered. A human being with the dead brain has to be regarded as dead. Finally, asystole occurring with other types of cerebral failure is not an indication for artificial respiration.

Secondary, severe and long-lasting anoxic brain lesions with predominant destruction of the grey matter, mainly of the cortex, and with diffuse damage to the white matter with disruption of interconnecting pathways cause irreversible loss of specific human properties. The central regulation systems in such patients are and remain at least partially intact. This condition, according to my experience and belief, cannot be equated with the death of the brain. However, there is no more human life without cortical function.

I do hope that this commission may give to us physicians help and assistance in one of the most difficult decisions of our medical consciousness: whether to cease action or to continue with treatment.

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EXPERIMENTAL ASPECTS OF BRAIN RESUSCITATION

K.-A. HOSSMANN
Max-Planck-Institut für neurologische Forschung
Abteilung für experimentelle Neurologie
Ostmerheimer Str. 200, 5000 Cologne 91, FRG

INTRODUCTION

In most countries of the world, medical sciences and legislation have established that the death of the brain determines the death of the human being. Brain death is the irreversible loss of all brain functions; the determination of death, in consequence, requires unequivocal evidence of the irreversibility of functional and metabolic suppression of the brain.

Under most conditions of naturally occurring death, such evidence is provided by inference. If heart function stops and the circulation of the blood is arrested, higher central nervous functions are almost immediately suppressed, followed by a break-down of cell metabolism within a few minutes (Lowry *et al.*, 1964). Under conditions of irreversible heart arrest, functional and metabolic suppression of the brain is also irreversible. Following transient heart arrest, however, the occurrence of irreversible suppression is more difficult to define. In order to determine this moment, the revival time of the brain has to be known, i.e., the longest duration of cerebrocirculatory arrest the brain can endure without irreversible injury. Over the past years, considerable controversy has arisen about the length of this time. In normothermic animals the upper limit of ischemia with full neurological recovery varied between 10 (Crowell and Smith, 1956) and 24 min (Miller and Myers, 1970), and that with revival of the EEG between 15 (Ten Cate and Horsten, 1952) and 60 min (Hossmann and Zimmermann, 1974). A wide range of ischemia times also exists for the development of morphological lesions. Irreversible neuronal damage has been observed in so-called *selectively vulnerable*

areas of hippocampus after only 5 min. of ischemia (Kirino, 1982), but there is histological and autoradiographic evidence that neurons in the *resistant regions* of the brain remain intact after arrest of blood flow for as long as 1 hour (Hossmann and Kleihues, 1973).

These differences may be explained by the following considerations. During the past years evidence has accumulated that damage inflicted upon the brain by ischemia occurs in 2 successive phases (Hossmann, 1985): (a) the primary impact of ischemia producing severe but not necessarily irreversible changes of the functional and biochemical properties of the brain and (b) secondary post-ischemic effects which, by imposing an additional stress on the brain, lead to delayed damage during the recirculation period.

The pathomechanism of these post-ischemic effects is still unclear. Some authors stress the importance of biochemical/molecular processes, whereas others consider recirculation disturbances as the most important event limiting revival of the brain after prolonged ischemia (for review see Hossmann, 1985). It is obvious that post-ischemic recirculation disturbances must prevent *eo ipso* post-ischemic recovery, but it is still disputed if such disturbances are merely an epiphenomenon of irreversible brain damage rather than the reason for it.

In the first part of this communication the pathophysiology of some of these complications as well as their therapeutical implications will be reviewed. The second part deals with the potentials of post-ischemic brain resuscitation under experimental conditions that have been developed to prevent or ameliorate these complications. Finally, the bearing of these observations on the determination of the precise moment of brain death will be discussed.

I. Pathophysiology of brain resuscitation

A) *Post-ischemic recirculation disturbances*

Following a period of global ischemia of the brain, recirculation disturbances and hence secondary ischemic lesions may develop which are indirectly linked to the primary ischemic impact. Such disturbances may be present at the beginning of the post-ischemic period (*no-reflow phenomenon*) or may appear after a period of unimpaired or even increased reperfusion (*post-ischemic hypoperfusion*). These two forms of post-

ischemic recirculation disturbances are basically different and will be described separately.

Early recirculation disturbances (no-reflow phenomenon)

The term "no-reflow phenomenon" was introduced by Ames *et al.* (1968), who observed reperfusion deficits of the rabbit brain after strangulation ischemia of more than 7-10 min. In earlier investigations of Hirsch and Müller (1962) a vascular pattern of histological damage was also noted but not considered to be of pathogenetic relevance because the revival time of the brain was thought to be shorter than 10 min. In the following, however, numerous authors have stressed the importance of homogeneous reperfusion of the brain tissue for reactivation of metabolic activity, not only in the brain (Ginsberg and Myers, 1972; Gurvitch *et al.*, 1976; Deb *et al.*, 1978) but also in peripheral organs such as heart (Kloner *et al.*, 1974; Tranum-Jensen *et al.*, 1981) and kidney (Flores *et al.*, 1972; Brodman *et al.*, 1974).

The pathogenesis of the no-reflow phenomenon is multifactorial. The most important factors are post-ischemic hypotension, changes in blood viscosity, intravascular disseminated coagulopathy, and brain edema. *Post-ischemic hypotension* depends on the type and duration of ischemia. If blood flow of the brain is interrupted without affecting cardiac function, blood pressure initially tends to increase because reduction of oxygen supply to the brain stem evokes a Cushing response (Fig. 1). This response may last up to 10 min and is followed by a return of blood pressure to or below pre-ischemic level when ischemia persists. Beginning of recirculation, in such instances, causes a further decrease of blood pressure because the release of acid equivalents from the ischemic tissue into the systemic circulation causes vasodilation of the peripheral bed. After ischemia of 30 to 60 min., blood pressure without pharmacological treatment may decrease to values below 50 mm Hg, precluding adequate recirculation of the ischemic brain (Hossmann and Kleihues, 1973).

If cerebral blood flow ceases as the consequence of cardiac arrest, even shorter periods of ischemia may be complicated by post-ischemic hypotension because the ischemic heart does not resume immediately its function. This is the reason for the fact that the revival time of the brain after cardiac arrest is shorter than that after selective ischemia of the brain (Hirsch *et al.*, 1957).

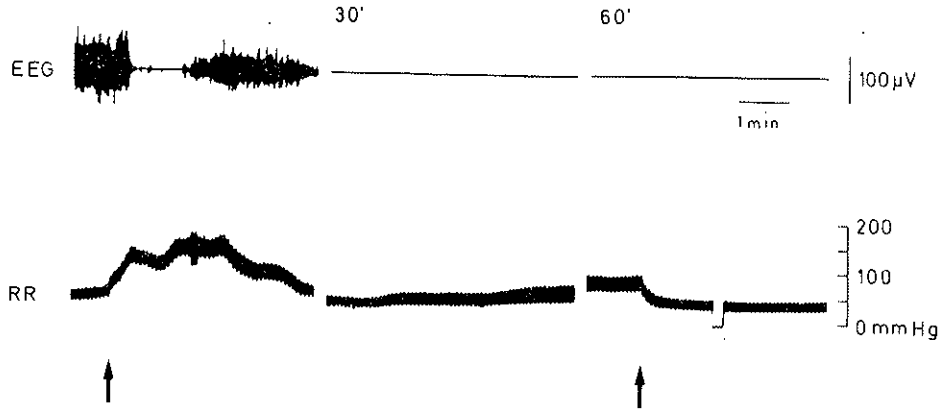

FIG. 1. Recording of electroencephalogram (EEG) and arterial blood pressure (RR) during and after occlusion of arterial blood supply to the brain of cat for 1 hour. First arrow: intrathoracic occlusion of the innominate and left subclavian artery; second arrow: release of vascular occlusion after 1 hour ischemia. Note the increase of blood pressure after vascular occlusion (Cushing's response) and the fall of blood pressure after restoration of blood flow to the brain (post-ischemic hypotension). EEG flattens immediately after vascular occlusion, but it transiently recovers on the peak of the blood pressure increase due to collateral blood supply via non-occluded vessels.

Disseminated coagulopathy occurs shortly after the onset of ischemia and further increases in severity during the early recirculation period (Fig. 2, Stullken and Sokoll, 1976; Hossmann and Hossmann, 1977). The main reason for intravascular coagulopathy is a massive ischemia-induced sympathicotonic discharge, which is further aggravated by pharmacological application of sympathicomimetics necessary for stabilization of blood pressure during the early recirculation period. The effect of intravascular coagulation on post-ischemic recirculation is at least threefold: aggregation of platelets in the ischemic vascular bed causes mechanical obstruction (Hekmatpanah, 1973; Dougherty *et al.*, 1977), the release of serotonin from aggregated platelets induces vasoconstriction (Welch *et al.*, 1972), and the additional involvement of peripheral organs causes general disturbances with adverse effects on the brain (Hossmann *et al.*, 1980). The most important of these effects is pulmonary distress causing impairment of blood oxygenation and, in consequence, an increase of post-ischemic brain edema (see below) if not adequately treated (Hossmann and Hossmann, 1977). Intravascular coagulation is further aggravated by changes of *blood viscosity* which increases as blood flow slows down (Schmid-Schönbein, 1977). This increase is rapidly reversible as soon as blood starts

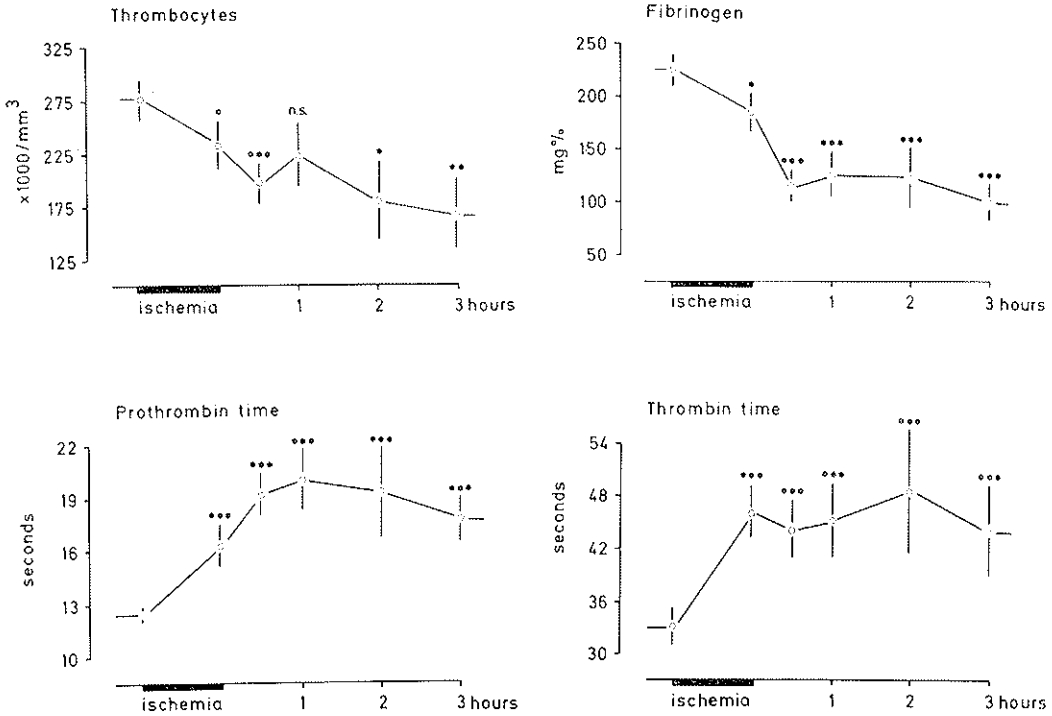

FIG. 2. Disseminated intravascular coagulopathy during and after 1 hour cerebro-circulatory arrest in cats. Note the gradual decline of thrombocytes and plasma fibrinogen, and the associated increase of coagulation times (Hossmann and Hossmann, 1977).

flowing, but for initiation of recirculation, higher perfusion pressure is necessary than for maintaining flow.

The effect of ischemic *brain edema* on post-ischemic recirculation is complex (Hossmann, 1976). The main reasons for the development of ischemic brain edema are an increase of intracellular osmolality (Hossmann and Takagi, 1976; Bandaranayake *et al.*, 1978) and the breakdown of membrane potentials (Astrup *et al.*, 1977) which results in an equilibration of intra/extracellular ion and osmotic gradients (see below). If ischemia is complete, development of brain edema is negligible because cessation of blood flow also interrupts supply of water (Hossmann, 1976). However, in such instances brain edema develops in the moment of blood recirculation causing an abrupt increase of intracranial pressure (Fig. 3). If ischemia is incomplete, and sodium and water supply to the brain persists,

edema develops already during ischemia and may impede cerebral blood flow from the beginning of recirculation. Such disturbances are most severe in hyperglycemic animals because the high concentration of lactate increases tissue osmolality (Ginsberg *et al.*, 1978). The situation is further complicated by the fact that ischemia causes an increase of extracellular potassium which, in turn, produces vasoconstriction (Wade *et al.*, 1975; Hart *et al.*, 1978; Hansen *et al.*, 1980). During ischemia this effect is counteracted by the simultaneous decrease of pH but during the early recirculation phase normalization of extracellular potassium and pH may proceed with different time courses. All these factors make it almost impossible to foresee, in a given experiment, to what extent edema will interfere with blood recirculation. It also explains that blood recirculation after ischemia may be initially restored but ceases a few minutes later, when ischemic brain edema becomes critical. The no-reflow phenomenon, in a more general sense, may therefore be defined as the phenomenon of early recirculation disturbances.

Treatment of no-reflow is possible by interfering with these pathogenetic factors (Fig. 4). Increasing post-ischemic blood perfusion pressure

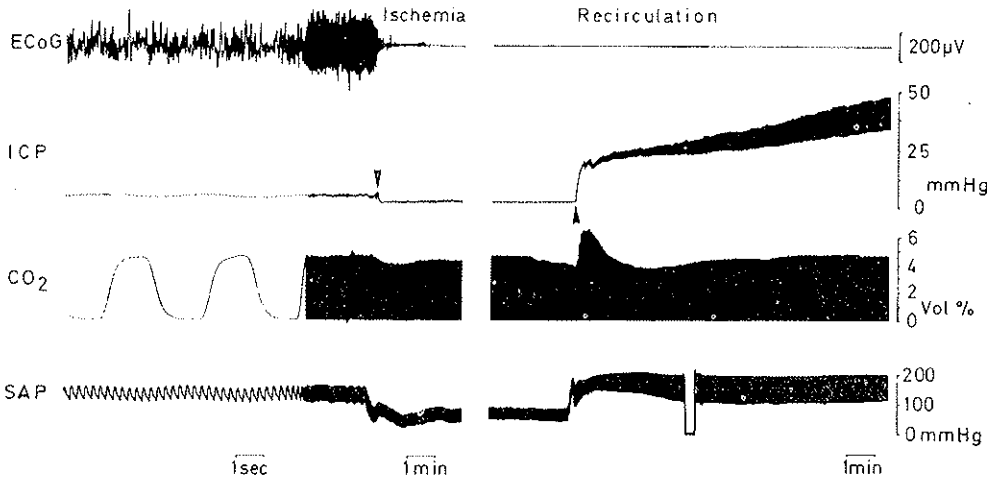

FIG. 3. Recording of electrocorticogram (ECoG), intracranial pressure (ICP), endtidal CO_2 and systemic arterial pressure (SAP) during and after 1 hour cerebro-circulatory arrest in cat. Cushing's blood pressure response at the onset of ischemia was blocked by infusion of a ganglioplegic agent (downward arrow); blood pressure rise at the onset of recirculation was induced by infusion of catecholamines (upward arrow). Note the steep increase of intracranial pressure during post-ischemic recirculation of the brain (Zimmermann *et al.*, 1975).

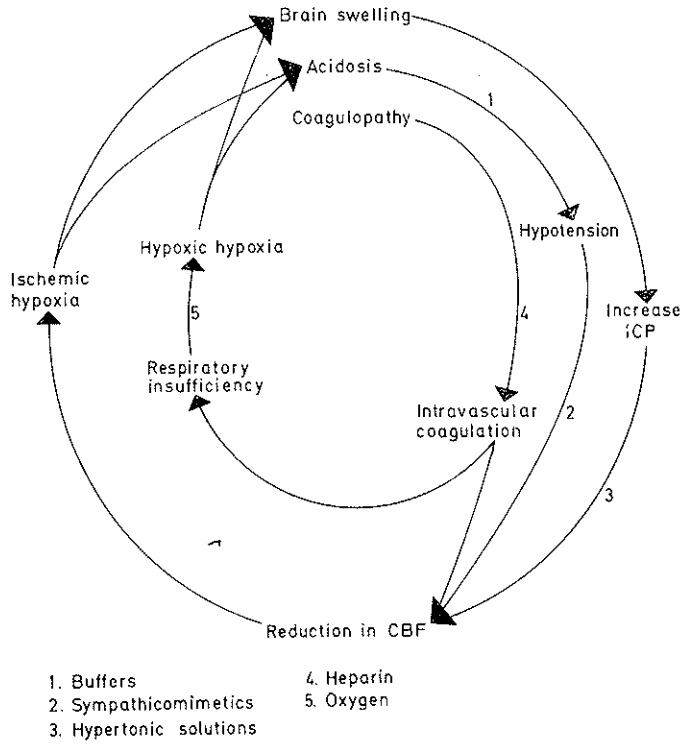

FIG. 4. Schematic representation of factors causing early recirculation impairment after prolonged ischemia. Numbers indicate therapeutical procedures recommended for blocking the vicious cycle.

reduces the area of no-reflow and improves homogeneity of microcirculation (Cantu *et al.*, 1969; Appelgren, 1972; Tweed *et al.*, 1977; Ito *et al.*, 1980). A beneficial effect is also obtained by preventing aggregation of platelets with indomethacin and prostacyclin (Hallenbeck and Furlow, 1979), by diminishing intravascular coagulation with heparine (Stullken and Sokoll, 1976) or streptokinase (Lin, 1978), by reducing blood viscosity with hemodilution (Fischer and Ames, 1972; Siemkowicz, 1980) and by treating ischemic brain edema with osmotic dehydration (Hossmann and Takagi, 1976). In our laboratory a combination therapy consisting of anticoagulation with heparine, osmotherapy with 20% sorbit, controlled equilibration of blood acidosis with Tris-buffer, and induced hypertension with norfenefrine or dopamine is able to prevent no-reflow in most of the experiments even after 1 hour complete ischemia (Hossmann and

Zimmermann, 1974). In such instances reactive hyperemia develops and metabolic and electrophysiological functions begin to recover as described below. In animals with manifested no-reflow, on the other hand, recovery is absent. This is the reason that after prolonged ischemia a close correlation exists between the degree of post-ischemic hyperemia and the speed and quality of post-ischemic recovery (Hossmann *et al.*, 1973). It should be noted, however, that this opinion is not shared by all authors because, under certain experimental conditions, neuronal damage has been observed in the absence of no-reflow (Levy *et al.*, 1975; Harrison *et al.*, 1975).

Delayed post-ischemic hypoperfusion

Development of post-ischemic hypoperfusion is independent of the state of early post-ischemic recirculation. In fact, it develops regularly in animals with pronounced reactive hyperemia (Fig. 5), although a direct relationship between the degree of hyperemia and post-ischemic hypoperfusion does not seem to exist (Hossmann *et al.*, 1973; Snyder *et al.*,

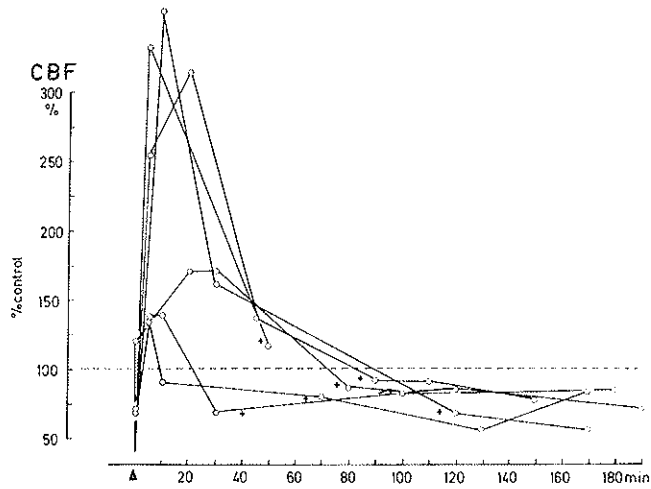

FIG. 5. Measurement of cerebral blood flow in cats during recirculation following 30 min complete cerebro-circulatory arrest. Blood flow was measured by the intra-arterial ^{133}Xenon injection method and expressed as percent of pre-ischemic control value. Note pronounced hyperemia during the early recirculation phase, followed by delayed post-ischemic hypoperfusion after 30-60 min. The onset of post-ischemic hypoperfusion correlates with the beginning return of EEG activity, as indicated by the crosses (Hossmann *et al.*, 1973).

1975; Levy *et al.*, 1979; Miller *et al.*, 1980; Pulsinelli *et al.*, 1982a; White *et al.*, 1983). It is interesting to note, however, that also in other instances of transiently increased blood flow, such as hypoglycemia (Siesjö and Abdul-Rahman, 1979; Abdul-Rahman *et al.*, 1980), epilepsy (Meldrum and Nilsson, 1976; Ingvar *et al.*, 1981), spreading depression (Lauritzen *et al.*, 1982), or subarachnoid hemorrhage (Mendelow *et al.*, 1981), a secondary reduction of blood flow below control has been observed.

Angiographic findings as well as vital microscopy of the pial vasculature have revealed that post-ischemic hypoperfusion, other than the no-reflow phenomenon, is due to an increase in vascular tone (Hossmann *et al.*, 1973; Takagi *et al.*, 1977). Factors like post-ischemic brain edema, intravascular coagulation or hypotension are not involved, as evidenced by normalization of water and ion homeostasis, disappearance of intravascular platelet aggregates, and normalization of blood pressure before post-ischemic hypoperfusion begins to develop (Hossmann and Kleihues, 1973).

The leading pathophysiological symptom of post-ischemic hypoperfusion is the disappearance of *CO_2-reactivity* in the presence of a normal autoregulatory response to increasing blood pressure (Fig. 6, Hossmann *et al.*, 1973; Nemoto *et al.*, 1975; Miller *et al.*, 1980). This dissociated disturbance of flow regulation results in stabilization of blood flow at subnormal level which cannot be influenced by either changes in cerebral perfusion pressure or activation of metabolism. The latter is of particular importance because failure of metabolic regulation may result in tissue hypoxia when arterial oxygen supply does not or only partially covers the oxygen demands of the recovering brain. In this situation *anaerobic glucose utilization* is stimulated, as evidenced by the increase of the glucose/oxygen uptake ratio of the brain, leading to secondary brain edema (Hossmann, 1979). Interestingly, anaerobic glycolysis begins to appear already at a time when only 50% of available blood oxygen is extracted (Hossmann, 1979), indicating that during post-ischemic hypoperfusion a substantial degree of non-nutritional flow must exist.

There is evidence that post-ischemic hypoperfusion is not an epiphenomenon but a limiting factor for progression of recovery of the brain after ischemia. In our laboratory, we regularly observe that following ischemia up to 1 hour duration evoked potentials and EEG activity steadily improve during the initial 2 to 3 hours of recirculation but then frequently deteriorate and even secondarily disappear after 4 to 6 hours. Autopsy of such brains reveals severe edema with secondary circulatory

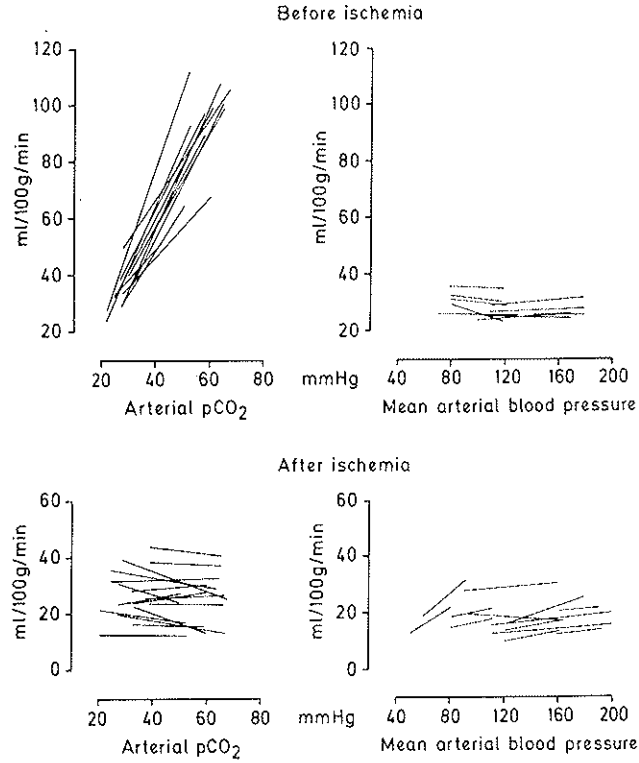

FIG. 6. Cerebrovascular reactivity to changes of arterial pCO_2 (left) and changes of mean arterial blood pressure (right) before and after 60 min complete cerebro-circulatory arrest in cats. Blood flow was measured by the intra-arterial ^{133}Xenon injection method; measurements after ischemia were carried out during the phase of post-ischemic hypoperfusion. Note the complete suppression of CO_2 reactivity and the preservation of autoregulation during post-ischemic hypoperfusion (Hossmann *et al.*, 1973).

arrest. In other instances in which post-ischemic hypoperfusion is less severe, EEG continues to improve and may even normalize when the animals survive for more than 12 hours (see below).

Improvement of blood flow during the phase of post-ischemic hypoperfusion succeeded up to now only by lowering viscosity with *hemodilution* (Hossmann *et al.*, 1973; Hossmann *et al.*, 1981; Bleyaert *et al.*, 1980). However, the increase of flow is parallelled by a decrease of oxygen-binding capacity of arterial blood, and calculated oxygen availability to the brain does not improve. *Vasoactive substances* such as papaverine, phenoxibenzamine, and prostacyclin did not improve blood flow or the

disturbed regulation of blood circulation (Hossmann *et al.*, 1973; van den Kerckhoff *et al.*, 1983). Attempts have also been made to decrease *metabolic activity* of the brain during post-ischemic hypoperfusion in order to ameliorate the misrelationship between oxygen supply and oxygen requirements of the tissue. For this purpose, pentobarbital, thiopental or hypothermia were used, but none of these approaches had a reproducible effect on post-ischemic recovery, mainly because of a further reduction of blood flow (Snyder *et al.*, 1979; van den Kerckhoff *et al.*, 1980; Gisvold *et al.*, 1984). Recently it has been hypothesized that blood flow and the efficiency of mitochondrial respiration can be improved by reducing ischemic and post-ischemic intracellular *calcium uptake* (Hass, 1981; Siesjö, 1981). In some experiments application of the calcium antagonists lidoflazine and nimodipine had, in fact, a beneficial effect on both post-ischemic blood flow and functional recovery (Kazda *et al.*, 1982; White *et al.*, 1982; Steen *et al.*, 1983). However, another calcium entry blocker, flunarizine, failed to reduce post-ischemic calcium accumulation in the brain after 60 min global ischemia and had no beneficial effect on biochemical or functional recovery (Hossmann *et al.*, 1983).

The therapeutic possibilities for improvement of post-ischemic hypoperfusion, in consequence, are still very poor; however, substantial progress in brain resuscitation can be expected when this pertinent problem is solved.

B) *Biochemical disturbances*

Metabolic disturbances leading to ischemic cell damage are closely related to substrate exchange between blood and brain and, therefore, cannot always be differentiated from hemodynamic phenomena. In the following discussion of the molecular mechanisms of ischemic injury this interrelationship will be considered.

Post-ischemic hypermetabolism

Post-ischemic hypermetabolism has been described in various species after cerebro-circulatory arrest ranging between 10 and 30 min (Levy and Duffy, 1977; Diemer and Siemkowicz, 1981; Nemoto *et al.*, 1981; Choki *et al.*, 1983). Although the methods used for measuring metabolic activity are not comparable in the different models, the reported data

suggest that hypermetabolism is more pronounced after shorter than after longer periods of ischemia (Fig. 7). Several factors may explain increased metabolic activity: post-ischemic functional hyperactivity (Suzuki *et al.*, 1983) — in gerbils occasionally even epileptic seizures (Brown *et al.*, 1979), post-ischemic stimulation of repair processes (Levy and Duffy, 1977), and mitochondrial damage (Rehncrona *et al.*, 1979). The latter results in an inhibition of state 3 respiration and hence increased glucose and oxygen consumption in order to yield a constant production of energy-rich phosphates. It should also be considered that increased cytosolic level of calcium (see below) stimulates mitochondrial Ca^{2+} sequestration at the expense of ATP production, and thus further enhances mitochondrial insufficiency (Nicholls, 1985).

It has not been established if post-ischemic hypermetabolism damages the brain *per se*; however, it is reasonable to assume that it may be deleterious during the phase of post-ischemic hypoperfusion, as described above. Considering the fact that both hypermetabolism and hypoperfusion may appear after very brief periods of ischemia, a relationship with the development of selective vulnerability cannot be excluded. This notion is supported by the finding that low dose of barbiturates given shortly after 5 min ischemia in gerbils reduces morphological lesions in hippocampus, presumably by inhibiting post-ischemic functional hyperactivity (Kirino *et al.*, 1985). A similar mechanism could also be responsible for the prevention of hippocampal lesions using other means of inhibiting functional hyperactivity, such as local injection of aspartate-antagonist (Simon *et al.*, 1984a) or by deafferentation (Wieloch *et al.*, 1985; Pulsinelli, 1985). On the other hand, it should be remembered that barbiturates or other metabolic depressants do not ameliorate brain damage after prolonged ischemia (Pulsinelli *et al.*, 1979; Gisvold *et al.*, 1984). This difference can be explained by the fact that post-ischemic hyperactivity is most pronounced after brief episodes of ischemia, and that barbiturates inhibit metabolic activity indirectly by reducing functional activity. In fact, when thiopental was administered after 12-16 min cardiac arrest, an amelioration of ischemic brain lesions was observed in animals with epileptic but not with normal EEG pattern (Todd *et al.*, 1982). The controversial results obtained by barbiturate treatment, therefore, do not refute post-ischemic hypermetabolism as a mechanism of ischemic brain damage in either selectively vulnerable or resistant brain regions.

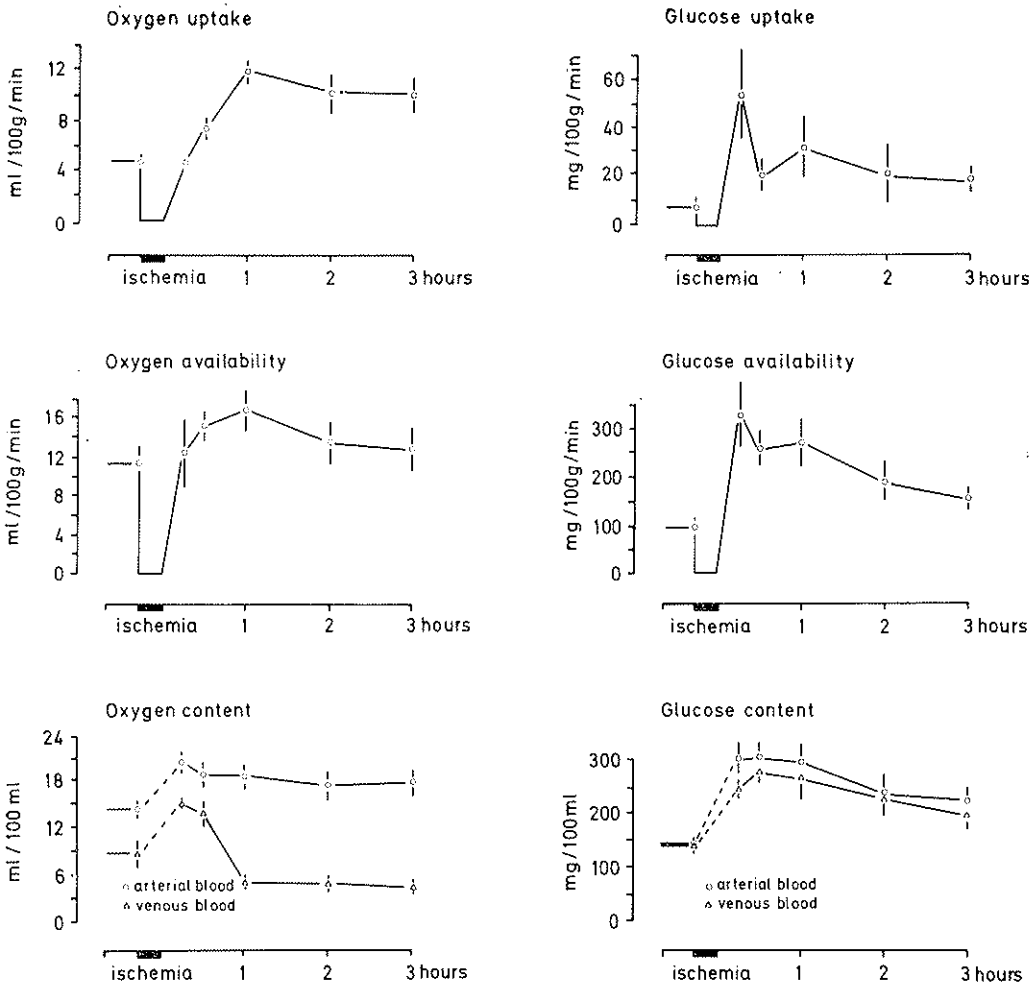

FIG. 7. Post-ischemic hypermetabolism following 16 min complete cerebro-circulatory arrest in cats. Oxygen and glucose uptake were measured by arterio-cerebro-venous sampling technique, and blood flow by the intra-arterial ^{133}Xenon injection method. Note the increase of both oxygen- and glucose uptake during the initial 3 hours of recirculation. Post-ischemic hyperglycemia is a spontaneous event; post-ischemic increase of arterial oxygen content was induced by ventilating animals with pure oxygen (data from Nemoto *et al.*, 1981).

Tissue acidosis

The molecular mechanisms of tissue acidosis and ischemic brain lesions have recently been discussed (Siesjö, 1985), and therefore will be only briefly considered. During complete ischemia the degree of tissue acidosis depends mainly on the hydrolysis of ATP and hence on the stores of glucose and glycogen which are used to replenish ATP by anaerobic glycolysis. Acidosis, therefore, is more severe in hyperglycemic than in starved animals. The duration of ischemia is of secondary importance because production and hydrolysis of ATP cease within a few minutes after the onset of ischemia if ischemia is complete (Ljunggren *et al.*, 1974).

During incomplete ischemia the situation is different. Continuous supply of glucose by a trickle of blood flow maintains some anaerobic glycolysis, the degree of which depends on both the duration of ischemia and the glucose concentration of blood. Tissue acidosis, in consequence, may vary considerably in different ischemic models. This explains that complete ischemia is in general better tolerated than incomplete ischemia (Hossmann and Zimmermann, 1974; Nordström *et al.*, 1976; Rehncrona *et al.*, 1979), and that damage is less severe in hypoglycemic than in hyperglycemic animals (Myers and Yamaguchi, 1976; Siemkowicz and Hansen, 1978; Ginsberg *et al.*, 1980; Pulsinelli *et al.*, 1982b).

Although the general relationship between tissue acidosis and ischemic brain damage seems now to be well established, its particular role for selective vulnerability is less clear. It is unlikely that global ischemia produces more pronounced acidosis in the vulnerable than in other regions of the brain because the content of glucose and glycogen is relatively constant throughout the brain (Paschen *et al.*, 1983a, b). On the other hand, the appearance of neuronal lesions in hippocampus after brief periods of ischemia is not an argument against the acidosis hypothesis because acidosis reaches its peak within a few minutes after circulatory arrest. Selective vulnerability, therefore, may be linked to acidosis in a similar way as to other global complicating events such as post-ischemic hypoperfusion or post-ischemic hypermetabolism.

Disturbances of water and ion homoiostasis

During and after cerebral ischemia severe disturbances of water and ion homoiostasis occur (Fig. 8). During complete ischemia, the brain is converted into a closed system, i.e., fluid and ion shifts occur between the various compartments of the brain with little changes of net water and

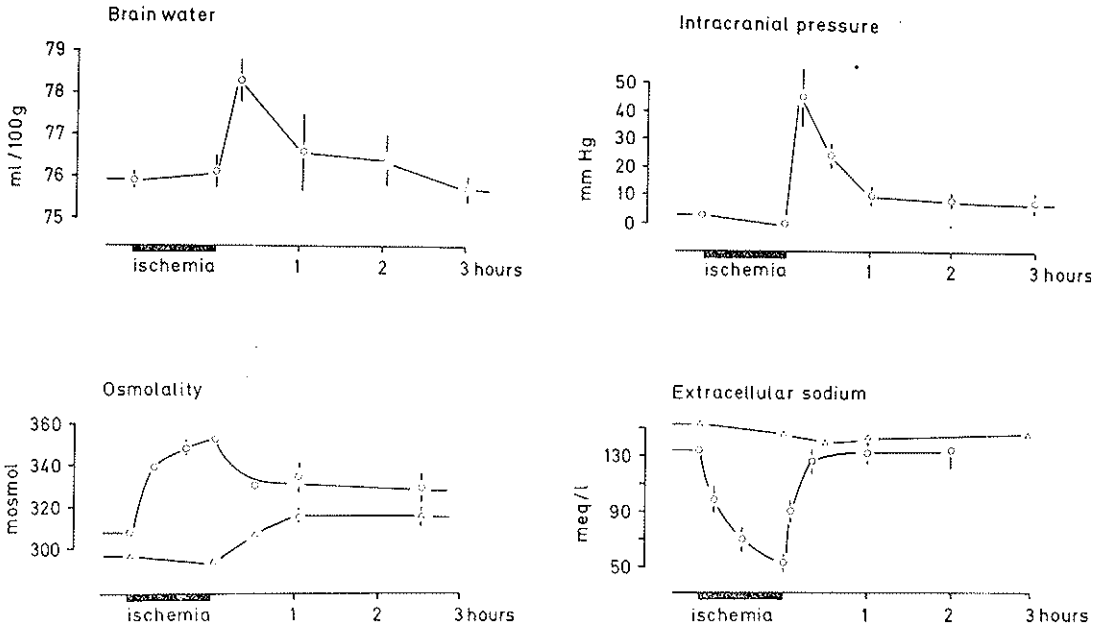

FIG. 8. Development of post-ischemic brain edema in cats following 1 hour cerebro-circulatory arrest. Measurement of brain water, intracranial pressure, osmolality of brain tissue (circles) and blood serum (triangles), and of sodium in extracellular space of cerebral cortex (circles) and serum (triangles). During ischemia osmotic and ionic gradients build up between brain and blood, which are equilibrated during recirculation after ischemia. Equilibration is associated with transient increase of brain water, which in turn causes an increase of intracranial pressure. After restoration of ion homoiostasis brain edema is resolved, and intracranial pressure normalizes. The post-ischemic increase of serum osmolality is a therapeutic effect induced by systemic application of 20% sorbitol for prevention of fatal post-ischemic brain edema (Hossmann, 1976).

electrolyte content (Hossmann, 1976). During incomplete ischemia or during the recirculation phase after ischemia, blood provides an almost unlimited reservoir for supply and/or removal of fluid and electrolytes, resulting in considerable net changes of tissue content. The most important factors responsible for edema formation are an increase in tissue osmolality (Hossmann and Takagi, 1976; Bandaranayake *et al.*, 1978), inhibition of ion exchange pumps due to energy failure (Astrup, 1982), and permeability changes of cell membranes. The latter may be a functional change induced, for instance, by the release of glutamate, which causes a transient increase in permeability of sodium and chloride (van Harreveld, 1970). However, permeability changes of membranes may also be the

consequence of strutctural lesions, e.g. due to peroxidation of phospholipids (Yoshida *et al.*, 1982; Nemoto *et al.*, 1983; Watson *et al.*, 1983; 1984).

The resulting fluid and electrolyte shifts are reversible in all regions of the brain, even after complete ischemia of one hour (Hossmann, 1976). Prerequisite is rapid and homogeneous post-ischemic reperfusion because energy metabolism and hence the function of ion exchange pumps have to be restored before post-ischemic brain swelling becomes fatal. In cases of successful reperfusion, post-ischemic brain swelling is reversed within 2 to 3 hours after ischemia as long as one hour, and electrolytes return to or close to control levels after the same interval (Hossmann *et al.*, 1977). Structural alterations of neuronal membranes, if any, are either reversible or of little functional significance because membranes recover their electrophysiological properties within 45 min after 1 hour ischemia (Hossmann and Sato, 1970). The major psysiological importance of water and electrolyte disturbances, in consequence, is the contribution to the development of the no-reflow phenomenon (see above) but it does not seem to be a damaging factor per se. This conclusion may not be true as far as disturbances of *calcium homoiostasis* are concerned. Between extra- and intracellular compartments a considerable calcium concentration gradient exists, which is maintained by various pump mechanisms. During ischemia Ca^{2+} enters the intracellular compartment through voltage-dependent channels and accumulates in the cytoplasm because both mitochondrial sequestration and outward calcium transport are energy-consuming mechanisms. *In vitro* experiments suggest that this process is a mediator of ischemic cell death because irreversible changes can be delayed or prevented when calcium is removed from the incubation medium (Farber *et al.*, 1981; Ames and Nesbett, 1983). However, *in vivo* studies of 60 min cerebral ischemia revealed progressive recovery of both metabolic and electrophysiological functions despite substantial increase of tissue calcium content (Hossmann *et al.*, 1983), and there was no significant difference of calcium between vulnerable and resistant areas. Electronmicroscopy demonstrated that calcium deposits were most conspicuous in damaged mitochondria, but the occurrence of such mitochondria was the same in the hippocampus and cortex (Hossmann *et al.*, 1986).

A similar observation was made after brief periods of ischemia in gerbils (Dux *et al.*, in preparation). There was no difference between the resistant dendate gyrus and the vulnerable CA1 sector of hippocampus: in both areas relatively mild mitochondrial sequestration of calcium was noted 15 min after the beginning of recirculation which was reversible

after one hour. However, massive uptake occurred in the selectively vulnerable CA1 sector of hippocampus after a few days, i.e., at a time when histological lesions had become manifest. These findings suggest that intracellular calcium accumulation after ischemia is neither a unique feature of selectively vulnerable neurons nor the primary reason for the development of ischemic cell damage but rather an unspecific accompaniment of manifested cell injury. This conclusion conforms to observations made in different experimental models of ischemia (Yanagihara and McCall, 1982; Dienel, 1984; Simon *et al.*, 1984b) and is also corroborated by the recent observation of Dienel and Pulsinelli (1984), who observed that irreversibly damaged neurons incorporate not only Ca^{2+} but also a variety of other substances such as tetracycline, nickel, pertechneate or sodium. It should be stressed, however, that selectively vulnerable neurons may react to the initial influx of calcium in a different way than resistant neurons, i.e., an unspecific event may provoke specific pathological reactions. This will be discussed in more detail in the following chapter.

Disturbances of protein biosynthesis

Most of the biochemical studies which have been carried out during post-ischemic resuscitation have dealt with the energy-producing metabolism. However, restoration of the energy state of the brain is not equivalent to restoration of specific metabolic pathways. An example is protein biosynthesis (Fig. 9). During complete ischemia, protein synthesis is inhibited because of energy failure but polyribosomes remain in an aggregated state (Kleihues and Hossmann, 1971; Kleihues *et al.*, 1975; Morimoto and Yanagihara, 1981) and incubation of such ribosomes *in vitro* reveals that the protein synthetizing machinery remains intact (Cooper *et al.*, 1977). Immediately after the beginning of recirculation, however, polyribosomes disaggregate and protein synthesis remains severely suppressed although energy-producing metabolism recovers. Presumably the reason for polyribosomal disaggregation is a selective inhibition of polypeptide chain initiation (Cooper *et al.*, 1977), changes in RNA by either increased ribonuclease activity or reduced synthesis being of lesser importance (Kleihues and Hossmann, 1971; Yanagihara, 1976; Albrecht and Yanagihara, 1979; Bodsch and Takahashi, 1984).

The inhibition of protein synthesis is reversible in most regions of the brain, provided a no-reflow phenomenon can be prevented (see below).

In the selectively vulnerable areas protein synthesis initially recovers as fast as in the rest of the brain but after a delay which depends on the duration of ischemia it is secondarily suppressed: after 5 min ischemia delayed suppression occurs after 2 hours (Bodsch and Takahashi, 1984), and after one hour ischemia after 12 hours (Bodsch *et al.*, 1986). The mechanisms responsible for the delayed suppression are still under investigation. It has been demonstrated that Ca^{2+}-calmodulin-dependent protein phosphorylation is disturbed in stratum radiatum of hippocampus 2 hours after 5 min ischemia, followed 2 hours later by abnormalities of the pattern of phosphoproteins. This finding may be a key for the understanding of selective vulnerability. Since the Ca^{2+}-calmodulin-dependent protein phosphorylation system provides the depolarization-induced trigger for the

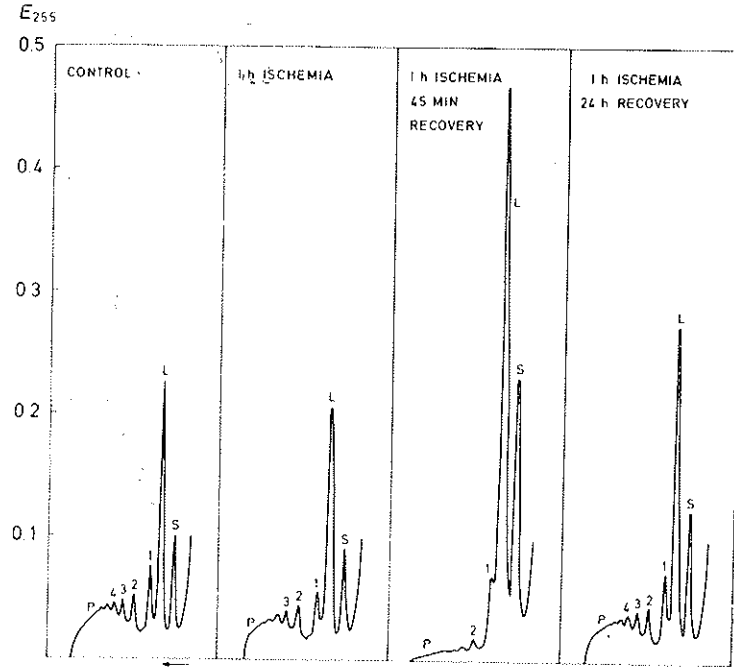

FIG. 9. Polysome profiles from monkey brain before and after 1 hour complete cerebrocirculatory arrest. Polyribosomes (P), oligoribosomes (2-4), monoribosomes (1) large (L) and small (S) ribosomal subunits were separated on exponential sucrose gradients, the direction of sedimentation being indicated by the arrow. During 1 hour ischemia polysome profile does not change, but shortly after the beginning of recirculation almost complete disaggregation of polysomes occurs. After 24 hours polysome profile has returned to normal (Kleihues *et al.*, 1974).

release of neurotransmitter molecules (De Lorenzo *et al.*, 1979), its damage may be the link between increased post-ischemic functional activity and calcium fluxes on one hand, and permanent structural damage on the other. The delay between the onset of these disturbances and cell death could be explained by the long half life of proteins which would enable the cell to survive for some time despite this deficit. This interpretation would also conform to the fine-structural changes of hippocampal neurons which during the maturation phase exhibit changes uncommon for acute anoxia, such as accumulation of cisterns of endoplasmic reticulum (Kirino *et al.*, 1985).

A puzzling observation in this context is the increasing delay of secondary suppression with increasing duration of ischemia (Bodsch *et al.*, 1985). One might speculate that after prolonged ischemia the equally delayed primary recovery process reduces the production of non-functional proteins and that a critical level of such proteins is reached at a later time. Arguing further on this line, one might also speculate that the recovery of protein synthesis in resistant areas of the brain after prolonged ischemia may also be a transient phenomenon, followed by a secondary suppression after an even longer interval. However, all these considerations are purely speculative and not yet supported by experimental data.

II. Potentials of brain resuscitation

In the first part of this communication an attempt was made to review the current knowledge about hemodynamic and molecular factors responsible for the development of post-ischemic damage in selective vulnerable and resistant areas of the brain. The analysis of these mechanisms has led to therapeutic procedures by means of which some of the interfering complications could be alleviated. As a result, the revival time of the brain and the quality of post-ischemic resuscitation have steadily improved over the years. The efficiency of therapeutic procedures, however, varies greatly in different experimental situations.

Following induced cardiac arrest, the recovery time of the heart has to be added to the duration of brain ischemia because reperfusion of the brain is delayed until a sufficiently high blood pressure has been built up. Models in which blood flow to the brain is selectively arrested may also vary, depending on the extent and completeness of ischemia, brain temperature, post-ischemic control of physiological variables, etc. (for review see Hossmann 1984). The by far longest revival times have

been reported in cats and monkeys using an intrathoracic vascular occlusion model. This model was developed to demonstrate that basic electrophysiological and metabolic functions may recover after 1 hour complete cerebrocirculatory arrest at normal body temperature provided blood recirculation could be restored after the ischemic impact (Hossmann *et al.*, 1973). Over the years, the model has been gradually improved, resulting in further amelioration of the quality of resuscitation. The following evaluation of the resuscitation potentials of the brain is based mainly on observations which have been made in this particular experimental model.

Ion homoiostasis and electrophysiological recovery

Several parameters were measured to evaluate these functions. Electrical and synaptical excitability of cortical neurons was tested by recording the response in the pyramidal tract at the bulbar level following electrical stimulation of the somatomotor cortex (Fig. 10). This response consists of several components, the short latency D-wave evoked directly by the electrical stimulus, and the delayed I-wave or indirect response evoked synaptically by interneurons which are activated by the same electrical pulse (Hossmann and Sato, 1971). The cortical steady potential was recorded to evaluate global changes of cell membrane polarization (Hossmann, 1971), and somatically evoked potentials and spontaneous EEG activity in order to evaluate higher levels of electrophysiological integration (Hossmann *et al.*, 1977). Disturbances of intra/extracelluar ion and water homoiostasis were followed by recording extracellular sodium and potassium activity (Hossmann *et al.*, 1977), and by measuring cortical impedance (Hossmann, 1971) which is a function of the size of extracellular space.

All these parameters are rapidly disturbed after the onset of ischemia. EEG becomes isoelectric within 10 sec, somatically evoked potentials and the I-wave of the pyramidal response disappear after 2-4 min, and electrical excitability of cortical neurons is suppressed after 4-6 min. At the same time, extracellular potassium activity sharply increases and the cortical steady potential is shifted towards negativity, indicating cell membrane depolarization. Equilibration of extra/intracellular ion gradients is associated with fluid shifts from the extra- into the intracellular compartment, resulting in an increase of cortical impedance. After 1 hour ischemia cortical impedance has increased by more than 100%, cor-

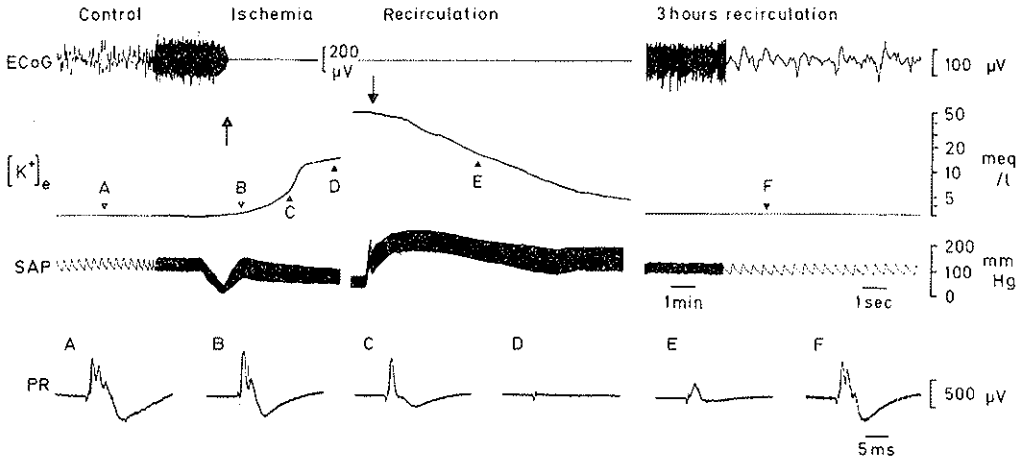

FIG. 10. Recording of electrocorticogram (ECoG), extracellular potassium activity $[K^+]_e$, systemic arterial pressure (SAP), and the pyramidal response following electrical stimulation of the somatomotor cortex (PR) during and after 1 hour complete cerebro-circulatory arrest of cat. The beginning of ischemia is indicated by the upward arrow, and the beginning of recirculation after 1 hour ischemia by the downward arrow. Recording of PR is indicated by letters A-F. Immediately after beginning of ischemia ECoG flattens, followed by a steep increase of $[K^+]_e$ after 3 min and suppression of PR after 4.5 min. Post-ischemic recirculation results in a rapid decrease of $[K^+]_e$ and recovery of PR. After 3 hours recirculation $[K^+]_e$ and PR have normalized and continuous background ECoG activity has returned (Hossmann *et al.*, 1977).

responding to a shrinkage of the extracellular compartment from about 20 to less than 10%. After the same duration of ischemia, extracellular potassium activity has increased from 3.3 to about 60 meq, and extracellular sodium activity has decreased from 135 to less than 60 meq.

Despite these severe disturbances of ion and water homoiostasis, changes are rapidly reversed when the brain is adequately reperfused with blood after ischemia. Immediately after the beginning of recirculation, extracellular potassium and cortical impedance decrease, indicating the beginning normalization of water and ion homoiostasis (Hossmann, 1971; Hossmann *et al.*, 1977). Cortical steady potential exhibits a transient positive shift followed by a slow negative deviation, the peak of which correlates closely with the beginning return of electrical excitability (Hossmann, 1971). Cortical impedance, extracellular ion activities and cortical steady potential usually return to normal within 30-45 min. Electrical excitability of cortical neurons recovers within 10 min of

recirculation and synaptical excitability within 30 min (Hossmann and Sato, 1971).

Recovery of spontaneous electrocortical activity is variable and proceeds faster in cats than in monkeys. In cats spontaneous burst activity usually appears within 60 min of recirculation, followed by gradual return of continuous background activity over the following 2-3 hours (Hossmann *et al.*, 1973). In monkeys EEG bursts recover about 1 hour later, but also in these species continuous background activity returns (Hossmann and Grosse Ophoff, 1986). Frequency analysis of the EEG reveals that both the amplitude and the mean frequency are severely reduced during the initial recovery phase, but they gradually improve with increasing recirculation times, provided secondary complications such as severe post-ischemic hypoperfusion can be prevented. Under such circumstances EEG normalizes within 24 hours (Fig. 11).

Somatically evoked potentials recover in parallel with the EEG. Normalization of amplitude usually occurs within 3-6 hours, but the wave form of the potentials remains distorted for at least 24 hours (Hossmann and Grosse Ophoff, 1986). However, if animals are allowed to survive several days, also normalization of evoked potentials is possible (unpublished observation). The rank order of the recovery times of electrophysiological functions, in consequence, is D-wave of pyramidal response < I-wave of pyramidal response < cortical steady potential < EEG < somatically evoked potentials.

Energy producing metabolism

Restoration of metabolic activity was studied by measuring various metabolites of energy producing metabolism in cortical tissue samples taken during the recirculation period following 1 hour complete cerebrocirculatory arrest (Kleihues *et al.*, 1974). Using newly-developed bioluminescent imaging techniques, the regional distribution of ATP and glucose was also determined in intact cryostat sections of brain (Paschen *et al.*, 1983a). Finally, oxygen and glucose consumption of the brain was measured with arterio-cerebrovenous sampling techniques (Hossmann *et al.*, 1976).

During ischemia, oxygen and glucose supply to the brain is interrupted, and energy producing metabolism breaks down within a few minutes. Upon recirculation following 1 hour ischemia, metabolic rate of oxygen is initially severely inhibited, but it gradually improves and

returns to or above normal after 2-4 hours. Despite initially reduced oxygen consumption, the energy state of the brain is rapidly restored (Fig. 12). Energy charge of adenylate returns close to normal within 30 min of recirculation and remains at this level throughout the observation period. Phosphocreatin also rapidly recovers, and may even increase above normal. The content of ATP is a function of total adenylate and varies under different experimental conditions. During a 60 min

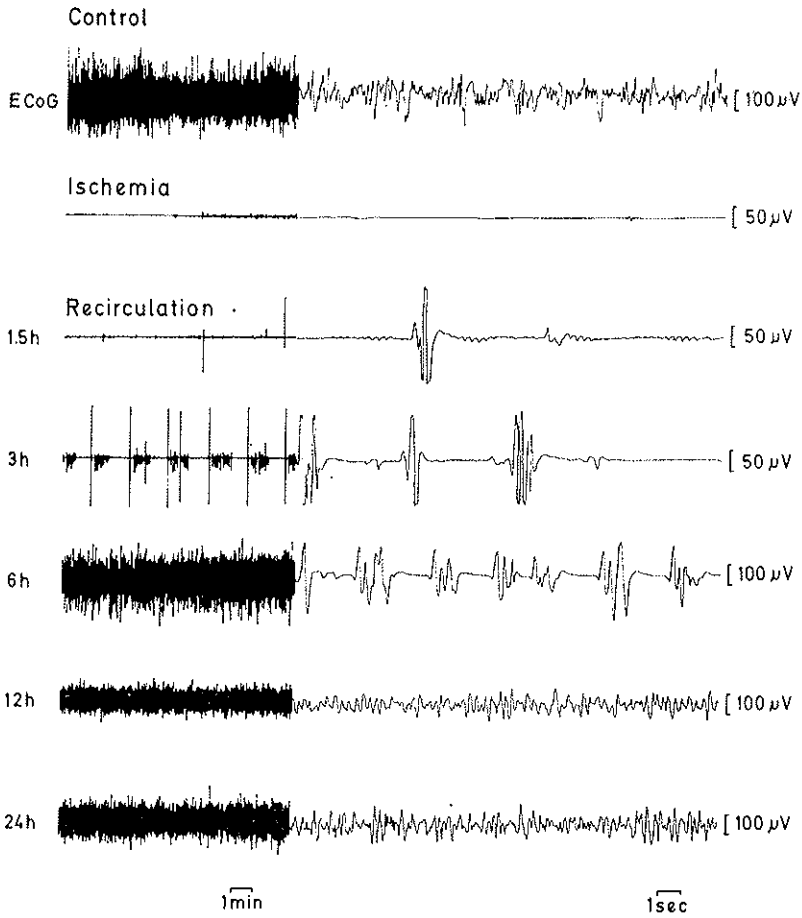

FIG. 11. Recording of electrocorticogram (ECoG) from parietal cortex of monkey before and after 1 hour complete cerebro-circulatory arrest. Note the reappearance of a burst/suppression pattern after 1.5 hours, and continuous background activity after 12 hours of recirculation. After 24 hours ECoG has normalized (Hossmann and Grosse Ophoff, 1986).

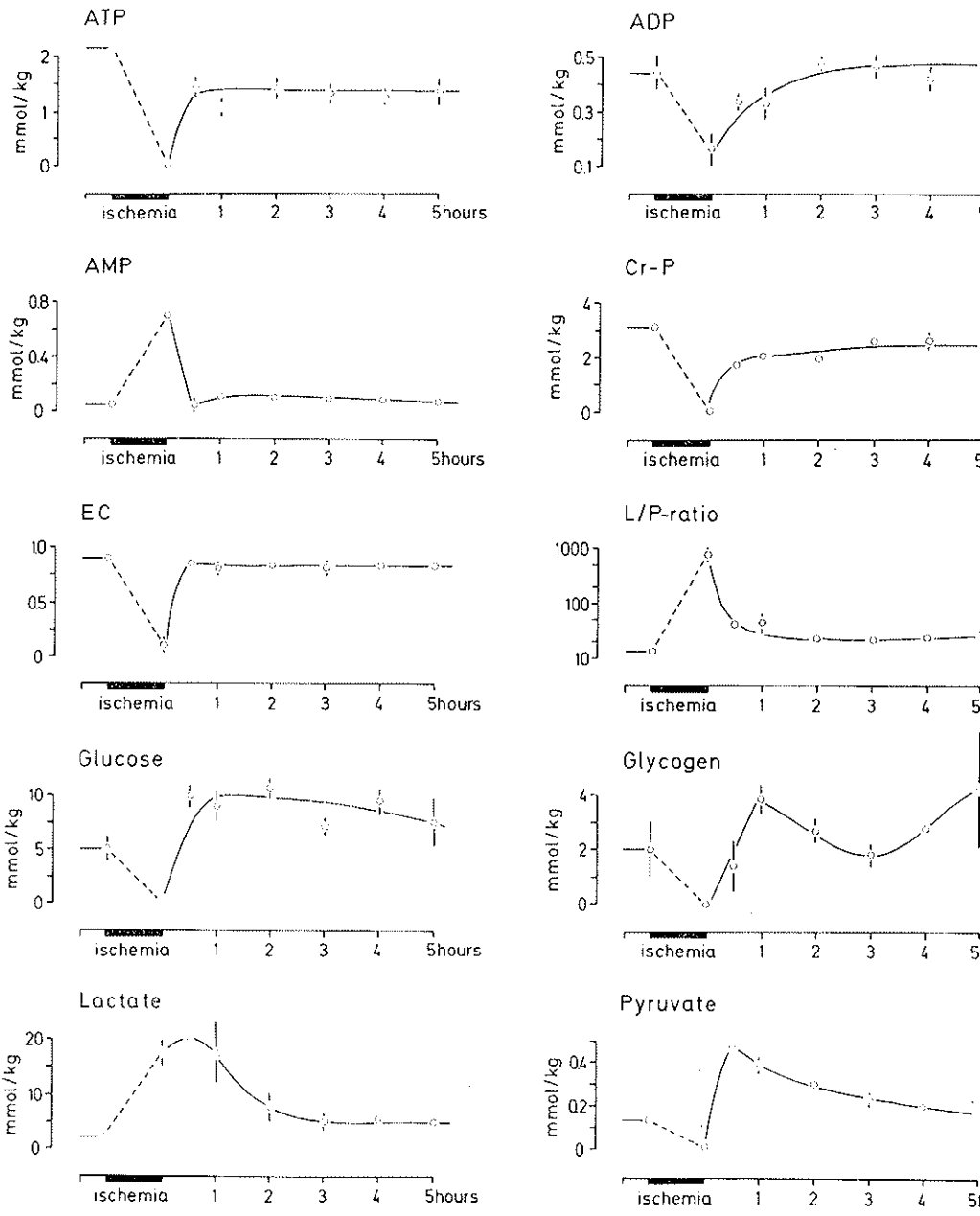

FIG. 12. Measurement of substrates of energy-producing metabolism before and after 1 hour complete cerebro-circulatory arrests in cats. EC: energy charge of adenylate; L/P: lactate/pyruvate ratio. Measurements were carried out in frontal cortex after *in situ* freezing with liquid nitrogen. Note the rapid normalization of EC despite reduced ATP content (Hossmann *et al.*, 1976).

period of ischemia the loss of total adenylate is about 60% in barbiturized cats (Kleihues *et al.*, 1974) but only 25% in monkeys (Kleihues *et al.*, 1975). During recirculation some of the degradation products — purine nucleosides and bases — are rapidly re-utilized by salvage pathways. Complete restoration of total adenylate requires substantial purine de-novo synthesis and may last 24 hours in monkeys and 2-3 days in cats. As long as total adenylate is reduced, ATP content is also diminished. However, normalization of the energy state of adenylate clearly demonstrates that this decrease does not lead to energy deficiency of the tissue.

More recently, the regional concentration of ATP has been evaluated on intact brain sections using induced tissue bioluminescence (Paschen *et al.*, 1983a). In control animals and in animals with recovery of spontaneous EEG this technique revealed homogeneous distribution of ATP throughout the brain. In animals with delayed or incomplete electrophysiological recovery, circumscribed regions of ATP depletion were present, which frequently were confined to the bordering zone of the arterial supplying territories. In animals without recovery, inhomogeneously distributed areas of ATP appeared only in white matter and a few subcortical structures but not in the cortex. The regional distribution of metabolic disturbances, in consequence, clearly followed a hemodynamic pattern and supports the notion that failure of recovery is mainly due to inadequate blood reperfusion.

Protein synthesis

As described above, the inhibition of protein synthesis is reversible after ischemia as long as one hour: polyribosomes gradually reaggregate (Kleihues *et al.*, 1975), and amino acid incorporation into proteins improves until, after 24 hours, almost control values are reached (Bodsch *et al.*, 1986).

The regional pattern of protein synthesis was studied after 1 hour ischemia by autoradiographic imaging of amino acid incorporation. During the initial 3 hours, neuronal protein synthesis was severely disturbed in most regions, but it gradually recovered over the following 6-12 hours until an almost normal pattern was observed after 24 hours (Fig. 13). However, several important exceptions were noted (Bodsch *et al.*, 1986): pyramidal cells of hippocampus and Purkinje cells of cerebellum recovered initially faster than any other cell population, but this was followed by secondary suppression after longer recirculation times. This phenomenon

may be related to selective vulnerability of these neurons, which apparently is preceded by an inhibition of protein synthesis. In the cortex, protein synthesis recovered faster in the center than in the bordering zones of arterial supplying territories, thus supporting the notion that hemodynamic factors are also of importance for the recovery process. The total number of cells, however, that did not restore protein synthesis after ischemia was very small in comparison to those that recovered, indicating that even complex biochemical processes can be revived after 1 hour ischemia.

Structural preservation

The regional pattern of structural preservation after prolonged ischemia resembled closely that of protein synthesis. In animals surviving

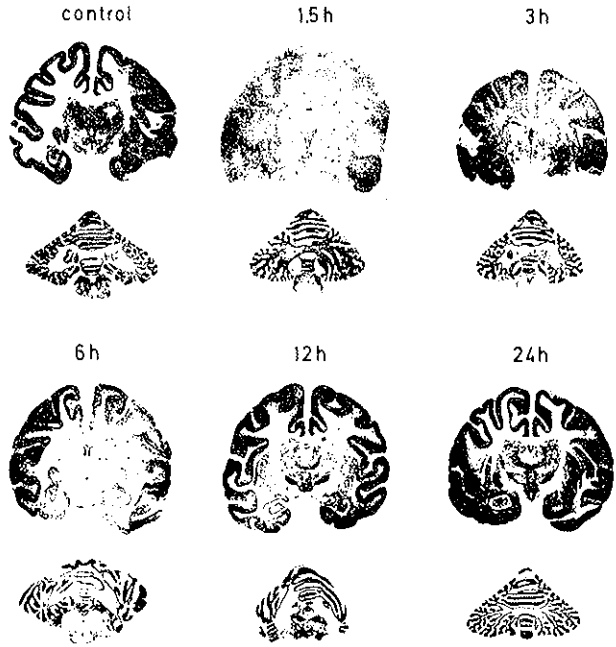

FIG 13. Unstained autoradiograms of ^{3}H amino acids incorporation into proteins of monkey brain before (control) and at various recirculation times (1.5-24 hours) following 1 hour complete cerebro-circulatory arrest. Note the gradual restoration of protein synthesis with increasing recirculation times (Bodsch *et al.*, 1986).

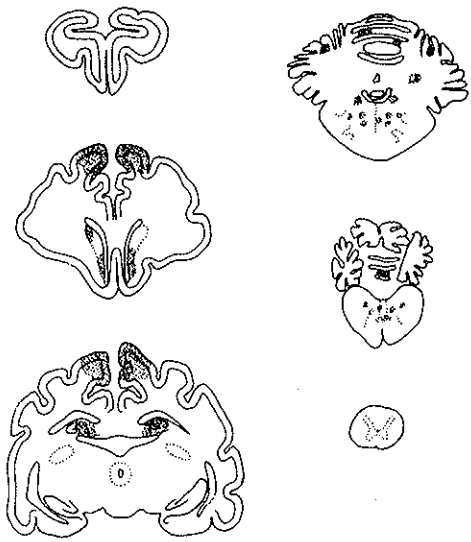

FIG. 14. Pattern of histological lesions in cat brain after 1 hour complete cerebro-circulatory arrest, followed by recirculation for 24 hours or longer. Hatched areas are superpositions of all histological lesions observed in 12 animals. The most consistent alterations are found in the lateral gyrus and in hippocampus (Hossmann, 1975).

for more than 24 hours, histological lesions were found consistently in hippocampus, and inconsistently in striatum, in cortical bordering zones of the supplying arteries and in brainstem (Fig. 14; Hossmann, 1975). In animals with impaired recirculation, the number of neurons with typical ischemic cell alterations was large, but it decreased considerably under conditions of unimpaired reperfusion. In one animal, surviving for 1 year after 1 hour complete ischemia (see below), a substantial degree of striatal atrophy was present in addition to the usual hippocampal lesion, indicating that a transient period of ischemia may induce chronic alterations which lead to progressive loss of neuronal elements.

Clinical observations

The intrathoracic vascular occlusion model for production of cerebral ischemia is of limited use for clinical studies in chronic experiments because the extensive surgical preparation requires the set-up of an intensive care unit for the post-ischemic treatment of animals. However,

despite these difficulties a number of chronic experiments have been successfully carried out, and preliminary information is available about the progression of the neurological recovery process after 1 hour of complete cerebrocirculatory arrest (Grosse Ophoff *et al.*, in preparation).

In all animals that could be kept alive for more than 24 hours, initial electrophysiological recovery was rapid: spontaneous EEG activity began to reappear after less than 1 hour, and a continuous EEG pattern returned after 3-5 hours. Pupils were maximally dilated during ischemia but began to constrict after 45-60 min, and first respiratory movements returned as soon as continuous EEG had recovered. Because of pulmonary involvement, animals were weaned from respiration not before 24 hours; at this time spontaneous respiration returned promptly in most animals. Between 12 and 24 hours, swallowing reflex returned, and animals began to react to painful stimulation by head movements or withdrawal of paws. Intermittently, alternate spontaneous movements of hind paws appeared, which after 2-3 days became quite vigorous. At this time, *per os* feeding was possible, but animals did not visibly react to the environment except for painful stimulation. This apparently vegetative state could last for many days, and most experiments were terminated after 1-2 weeks when no further progress in neurological recovery could be detected, although recording of EEG and of somatically evoked potentials revealed normalization of electrophysiological function. As described above, histological alterations in these animals were mild; electrophysiological recovery and the well preserved morphological appearance, in consequence, were in obvious contrast to the poor neurological performance of the animals.

In 2 cats, however, neurological recovery further progressed. These animals suddenly got up after 5 and 10 days, respectively, and started to walk a few days later. Initially they were severely atactic, but with longer survival times body posture and gait improved and became almost normal. One of the 2 animals was blind during the initial 3 weeks but later vision returned, and after 4-5 weeks the animal was able to avoid obstacles when walking around. This cat became clean within 4 weeks and exhibited normal purring behaviour. One of the 2 animals died intermittently after 3 weeks, due to aspiration of food; the other one was sacrificed after 1 year, after the neurological state had stabilized. Both animals exhibited hippocampal lesions, circumscribed lesions in the basal ganglia and brain stem and a certain degree of atrophy, the latter being more pronounced in the animal surviving 1 year.

These observations demonstrate that the brain is able to withstand 1 hour of complete cerebrocirculatory arrest with relatively little functional and morphological deficits. The distribution of histological lesions further suggests that some of them are manifested after rather than during ischemia. It therefore can be expected that progress of post-ischemic resuscitation medicine will further reduce these alterations.

III. Determination of brain death

It has now been firmly established by numerous experiments carried out in cats and monkeys that basic electrophysiological and biochemical functions of the brain can be revived after 1 hour complete arrest of blood flow at normal body temperature. It has also been demonstrated in 2 cats that following such an insult recovery of integrated neurological function is possible. The revival time of the normothermic brain, in consequence, is at least one hour. Resuscitation of the brain after this long time, however, is successful only under special experimental conditions which permit adequate treatment of otherwise fatal post-ischemic hemodynamic and metabolic complications. Under clinical conditions these methods are not or not yet practicable; this is the reason for the fact that resuscitation of the brain after one hour circulatory arrest has never been reported in man.

Brain death is the irreversible suppression of all functional and metabolic activities. During ischemia functional and metabolic suppression becomes irreversible as soon as the revival time of the brain has passed; however, this event cannot be determined with confidence before the latency of recovery has elapsed. If EEG is taken as an indicator of functional activity, and if the longest latency of EEG recovery which so far has been observed (3-4 hours) is added to the longest time of complete ischemia that has survived in animal experiments (1 hour), a positive statement about the irreversibility of functional suppression cannot be made earlier than 4-5 hours after the onset of ischemia. However, the identification of fatal post-ischemic complicating side effects permits a statement about the irreversibility of the lesion at an earlier time. The most important complication is post-ischemic secondary circulatory arrest and, as a direct consequence of this complication, failure or secondary suppression of metabolic activity. Neurological recovery has never been observed in animals in which

blood flow and metabolic activity were not promptly resumed after circulatory arrest. The demonstration of such fatal complications, therefore, allows the prediction of brain death before the recovery time of more complex electrophysiological or neurological functions has elapsed.

Modern technology permits the non-invasive measurement of these parameters. Positron emission tomography can be used for imaging blood flow, glucose utilization and oxygen consumption. In the near future, it will also be possible to measure the energy state of the brain by nuclear magnetic resonance spectroscopy. These methods will make it possible to determine within a few hours after the onset of ischemia if patients meet brain death criteria or not. However, it also has to be considered that with further progress in resuscitation medicine the number of patients will increase in whom criteria of brain death are not fulfilled but who do not or who only partially recover neurological or mental function after prolonged circulatory arrest. Animal experiments and clinical observations have demonstrated that progression of neurological recovery is very slow after prolonged ischemia and that it may take weeks or even months before a final decision can be made that the neurological deficit is reversible or not. Obviously, patients must receive intensive care during this interval. In view of the social and economic consequences of such a treatment, it will be as important to establish early prognostic criteria of the neurological outcome in the absence of brain death, as the determination of brain death itself.

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LA PROLONGATION ARTIFICIELLE DE LA VIE ET LE TEMPS

GÉRARD MILHAUD
Service de Médecine Nucléaire - Hôpital Saint-Antoine
184, rue du faubourg Saint-Antoine, 75571 Paris Cédex 12

Ces ailes intérieures qui battent le temps vrai...
PAUL VALÉRY

Le regard inspiré du poète, comme celui de l'aigle, embrasse l'étendue; il transcende l'apparence. Les poumons paraissent avoir pour principale fonction de fournir le souffle à la vie. Mais ils permettent aussi à la vie fragile et éphémère de s'inscrire dans le temps et ils rythment le temps qui passe.

Toute réflexion sur la prolongation artificielle de la vie et sur la déterminaison exacte du moment de la mort conduit à s'interroger sur le temps, sur son unicité et sur sa réversibilité. Il faut distinguer le temps sidéral, absolu, qui s'écoule d'une manière uniforme, sans subir ni accélération ni ralentissement, qui n'a ni commencement ni fin, et le temps physiologique propre à chaque individu, qui naît avec lui, qui s'écoule de plus en plus vite à mesure de l'âge et qui s'arrête avec la mort. A côté du temps sidéral, qui sert d'enveloppe, existe donc la multiplicité des temps individuels. L'organisme comporte en son sein des horloges particulières, qui égrènent le temps physiologique.

Du berceau à la tombe, le temps s'écoule dans le même sens. Pourtant à chacun des trois âges de la vie, le passage du temps provoque des effets très différents. Il est évident que, de la fécondation à la fin de la croissance, le passage du temps est constructeur: au cours de cette période des processus d'organisation se déroulent qui aboutissent à une différenciation plus poussée, à une plus grande complexité des fonctions, à l'acquisition de facultés nouvelles.

A l'âge adulte le passage du temps s'effectue sans provoquer d'effets apparents puisque les processus physiologiques parfaitement ajustés, concourent à assurer l'équilibre de l'organisme.

Au cours du troisième âge, le passage du temps exerce des effets destructeurs. Progressivement, inéluctablement, des processus de désorganisation moléculaire font leur apparition, des « erreurs » perturbent le fonctionnement harmonieux de l'organisme. En réalité les modalités du vieillissement sont si semblables d'un individu à l'autre qu'elles ne peuvent résulter d'erreurs dues au hasard mais qu'elles expriment des processus programmés dans les gènes de l'Homme. La perte différentielle des fonctions — audition, vision, mouvements, pensée, défenses immunitaires — caractérisent la progression du vieillissement et marquent les étapes qui conduisent à la mort. Si la situation paraît claire en ce qui concerne le déroulement normal de la vie, son inscription dans le temps et son aboutissement, la mort, en revanche la prolongation artificielle de la vie introduit une complexité nouvelle. Elle interfère avec le passage du temps qu'elle ralentit, arrête ou inverse; elle se propose de reculer le moment de la mort.

La médecine et le temps

L'acharnement thérapeutique, rendu possible par le progrès technique des vingt dernières années, devient question d'éthique dès lors que l'objectif n'est plus d'assurer une survie végétative par le maintien artificiel de la respiration et de la circulation. L'objectif est de permettre le passage de l'état végétatif à l'état sensitif puis le retour à l'état cognitif puisque la vie — unique et irremplaçable — implique la capacité d'intégrer les fonctions physiques et mentales.

La prolongation artificielle de la vie interpelle la médecine sur la question de la vie et sur celle du passage du temps. Naguère la médecine ignorait le temps. Le traitement des affections aigües et des maladies infectieuses, objet et succès de la révolution thérapeutique, ignore le temps: la crise surmontée, tout continue comme avant. Cette attitude est dans la droite ligne des concepts de la science classique. Pour elle, depuis plus de deux siècles, en commençant par d'Alembert pour finir par Einstein, l'assimilation du temps à une quatrième dimension est une tentative désespérée pour réduire l'évolutif au permanent, ce qui aboutit à supprimer le temps. Or, la vie ne supprime pas le temps; elle s'inscrit dans le temps sidéral, elle naît et meurt avec le temps physiologique, dont

le passage s'accélère du berceau à la tombe. Nous avons précisé que la prolongation artificielle de la vie pose la question du ralentissement, de l'arrêt et même de la réversibilité du passage du temps.

La réversibilité du temps

Heurte-elle un principe de la physique classique? La réversibilité de la dynamique est la propriété de toute évolution. A partir de l'observation suffisamment complète d'un état instantané, il est possible de calculer l'avenir et le passé.

L'avenir est donc défini par le passé et, par conséquent, la connaissance des conditions initiales détermine l'avenir. L'avenir et le passé sont équivalents.

Le premier principe de la thermodynamique, celui de la conservation de l'énergie à travers les transformations que subissent les systèmes mécaniques, chimiques et vitaux, à travers les conversions, reste vrai quelle que soit la direction du temps.

Le second principe de la thermodynamique dissocie conservation et réversibilité de l'évolution du système. L'entropie impose l'évolution du système et le sens de la flèche du temps, puisque, quelles que soient les conditions initiales, le futur est la direction de l'augmentation de l'entropie vers l'équilibre, vers l'état d'entropie maximum. La croissance de l'entropie, c'est aussi la montée du désordre moléculaire, l'évolution vers l'état de probabilité croissante et de symétrie maximum, peu importe les conditions initiales d'organisation du système.

Appliqué au vivant, le second principe de la thermodynamique ne se vérifie que pour la partie de son évolution, qui comporte le vieillissement et qui conduit à la mort. Ce sont des processus de désorganisation moléculaire au cours desquels l'entropie, le désordre, les « erreurs » augmentent. La flèche du temps est orientée vers la rupture de l'organisation et la destruction.

En revanche, pendant toute la croissance, des processus d'organisation se déroulent, qui aboutissent à une plus grande complexité, à un ordre plus poussé et par conséquent à une diminution d'entropie. Ainsi donc, le premier âge de la vie évolue en contradiction flagrante avec le deuxième principe de la thermodynamique. La flèche du temps est orientée vers l'organisation et la complexité. Remarquons que toute l'évolution des espèces dans son cheminement, à partir de l'unité fondamentale qu'est la cellule, s'inscrit comme un défi aux lois de la nature, à l'homogénéisation et à la

mort. La vie, fragile et indestructible, est liée au temps constructeur. Comment peut-on expliquer ce paradoxe?

Faut-il revenir aux théories vitalistes du XIXe siècle ou dire avec Schrödinger que les êtres vivants paraissent capables « de boire de l'entropie négative »?

Introduire le concept de « néguentropie » ne résoud rien et aboutit à confondre description et analyse.

Il est préférable de préciser le domaine d'application du deuxième principe de la thermodynamique. Il s'agissait à l'origine de décrire le fonctionnement des moteurs rougeoyants et de reconnaître la tendance à la dégradation de l'énergie mécanique dans une évolution vers un équilibre thermique, où tout effet finira par devenir impossible. On voit se profiler à l'horizon, la menace de l'épuisement des ressources de la planète qui ne pourrait être retardée que par la croissance zéro, chère au Club de Rome.

Dans cette conception, l'arrêt des moteurs dans l'irréversibilité du déclin n'en demeure pas moins inéluctable. Remarquons toutefois qu'il s'agit de systèmes fermés, fonctionnant sans échange avec leur milieu. Or, il est exclu qu'un être vivant puisse se développer ou même seulement survivre coupé de son milieu, isolé du monde qu'il contribue à transformer. Les systèmes biologiques sont ouverts; ils fonctionnent dans un état qui est loin de l'équilibre postulé par le deuxième principe. Un flux continuel d'énergie s'écoule à travers le système, dont l'entropie propre peut décroître. L'énergie est utilisée pour produire le travail nécessaire au maintien du système dans un état éloigné de l'équilibre. En échange continuel de matière et d'energie avec la biosphère, le vivant compense la diminution d'entropie qui se manifeste à son niveau par une augmentation de l'entropie au niveau de la biosphère, en sorte que la résultante de l'ensemble est bien un accroissement de l'entropie. Mais il faut pousser nos réflexions plus loin. Le flux d'énergie qui traverse un système agit dans le sens de l'organisation: il y a création d'ordre. Le flux d'énergie aboutit à la formation de *structures dissipatives* selon Prigogine, qui augmentent leur énergie interne aux dépens du flux d'énergie qui traverse ce système. L'accumulation de l'énergie, l'organisation du système se manifestent au cours de la croissance des organismes et au long de l'évolution des espèces. Les fluctuations, en s'abreuvant du flux d'énergie, loin de régresser ou de s'annuler, s'amplifient et donnent naissance à des effets macroscopiques. L'ordre naît ainsi des fluctuations.

A la recherche des temps perdus

Arrêter un processus de vieillissement revient à conserver l'organisation et l'ordre de l'organisme. Le temps est suspendu. Renverser un processus de vieillissement implique une augmentation de l'organisation, de l'ordre moléculaire au niveau de l'individu. Il faut donc recréer les conditions qui furent celles qui prévalaient lors de la croissance, quitte à augmenter le désordre de l'entropie de l'environnement. La direction du temps est inversée et rien ne s'oppose à cela au niveau d'un système donné de l'organisme, à condition que la forme de ce système ne soit pas définitivement fixée et qu'il se trouve en état d'équilibre dynamique auquel concourrent les processus anaboliques et cataboliques.

Une définition inhabituelle de la mort

La mort cérébrale est le véritable critère de la mort puisqu'elle entraîne la disparition de ce qui faisait l'individu unique et irremplaçable. On peut aussi définir la mort par l'arrêt irréversible du passage du temps physiologique. L'individu, qui se trouve réduit à l'état végétatif vit hors du temps. L'arrêt du passage du temps est réversible dans la mesure où le retour à l'état cognitif demeure possible. En cas de coma irréversible, dès lors que tout espoir de récupérer les fonctions cérébrales a disparu, le passage du temps s'est définitivement arrêté, même si les fonctions cardiaques et respiratoires persistent.

En conclusion, la prolongation artificielle de la vie s'inscrit en contradiction avec le deuxième principe de la thermodynamique. Elle est justifiée pour autant que persiste l'espoir raisonnable de récupération des fonctions physiques et mentales de l'individu, pour autant que pour lui, le temps puisse être retrouvé.

A COMMENTARY ON THE EXTENSION OF HUMAN EXISTENCE AND THE REDEFINITION OF HUMAN LIFE AND DEATH IN TERMS OF BRAIN FUNCTION

ROBERT J. WHITE, M.D., Ph.D.
Professor of Surgery, Case Western Reserve University
Director of Neurosurgery, Cleveland Metropolitan General Hospital
Cleveland, Ohio 44109, U.S.A.

Introduction

The provocative and exciting title of this symposium presents at least two separate, rather divergent concepts, which will require careful examination in order to establish a meaningful relationship between the moral and scientific justification of prolonging human existence and an appropriate definition of biological death to justify the termination of such therapeutic interventions.

The first part of this written equation, "The Artificial Prolongation of Life", requires, obviously, a definition of "Life", and so, too, the second part, "The Determination of the Exact Moment of Death", requires an equally important definition, in this case the presumed absence of life, that of "Death".

In recent years, medical science has developed extraordinary instrumentation, which provides an extension of life well beyond what was imaginable just a few decades ago and, in the process, brings into serious question the use of such terms as "extraordinary" or "ordinary" means of treatment. In other words, what was considered to be an extraordinary therapeutic intervention yesterday may be considered only a routine means of medical treatment today. Yesterday's extraordinary become today's ordinary.

While the term "artificial" would seem to imply something other

than the organic — for example: mechanical, instrumental, or even pharmaceutical — we must remember that modern-day biotechnology can literally and successfully replace, temporarily, many of the individual organs of the human body with mechanical systems, such as the artificial kidney, heart, lung, and liver. Thus, whereas formerly a person was destined to die from documented organ failure, it is now immanently possible that, in advanced cultures, the diseased organ or organs can be "rested" while laboratory-designed equipment can assume their physiological responsibilities and life continued. Certainly, with availability of such technologically advanced devices as the artificial kidney and, most recently and spectacularly, the artificial heart, human life can even be extended for a considerable period of time (upwards of years) through biotechnological intervention.

In a more conventional sense, one sees the everyday "Prolongation of Life" in hospital intensive care units or even in a common chronic nursing setting where patients who are without demonstrable cortical function are maintained with a modicum of instrumentation or pharmacological application. The outstanding example of such individuals would, of course, be exemplified by the case of Karen Ann Quinlan, a young woman who was maintained over a ten-year period without regaining consciousness, employing ordinary nursing care and provided only exogenous food, fluid, and routine drugs.

Defining Human Death

Modern-day medical thinking is rapidly advancing the concept that the uniqueness of human existence, as we know it, is characterized and exemplified by the unique tissue structure and function of the human brain, and it is within this cellular substrate that the human mind resides and, very possibly, the human soul or spirit is expressed. Certainly for years it has been recommended that human death be considered the total and irreversible loss of brain function. As a consequence, is it not conceivable that human life and human existence, as we know it, is appropriately and intimately associated with this organ?

Individual Organ Replacement

Already, the advances of medical science strongly suggest that, in a relatively short period of time, all of the organ systems, other than

the brain, will be replaceable by compatible biological tissue or truly artificially designed mechanical systems. Thus, it would appear that the only organ system that can escape this sort of replication or replacement is the human brain. Nevertheless, for several decades now it has been known that the subhuman primate brain could be surgically separated from the body and viably supported exclusively by miniaturized extracorporal equipment. There is also experimental evidence that the brain itself as high up the phylogenic scale as the subhuman primate level can be successfully transplanted, either within the intact cephalon or separately. Under these circumstances, it must be mated to a compatible somatic system of organs to ensure its survival. Equally significant are the successes with the artificial heart implacements, which already indicate that the brain can be supported for considerable periods of time, even at a human level, when its circulation is totally furnished by an implanted extracorporeal circulatory system. Thus, even human brain transplantation is not beyond the realm of scientific possibility, as far as advanced biotechnology is concerned. Unfortunately, at present there seems to be little evidence that central nervous system regeneration is possible, which would obviously be required to gain functional relationships between transplanted and residual CNS tissue. However, if we recall the human patient example of an individual who has suffered a high cervical cord lesion/transection, such as that resulting from a spinal fracture and who has no motor or sensory function below the neck, such a patient would be, for all practical purposes, totally representative of a human cephalic brain transplantation. In each case, the brain would have no control over the body, nor would there be any sensory information provided the brain from below the point of injury or transection; yet, neuroscientific investigation has demonstrated that, through cranial nerve input (visual, auditory, olfactory, etc.), the human brain, under these limited circumstances, would not only be fully capable of receiving and perceiving a rich array of environmental information through these normal sensory systems, but would also be capable of expressing itself through presently available electronic technology.

When one speaks of the "Artificial Prolongation of Life", it seems that one must speak of the artificial prolongation of brain life, for, as we have already discussed, the various organ systems of the human body can be replaced individually or in toto as in the model of a cephalic transplantation.

Brain Death

If we now deal with the second part of the written equation that forms the title of this symposium, that is, "The Determination of the Exact Moment of Death", we, once again, must acknowledge that we are dealing with a "single organ" concept; that is, once again, the human brain. Since the original Harvard criteria, which were set forth in 1968 and discussed the concept of brain death under the rubric of "irreversible coma", western society, as indeed western medical science, has grown more and more accustomed and comfortable, scientifically, socially, legally, and theologically, in defining death in relation to the functioning of the human brain. While the wording in the title speaks of determining or "isolating" the exact moment of death, it must be acknowledged, even dealing with the brain organ, that it is literally impossible to determine the "exact moment of death", unless one has established, in a scientific or clinical way, the criteria for such a determination. It is well also to remember that many authorities in this field argue that body or organ death is really a continuum and, unless one accepts total dissolution of cellular architecture and absolute putrification of tissue, one is always left with the responsibility of designing a set of criteria for defining death, which must be met for the body as a whole or each organ individually, that are less than biologically perfect. Thus, such criteria must admit to "some biological failure or imperfection" within any definition. Simply stated, this "failure" argues that, for an organ such as the brain, one might find, some days or even weeks later, particularly if the brain were maintained at a low temperature, that cells, particularly glial cells of a supportive nature, could be grown in tissue culture. This, of course, would occur after a definition of death had been made. Granting such biological possibilities or exceptions, modern-day medical science prefers the incisive concept of the organizational structure and functioning, particularly in relation to the human brain, which would seem to argue most appropriately for either the viability or nonviability of the organ. Without question, the human brain is the most complex and sophisticated structure in the entire universe. When it has been demonstrated that its multitudinous functions are totally absent and there is absolutely no possibility of reconstituting any or all of these functions, then it seems most appropriate to declare this organ, and therefore the individual, as being dead. While there are now hundreds of specially designed clinical criteria set up throughout the world to define brain death, and

therefore human death, all presume to document the irreversibility and totality of brain failure.

Having acknowledged the practicality and even "good sense" of these brain failure criteria for the definition of brain death, it should be remembered that, through the simple operation of temperature reduction, the brain itself, in the surgical theatre or experimental laboratory, can literally be preserved for extended periods of time with complete return of all functions with rewarming, provided the temperature reduction was low enough. In the process, these hypothermic maneuvers bring about a "suspended animation" state of brain so that at present, under these experimental circumstances, the brain meets all criteria established for brain death.

Notwithstanding these laboratory and operating room exceptions, the availability and the application of the concept of brain death — being equated with human death, and therefore with the absence of human existence — have been of inestimable value in human medicine, for, on one hand, they have significantly reduced the numbers of patients being artificially supported who have no possibility of regaining meaningful function and, on the other, made available organs for transplantation to those many individuals throughout the world who are in such desperate need of such therapy. Often, patients who are young and disease-free and would serve as ideal organ donors would not be available as organ donors without the availability of a brain death diagnosis.

In summary, then, the decision as to whether artificial prolongation of life is appropriate for an individual patient must, to a large extent, be based on the functional capability of the human brain, just as the definition of the presence or absence of human life now must also be related to the functional state of the brain.

There are future concerns, however, in this area, and they have to do with those cerebral states in which there is some residual evidence of brain activity, and, as a consequence, the criteria for brain death are not fulfilled. Perhaps the most disturbing, and yet most important, group who fail brain death criteria, and are and will remain in deep coma, are those who are only without measurable cortical function.

Many authorities believe that the uniqueness of the human is best characterized by the cortex of man's brain and, regardless of the functioning of lower centers, it remains the repository for the higher functions of man incorporated into its cellular architecture. Such patients are often spoken of as in the vegetative state, a clinical condition in which they

may remain for years, provided they are supported with nutrition and fluids. These are patients, of course, who can initiate their own respiration, but, from time to time, they do require a modicum of medical therapy to control infection. A recent article in the prestigious American medical journal, *The New England Journal of Medicine,* strongly questioned whether or not these patients could be removed from these simple and ordinary exogenous treatments, particularly if there was family and physician agreement. It would certainly appear that such medical decisions would require very careful theological and legal deliberation. In this same seminal article, consideration was also given to those geriatric patients who had reached a point where they could no longer feed themselves, nor be fed by mouth and would thus require, henceforward, tube feeding. Once again, in the judgement of these American medical experts, it was felt that, with family agreement and presumed knowledge of the patient's own wishes, nasogastric feeding need not be instituted!!

Without question, the advances of medical science are rapidly providing the coupling of artificial systems and transplanted organs to overcome a failing somatic organism and, in the process, markedly extend human life far beyond what has been recently conceived as possible. Now it appears obvious that all such advances must be predicated and justified on the state of functioning of the human brain. We have now reached a time in human existence where we must acknowledge the supremacy of man's brain in defining the presence or absence of human life as we have come to know it.

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THE CONCEPT OF DEATH
COMMENTS ON AN OFFICIAL INQUIRY IN SWEDEN

DAVID H. INGVAR, M.D.
President of the Swedish Society of Medicine
Professor of Clinical Neurophysiology
University of Lund, Sweden

In 1982 an official committee was appointed by the Swedish Government to study the concept of death. The committee was headed by Judge Erland Aspelin, head of Division of The Court of Appeal. Several experts participated, representing legal, philosophical, psychological, ethical and theological expertise. Medical experts, including the present author, were also called in. The committee delivered its final report, "The Concept of Death" [1], to the Swedish Minister of Health and Medical Services, Mrs. G. Sigurdsen, in December 1984. The present comments include a brief summary of the Swedish report and a general discussion related to the topic of the present meeting.

There is no need to explain the background of the initiative of the Swedish Government to appoint a committee of experts to study the concept of death. Briefly, the advances within intensive care and transplantation surgery have made it increasingly urgent to establish firm and unambiguous rules to determine the borderline between life and death. The directive given by the Swedish Government stated that such rules must be based upon a *definition of death*. Such a definition must furthermore be made without preconditions and based not only on biological-medical facts, but also with due regard to psychological, philosophical, theological, ethical and legal aspects. The directives of the committee further explicitly stated that the definition of death must not, under any circumstances, be defined on the basis of requirements raised by transplantation surgery. There should thus be no suspicion that the con-

clusions arrived at by the committee had been "tailored" to suit a given medical specialty. It is hoped that the following brief account will demonstrate how the committee succeeded in its work by proceeding systematically in four steps:

1. To define a concept of death;

2. To define the central role of the brain for human life;

3. To establish *direct* (brain-related) and *indirect* (heart-related) criteria of death;

4. To outline the diagnostic procedures which are necessary to establish the two types of criteria of death.

Step 1: The concept of death

Much of the prevailing, often rather heated discussions and differences in opinion about death stems from the fact that no differentiation is made between the *concept* and the *criteria* of death.

The concept of death has, as our committee concluded early, hardly ever been the object of a thorough general study based upon current scientific evidence. Such a concept is indeed not a purely medical question. It is of general importance for every human being, and hence it includes philosophical, theological, ethical, psychological and legal aspects in addition to biological-medical ones. This point was strongly emphasized by our committee, and in this respect the Swedish report differs from similar ones in other countries, e.g., in the U.S. [2], in which biological and medical problems have been more in the foreground.

In its open-minded search for an acceptable, generally applicable concept of death the committee *rejected* several alternatives:

— Death being the *"irrevocable separation of the soul from the body"*, was rejected since there is a general agreement that the "soul" cannot be described in sufficiently exact terms to provide a basis for clinical and legal decisions.

— *"The irreversible cessation of metabolism of each individual cell in the body"* as a definition of death was also rejected, since it would be impossible — and indeed unpractical — to postpone a declaration of death of an individual until all cells had ceased to function and succumbed. Furthermore, this type of definition includes only bodily functions of the individual. Mental functions are not considered.

— *"The irreversible loss of the capacity for circulation of oxygenated blood in the body"* has, as everybody knows, long been used as the main criterion of death. Is it then possible, as many people still claim, to use cessation of circulation (and respiration) not only as a *criterion,* but also as a *concept* of death? First, such a concept again emphasizes bodily functions solely. Secondly, a failing circulation can, as everybody knows in our days, be maintained mechanically with the aid of a respirator, a heart-lung machine, a pacemaker, or even an artificial heart. The committee therefore found it inappropriate to define death as irreversible loss of capacity for circulating oxygenated blood in the body, since this would reduce human life to a basic bodily function, a function which, furthermore, can be substituted by artificial means.

— *"The irreversible loss of all mental functions (including consciousness)"*. This definition of death is at variance with several general concepts about death. There are many forms of coma with permanent loss of consciousness — and mental functions (speech, memory, voluntary motor activity, emotions) — which cannot be equated with death. The majority of deeply and chronically comatose patients (due to brain injury, degenerative disorders, senile dementia, etc.) also have a well preserved respiration and heart activity. Finally, there is still no exact definition of what is meant by "mental functions", or by "consciousness". Therefore a concept of death cannot be based upon irreversible loss of mental functions including consciousness.

Departing from a *holistic* view of man, and emphasizing that death implies that the organism as a functional unit has succumbed and not that the whole organism and its cells are dead in the strict biological sense, the committee arrived at the following definition: *A person is dead when he/she has suffered a total and irreversible loss of all capacity for integrating and coordinating functions of the body — physical and mental — into a functional unit.*

This definition is exempt from the criticism levelled above against the other alternatives. It does not over-emphasize mental or physical functions, but takes both into account. It does not involve any quantitative or qualitative value judgments. It does not highlight particular physical or mental "properties" of the human organism. It stresses instead the coordination of mental *and* physical functions into a unit.

The definition given by our committee also emphasizes that the capacity to coordinate physical and mental functions should be lost in

all respects and that this state should be *irreversible*. Thus a person can be dead although certain functions still remain, such as some metabolism and circulation as well as some functions in individual tissues and organs. This fact is of no interest, however, if all *capacity to coordinate mental and bodily functions* has been lost. Evidence of remaining tissue and organ function may be looked upon as signs that the *biological* process of life which ends in complete cell destruction has not yet reached its terminal point. Such remaining tissue and organ functions cannot persist as isolated phenomena for any considerable length of time, since the coordination between the functions has been lost. This unique capacity of the organism to unite and coordinate mental and physical functions into a unit cannot be replaced by artificial means or medical technology.

It should be observed that the definition above includes the word *"total"* capacity for integration, etc. This means that various types of mental deficiencies — even very severe ones — caused by congenital or acquired disorders can never be equated with death since in such cases, even in, e.g., autistic, demented, senile and chronically comatose persons, a number of coordinating functions still remain, although in a highly reduced form in many cases. Thus, the definition arrived at by the Swedish committee is not only attuned to a general human view of what it means to die, but it is also in line with fundamental ethical viewpoints concerning the wholeness of man.

Step 2: Refinement of the basic definition

Once the basic definition was arrived at, this was refined by establishing an empirical relation between this definition and the functions of the various organs of the human body. The question raised was the following: "Which are the functions of the human organism whose total and irreversible loss can be said, empirically, to imply that the individual has irreversibly lost all capacity for uniting and coordinating the functions of the body — physical and mental — into a functioning unit?".

In this respect the *brain* obviously occupies a special position. There is no need to recapitulate here the extensive medical and biological research which proves the overriding and coordinating functions of the central nervous system (the brain) for all mental and bodily functions. The brain is a prerequisite for mental functions such as consciousness, intellectual activity, memory and emotions, etc., *as well as* for the regula-

tion of respiration, blood pressure, temperature, digestion, etc., If *all* such 'higher' and 'lower' regulatory functions of the brain are totally and irreversibly lost, there is no remaining coordination in the organism, which therefore ceases to be alive.

It should again be observed, however, that the physical functions of the body are not instantaneously, but only successively eliminated once the brain has ceased to function. Some of them, e.g., respiration — and heart activity — cease almost instantaneously, but these functions can, as mentioned, be sustained for a limited time, usually not more than a few days, with the aid of a respirator. Also some spinal reflexes may survive for a few days even after complete and irreversible cessation of all brain functions. Other biological signs, often quoted, are that hair and nails may continue to grow following the cessation of all brain functions — as well as the cessation of circulation of oxygenated blood. Thus, in accordance with this view, an individual is dead when all his *brain functions* are totally and irreversibly lost.

Step 3: Indirect (heart-related) and direct (brain-related) criteria of death

Any *criteria* of death must be based upon accepted medical and biological facts. They must, in addition, be well founded and dependable and enable a completely certain differentiation between a living individual and a dead one. The criteria must also be so clear and unambiguous that every physician can apply them without any risk of making an error. Finally, the criteria of death should be possible to satisfy by practically serviceable methods of diagnosis.

In the light of the conclusions reached in step 1 and step 2 above, it follows that there are two types of criteria of death: the *indirect* and the *direct* ones.

The indirect, heart-related, criteria of death — that all brain functions are totally and irreversibly lost — are constituted by permanent cardiac and respiratory stand-still for, as a rule, more than 15 to 20 minutes, during which the brain tissue succumbs irreversibly due to lack of oxygen. Hence, the indirect criteria are always sufficient to prove a total and irreversible loss of all brain functions. However, as pointed out and as is well known by the readers of these comments, the indirect criteria are in our days not always valid, since respiration — and with it cardiac activity — can be artificially maintained even though all brain functions have been irreversibly lost. Nevertheless, the *indirect*

criteria of death — cessation of respiration and heart activity — will always, most likely even in the future, be applicable in more than 99% of all death. This point is to be strongly emphasized. The conclusions reached by the Swedish committee do not imply the introduction of a "new"type of death or of any new criteria of death. They only stress the central role of the brain and the basic fact that cessation of respiration and heart activity can be used as an *indirect* criterion of irreversible and total cessation of all brain functions.

Direct, brain-related, criteria of death are used in a small number of patients in whom heart and lung activity is artificially maintained by means of a respirator. The direct criteria are therefore used only in hospitals with intensive care units. It is estimated that in developed countries direct brain-related criteria of death will be used only rarely, in about 0.2-0.7% of all death, that is, e.g., in 200-700 cases in Sweden (population about 8 millions) per year.

The brain-related criteria must also demonstrate beyond any doubt that all brain functions have been totally and irreversibly lost and they must state unambiguously that the entire brain (the cerebrum, cerebellum, and brain stem) has permanently ceased to function. The direct brain-related criteria of death are based upon much new research. They are — as are the indirect heart-related criteria — based upon the extreme sensitivity of the brain tissue and its nerve cells to lack of oxygen.

Direct brain-related criteria of death are used in cases with so-called *total brain infarction.* (A much used, but confusing label for this state is "brain death", an expression which the Swedish committee explicitly avoids in its report). Total brain infarction is usually caused by brain swelling due to severe head injury, cerebral hemorrhage, or asphyxia. This leads to an irreversible disturbance and destruction of the cell membranes in the brain. The cells take up fluid and swell to such an extent that the intracranial pressure surpasses the arterial one. Then the blood flow to the brain ceases and total brain infarction ensues, with a destruction of all cells of the brain in an aseptic necrosis. At autopsy the complete liquefaction of the whole brain is highly evident ("respirator brain").

It must be strongly emphasized that the patient (always coupled to a respirator) who has suffered total brain infarction and who still has heart activity, rapidly undergoes a successive deterioration of all bodily functions — due to the fact that the central coordinating capacity of the brain has been totally and irreversibly lost. Thus, the body tempera-

ture falls, urine production fails, the skin becomes miscoloured, and, finally, in spite of all supporting measures, the blood pressure falls also and the heart stops, even if artificial ventilation is maintained. This course of events usually takes only from one to three, possibly five days. In children the state may last somewhat longer. This fact should be given much emphasis. The patients in intensive care who *survive* (since their brains were *not* totally destroyed) and who often become chronic cases (with spontaneous respiration or not) are most certainly still alive and should be given due treatment and care in spite of their often extensive and tragic brain injuries. They are alive since clinical examination demonstrates that due to preservation of some brain structures, some — often highly reduced — coordination of bodily and mental functions prevails.

Step 4: Examination procedures to establish death

The *indirect criteria of death,* i.e. permanent cessation of cardiac and respiratory activity, do not offer any difficulties according to routines established for centuries.

The indirect criteria, to establish total and irreversible loss of brain functions, do not present any problems today in view of the enormous clinical experience collected in many countries within this field. The direct, brain-related, criteria of death ("brain death") include in Sweden as in other countries:

1. Absence of all cerebral functions. The patient is comatose and unresponsive, with no signs of higher brain functions;

2. Absence of all brain stem functions. All cephalic reflexes are extinguished as a result of the brain stem functions being lost;

3. Absence of spontaneous respiration, apnea, (which in artificially ventilated cases must be ascertained by turning off the ventilator briefly);

4. Finally, the electrical activity of the cerebral cortex has ceased and the EEG is "isoelectric" ("flat").

The irreversibility of the total loss of cerebral function can only be established (1) in patients in which the cause of the brain injury is known, (2) when drug intoxications and hypothermia have been ruled out and (3) in cases in which the loss of brain functions has lasted long enough. Cessation of cerebral circulation in patients with total brain

infarct may also, as is well known, be ascertained by means of cerebral arteriography. Thus, it is demonstrated with certainty that cessation of intracranial blood circulation has existed for not less than about 15 to 20 minutes, and this implies a total destruction of the brain (see above).

The Swedish committee has concluded, like similar committees in other countries, that the *diagnosis of death* can be made with complete certainty, not only *indirectly* by establishing irreversible loss of respiration and of heart activity, but also *directly* by demonstrating that all brain functions have been completely and irreversibly lost.

Other aspects of the definition of death proposed by the Swedish committee

A comment might be made about the *"moment of death"*, one of the principal topics of the present meeting. If death is established by *indirect* heart-related criteria, death is commonly, as is indeed well known, considered to have taken place the moment when respiration ceases and the heart activity stops. This moment can usually in clinical circumstances be determined fairly exactly, although the final heart beat might necessitate sophisticated recording techniques. However, in most patients the process of dying is somewhat prolonged with failing vital functions, falling blood pressure, etc., which often cause irreversible and finally total brain damage. In this final stage it is evident that death has ensued since the patient has lost all coordination of mental and physical functions irreversibly.

In the few cases in which *direct* — brain-related — criteria of death are used in patients with total brain infarction, the exact moment of death is not so difficult to establish. Again, the increase of the intracranial pressure, the basic pathogenetic factor causing cessation of brain circulation and total brain infarction, is a process which may be fast (minutes) or slow (hours). However, the diagnosis of total brain infarction, i.e. of death, is made at the moment the clinician has the evidence in his hands, i.e. clinical signs of permanent loss of brain reflexes are present, including absence of spontaneous respiration and a flat EEG. In some cases the demonstration of cessation of brain circulation by means of cerebral angiography (contrast injection into the aorta with no contrast going intracranially) is also used.

The diagnosis of death by means of direct brain-related criteria thus does not suffer from any considerable lack of exactitude as to the point in time when death has occurred. This direct diagnosis (of death) is,

as mentioned, only made in intensive care units. It is therefore in fact often made with greater time exactitude than in a number of cases when death is diagnosed by indirect heart-related criteria, e.g., in cases found dead at home (or even in a hospital bed), in cases retrieved following accidents and catastrophes, etc.

The definition of death arrived at above relieves the clinician — and layman for that matter — from several difficulties in differentiating death from other states, especially cases with severe brain defects with permanent coma, reduced mental functions, etc. One criterion which should be emphasized is that total brain infarction, established by the abovementioned brain-related direct criteria of death, is a short-lasting state which does not persist more than one to five days in most cases. There are reports that total brain infarctions in children may last longer. A number of international studies, quoted in the Swedish report, demonstrate that all patients in whom the above direct brain-related criteria of death were applied, suffered cardiac stand-still within a few days. It can therefore be safely concluded that the risk of error, when applying direct brain-related criteria of death, is much smaller, i.e., virtually non-existent, when compared to other diagnostic methods used clinically.

The conclusions arrived at, especially the definition of death, should hopefully find general public support. It is hoped that this will be the case since the definition is founded upon much wider evidence than only biological-medical considerations, namely upon general human and ethical values with due regard to a holistic view which is in keeping with fundamental Christian and humanistic ideas. The introduction of brain-related criteria in a small number of patients undergoing treatment in intensive care units therefore does not by any means constitute a revolutionary reform. Direct brain-related criteria are in fact already now used in several countries, and their legal validity has been generally accepted in the majority of developed countries in which access to modern medical procedures, including intensive care, is available.

The acceptance of direct brain-related criteria of death in a small number of cases has an obvious advantage for the medical profession, for doctors, nurses and other personnel involved. It does eliminate the uncertainty which often today exists concerning the state of a given patient, and the prognosis. Thus, also the patient's family and next of kin can be informed in stricter terms about whether life still prevails (in reduced form or not) or whether death has ensued. Such information

is always of value. For any message it holds that "truth shall make you free" (St. John, 23), even if the message is the final one that death has occurred.

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THE ARTIFICIAL PROLONGATION OF LIFE AND THE DETERMINATION OF THE EXACT MOMENT OF DEATH

H.A.D. WALDER

Professor and Chairman, Neurosurgical Department, St. Radboud Hospital, Catholic University
Nijmegen, The Netherlands.

The title itself is already quite a subject of discussion and may provoke some questions.

Are we going to discuss the artificial prolongation of life of patients who are suffering from an incurable disease or even newborns with multiple congenital malformations? Are we going on with intensive care treatment, artificial feeding and/or administration of fluids, giving them all kinds of drugs and antibiotics, or are we just preventing them from too much suffering and giving them palliative treatment?

However, if we are going to discuss this, we undoubtedly will arrive at a discussion about euthanasia.

I don't think that this is the meaning of this meeting, and probably we are going to continue the discussion initiated by Pope Pius XII (1957) on whether it is appropriate to keep the body alive in the absence of a brain or at least of a functioning brain.

The determination of the end of the functioning of a brain may be a great problem and there is still some discussion on this. As an introduction to this I would like to give you a historical development of criteria for brain death with at the end a protocol on this subject, discussed in our hospital.

Historical development of Criteria for brain death *

Legal definition

The definition of death, while often made in a straightforward and simplistic manner, is, in fact, a highly complex construct, having many intricate facets and ramifications. Because of the limitations of knowledge surrounding the problem of death, the concepts and the criteria that developed were applied in a relatively direct and pragmatic manner in various societies.

Death has been considered with reference to the state of the organism in an all-or-none manner; that is, that an individual organism is either dead or alive. This notion is both simplistic and naive, since death is not an event but a process. The controversy over the nature of this process was discussed in 1971 by Morison and Kass. The process of death occurs over a finite period. Since the process may be brief, the duration and means of evaluating the state of the organism are often limited. Practical requirements over the past several thousand years demanded a yes or no answer to the question of whether an individual was dead. Therefore, it was both reasonable and convenient to consider death as an event.

Actually it is now known that death involves a complex series of changes which, if they occur rapidly enough, asymptotically approach the commonly used concept of an event. Before the advent of applications of modern science and technology to biology, the development of deeper understanding of the physiology of living systems, the utilization of intensive care units (ICU), and the therapeutic use of organs for transplantation, the distinction between death as a process and death as an event had limited significance. However, as the utilization of resuscitation and life-support systems increased, the necessity of defining the process of death has become essential. Although a statement of the moment of death is required by many agencies in our society, this "moment" may, in fact, be a period of long duration that cannot be precisely stated. The presumed end state of a multicellular organism, with all of its cells dead, is not the moment of death, nor is the time of pronouncement of death necessarily the moment of death, since many cellular components of the organism may still be alive.

* Julius Korein, *Anaesthesia and Neurosurgery* (chapter 14), Cottrell and Turndorf, 1980, Ed. D.C.V. Mosby & Co, St. Louis, Toronto, London.

We must, therefore, consider the dynamic, organizational, and cellular aspects of the deteriorating human organism in order to redefine the process of death.

Then we may obtain utilitarian criteria to define the moment of death.

Pius XII (1957)

The distinction between death of an organism and death of components of the organism was considered as a practical problem by a group of anesthesiologists who maintained patients on life-support systems although there was no evidence of brain viability. These patients had irreparable destruction of the brain. The question arose in the application of technical advances whether it was appropriate to keep the corpus or body "alive" in the absence of the brain, and the problem was presented in 1957 to Pope Pius XII. This resulted in a papal allocution entitled "The Prolongation of Life", which was published in the following year. Among the many significant statements contained in this document, two will be stressed. The first was that the pronouncement of death was not the province of the Church but the responsibility of the physician: "It remains for the doctor... to give a clear and precise definition of 'death' and the 'moment of death' of a patient who passes away in a state of unconsciousness."

The second point was that there came a time, in the course of a patient's disease, when the situation was hopeless and death should not be opposed by extraordinary means. The definitions of the words "hopeless" and "extraordinary" were not precisely stated in medical terminology, but it was clear that in hopeless cases resuscitative measures could be discontinued and death be unopposed.

It was at this time that brain death and associated problems became the subject of increasing general interest. Historically, this proclamation initiated the surge in concept development, research, application, and controversy in use of the construct "brain death". Using the papal allocution as a point of departure, the history of the development of criteria for brain death will be reviewed.

French neurophysiologists and coma dépassé (1959)

In 1959, several groups of French neurophysiologists were involved in salient research with patients who were in extremely deep coma. They

coined the term "coma dépassé", which was literally translated as "beyond coma" or "ultra coma", and by some authors unfortunately, as "irreversible coma".

The results of these studies were published by Fischgold and Mathis, Jouvet, and Mollaret and Goulon in 1959. The patients they studied were in deep states of unresponsive coma, in which the absence of spontaneous respiration necessitated the use of a respirator. These patients, in addition, were areflexic. Studies performed included electroencephalography (EEG) as well as multiple electrophysiologic recordings from the surface of the cortex and deep structures of the cerebrum such as the thalamus. The finding of absent electrophysiologic activity was considered by these investigators as confirmation of irreversible disfunction of the brain. Many other investigators published data relating to this problem and are referred to in general bibliographies by Smith and Penry (1972) and Walker (1977).

Harvard Criteria (1968)

Most often quoted are Harvard Criteria, developed in 1968, which define cerebral death as irreversible coma (brain death) in terms of the following characteristics.

1) Absence of cerebral responsiveness;

2) Absence of induced or spontaneous movement;

3) Absence of spontaneous respiration (requiring the use of a respirator);

4) Absence of cephalic and deep-tendon reflexes;

5) Absence of drug intoxication or hypothermia;

6) Presence of a flat EEG;

7) Persistence of these conditions for 24 hours.

Although the Harvard Criteria may be and have been used effectively, they have within them a set of limitations that requires close scrutiny. The definition of coma is considered in terms of cerebral unresponsivity. There are, however, several manifestations that occur in patients who are in coma and cerebrally unresponsive who present decerebrate phenomena, spontaneous seizures, and other forms of motor activity, who are in a variety of chronic comas or in persistent vegetative states, as previously noted. The common practice of considering brain

death and cerebral death as equivalent terms leads to confusion. This is most evident when one considers the states of the brain stem; for example, the cerebrum may be destroyed and the brain stem remain intact, or the reverse may occur. Rarely, the cerebrum and brain stem may be completely separated from each other.

Declaration of Sidney (1968)

In 1968, the Declaration of Sidney was made, which added two important statements to the problem of the diagnosis of brain death in relation to organ transplantation. The first was a reaffirmation that death is a process and that in a multicellular organism a large mass of cells might be alive but that this did not indicate that the organism as a whole was alive. Second, it declared that in situations related to organ transplantation, the pronouncement of death should involve two physicians unrelated to the transplant procedure itself.

Minnesota Criteria (1971)

In a clinical and pathologic study of brain death, Mohandas and Chou reported that in patients with brain damage the nature of which is known, who show no spontaneous movement, and who are apneic with absent cephalic (brain stem) reflexes, all persistent for 12 hours, the outcome is invariably fatal.

These criteria imply that the prediction of imminent death or a fatal prognosis is tantamount to brain death. The Minnesota Criteria are as follows:

1) Basic prerequisite: diagnosis of irreparable cerebral lesion;
2) No spontaneous movements;
3) No spontaneous respiration;
4) Absence of brain stem reflexes;
5) Persistence of condition unchanged for 12 hours.

Notice the absence of the use of either EEG or a test for intracranial blood flow in these criteria.

Scandinavian Criteria (1972)

In a symposium on brain death reported by Ingvar and Widen in 1972, criteria were recommended for use in Scandinavia in patients with

known primary or secondary brain lesions who were in unresponsive coma with apnea, absence of all cerebral functions including brain stem reflexes, and a single isoelectric EEG. Confirmation of absences in intracranial function was made by aortocranial angiography showing no circulation to the brain on two injections of contrast medium 25 minutes apart.

These criteria reduce the temporal delay to an absolute minimum (25 minutes). The circulatory criteria are not influenced by the presence of drugs that depress cerebral function, and since collectively clinical signs, EEG, and cerebral circulation are determined independently of one another, they are cross-confirmatory. While they imply total cerebral infarction as the definition of brain death, variations in the rate at which the circulation to the brain collapses would probably permit a variety of pathologic states to be observed at autopsy.

The following summarizes the Scandinavian Criteria:

1) Unresponsive coma;
2) Apnea;
3) Absent brain stem reflexes;
4) Isoelectric EEG;
5) Nonfilling of cerebral vessels on two aortocranial injections (bilateral carotid and vertebral) of contrast media 25 minutes apart.

Japanese Criteria (1973)

From data derived from a Japanese study of brain death. Ueki and associates reported that a diagnosed gross primary brain lesion, deep coma, bilateral dilated pupils with absent pupillary and corneal reflexes, and an isoelectric EEG predict brain death. In such patients, a fall in blood pressure of 40 mm Hg persistent for six hours signals that death is imminent.

The Japanese Criteria are as follows:

1) Basic prerequisite: diagnosis of primary cerebral lesion;
2) Deep coma;
3) Respiratory arrest;
4) Bilateral dilated pupils and absent pupillary and corneal reflexes;
5) Flat EEG;
6) Abrupt fall in blood pressure of 40 mm Hg with hypotension;
7) Persistence of condition for at least six hours.

Cerebral survival (CS) study Criteria (1977)

A collaborative study was sponsored by the National Institutes of Health in order to establish more firm criteria for the diagnosis of brain death. The study involved 844 comatose apneic patients evaluated between 1970 and 1973. The first set of 503 patients was statistically evaluated in order to develop more precise criteria. Other subsets of these patients were analyzed by Korein and co-workers, Allen and co-workers, and Bennett.

The conclusions may be summarized by the development of the criteria listed below:

1) Prerequisite: all appropriate diagnostic and therapeutic procedures have been performed (diagnosis established);

2) Criteria (to be present for 30 minutes at least six hours after the onset of coma and apnea):

a) Coma with cerebral unresponsivity,

b) Apnea,

c) Dilated fixed pupils,

d) Absent cephalic reflexes,

e) Electrocerebral silence;

3) Confirmatory test: absence of cerebral circulation.

Summary of the report of the advisory committee on the determination of brain death to the national council of health in the Netherlands

1. The death of a human being is determined by "brain death", which is understood to mean that the brain, the brain stem and the medulla oblongata have completely and irreversibly ceased to function.

2. Under normal circumstances it has been found sufficient to employ long-standing criteria to establish death (no pulse or respiration for at least ten minutes).

3. The normal criteria are not reliable or applicable in establishing death under exceptional circumstances, however (certain cases of poisoning, e.g., from narcotics or other opiates, and/or hypothermia, and in the cases of young children and patients in irreversible coma). The main aim of diagnosis will then be to establish brain death.

4. The complete cessation of brain function can be established on the basis of the anamnesis and a physical examination of the patient, supplemented by special tests. In the current state of scientific knowledge, the most appropriate supplementary tests are electroencephalography (EEG) and/or cerebral angiography.

Anamnesis (and/or hetero-anamnesis) and a physical examination are always necessary to establish brain death under exceptional circumstances, and an EEG examination will be required in almost every case as well.

5. Once the doctor has established that the brain has ceased to function according to the criteria set out in section 4, he/she will have to take into account the primary causal disease and the patient's condition to ascertain whether any additional tests would be useful or necessary to establish that the brain has completely and irreversibly ceased to function, i.e., to determine brain death. This may involve a second EEG six hours later or a cerebral angiography immediately following the first EEG.

6. The opinion of a large majority of the commission was that, in the present state of scientific knowledge, cerebral angiography should not be considered obligatory as a means of diagnosing brain death.

Protocol of the diagnosis of brain death

Date:
Name of the Examiner:

Conditions on before hand.	Mark correct answers:			
	A.	B.	A.	B.
1) Is the patient in deep coma?	yes	no	yes	no
2) Are we informed about the primary cause of the coma?	yes	no	yes	no
3) a: Is the patient on an artificial respirator?	yes	no	yes	no
b: Are muscle relaxants administered?	no	yes	no	yes
c: Are centrally respiration depressing drugs administered?	no	yes	no	yes
4) Are there reversible causes for coma present? Namely: hypothermia (rectal temperature < 35 centigrade Celsius)	no	yes	no	yes
gross metabolic disorders	no	yes	no	yes

gross endocrinological disorders	no	yes	no	yes
intoxication	no	yes	no	yes
shock	no	yes	no	yes
5) Is there a spontaneous tendency to hypotension?	yes	no	yes	no
6) Is there a spontaneous tendency to hypothermia?	yes	no	yes	no

CLINICAL TESTS:

	A.	B.	A.	B.
7) Are all the brainstem reflexes completely negative?				
— fixed dilated pupils	yes	no	yes	no
— cornea reflex: not any response occurs when each cornea in turn is touched	yes	no	yes	no
— not any movement in the head and neck present spontaneously or in response to any stimulus	yes	no	yes	no
— pharyngeal reflex: not any movement of the pharyngeal musculus when moving the endotracheal tube	yes	no	yes	no
— no cough reflex when suctioning the bronchia	yes	no	yes	no
— no nystagmus present when each ear in turn is investigated with ice cold water for one minute	yes	no	yes	no

CONFIRMATION:

	A.	B.	A.	B.
8a) Is there apnea? That means not any spontaneous respiration within 10 minutes after disconnecting the respirator?	yes	no	yes	no
b) Was the $PaCO_2 > 45$ mm.Hg. (> 6 KPa) before the respirator was disconnected?	yes	no	yes	no
c) Was via the endotracheal tube 100° O_2, 6 liter/minute administered during the apnea test?	yes	no	yeh	no

When, at the first examination as well as at the second one, the answers are exclusively marked in Column A, all the conditions are fulfilled for the clinical diagnosis of brain death. Eventually: further confirmation.

9) Is the EEG isoelectric during thirty minutes?	yes	no	yes	no
10) Is cerebral perfusion demonstrable during 10 consecutive minutes with four vessels angiography?	no	yes	no	yes

Conclusion

Taking into consideration the evolution of the criteria of brain death and the discussion on these criteria, I would like to propose the protocol, which we have discussed in our hospital (previously mentioned).

It is not complicated, so it will not lead to misunderstandings and mistakes. Generally speaking, it divides the diagnostics of brain death into three parts:

1) general conditions;
2) clinical tests mainly concerning the brain stem reflexes;
3) confirmation by the respiration test and the E.E.G.

I am not in favour of a four vessels angiography because it may harm the cerebral blood flow if there is still any, and if you are sure that there is a brain death, so no flow any more, there is no need for this test.

Concerning the time interval between the two examinations, clinical as well as electroencephalographical, I would propose six hours.

According to our knowledge *today,* this seems to be a safe time interval and not too long delay if we are considering transplantation.

ARTIFICIAL PROLONGATION OF LIFE AND THE DETERMINATION OF THE EXACT MOMENT OF DEATH

URBAN PONTÉN
University Hospital, Department of Neurosurgery
S-751 85 Uppsala 14, Sweden

In the last decades rapid advances in medical science and technology have provided means to substitute failing vital functions of the body, like respiration, circulation and metabolic homeostasis. Modern intensive care has saved many lives but it has created new problems regarding the definition of death and of human life. There are now well-defined clinical states which can persist for considerable time and for which the old criteria for life and death are no longer valid.

We cannot stop scientific and technological progress for better or for worse within this field. Treatment that seemed extraordinary some years ago is well established routine today. Artificial respiration for severe brain injuries and kidney transplantation as an alternative to chronic dialysis are good examples of this. We have to accept the technical possibilities now available and try to adapt them to an ethical framework that keeps human life with dignity as its center. A continuous ethical discussion with and among scientists is needed now and in the future about the ethical implications of medical progress. Consensus conferences like this one have to be repeated often in the future.

What is artificial prolongation of life?

In a wide sense this expression might include the treatment of many chronic diseases like diabetes mellitus, panhypopituitarism and respiratory insufficiency. No ethical concern will arise in such cases. The ethical problems arise mainly when there is a continued preservation

of vital functions in intensive care units by technical means such as respirators or artificial hearts in patients who have irreversibly lost consciousness or have a very poor prognosis with a short life expectancy.

Before discussing the ethical implications in detail, it is useful to make a distinction between treatment, basic care and intensive care. My definitions are the following.

Treatment means active procedures with the intention to cure illness, improve the condition of the patient or prolong the life of the patient.

Basic care means measures taken to comfort the patient physically and psychologically and to prevent or diminish the patient's suffering from agony, pain, suffocation, thirst and hunger.

Deeply comatose, non-arousable patients probably do not suffer. With patients in a "vegetative" state who are arousable we cannot exclude the possibility that they do suffer.

Intensive care is a well established medical concept which includes both basic care and very active treatment.

Care and treatment should always be given with full respect for the human dignity of the patient and in accordance with available resources. It should be of great concern, especially to all members of the affluent societies, that even resources for basic care are not available to a great number of the people of the world.

The Swedish law on health care specifically points out the right for everybody in Sweden to get good and equal care and treatment irrespective of where they live and of their economic resources. It is a great challenge to organize, e.g., efficient neurosurgical care in a large referral area according to these premises.

Treatment should be given in accordance with available resources, in the best interest of the patient and with his informed consent, if he is conscious and capable to make this kind of decisions. If the patient cannot decide for himself, due consideration should be given to individual circumstances, like the possibilities for the patient to recover to a conscious life with human dignity, to what is known about the patient's own will in terminal disease and to the opinion and wish of the family or next-of-kin. The decisions about treatment should be taken by the doctor to relieve the family from difficult and possibly guilt-producing decisions.

Treatments or other procedures which are not of specific benefit for the patient but are of considerable value for research, and thereby

for other patients with similar disease, may be used unless they cause harm, danger or suffering for the patient.

Especially during acute surgery and in the intensive care situation, doctors work with probabilities regarding outcome that are never 0 or 1 and often are inaccurately known in the individual case. The chance of curing the disease with a certain treatment has to be compared with the risks for dangerous side effects, which are possible with almost any therapeutic procedure. Survival at any cost cannot be the only object. Most neurosurgeons, e.g., are much more restrictive in their indications for operation in the dominant than in the non-dominant hemisphere since they know the risks for aphasia and that life without a language is a great burden to the patient. The ethical relevance of this policy may be questioned, but it is a fact that this practice prevails. To my mind it is acting in the true interest of the patient. However, even a short palliation with conscious awareness can be of invaluable benefit for the patient and his relatives. Every conscientious doctor sometimes withholds treatment which is out of proportion and not in the true interest of the patient, and he also certainly remembers and regrets other situations when he did not do so. An acute neurosurgical operation can relieve high intracranial pressure that will otherwise kill the patient. The result may be the long-time survival of a deeply comatose patient. The most difficult problem with those cases may be to know when to abstain from a useless operation. In the acute situation the most efficient treatment should be given immediately until clear indications for other actions are reached. Indecisive treatment easily causes unnecessary sequelae in surviving patients.

It is impossible to state or even give recommendations as to which odds our selection of treatment should be based on. Among other things it depends heavily upon available resources. Most of these ethically difficult decisions have to be taken by the doctor in charge (based upon what he considers to be in the best interest of the patient). Survival is not always in the best interest of the patient but should be aimed at if the prognosis or other circumstances are uncertain.

These views on the role of the doctor in intensive care are not a declaration about divine capabilities of doctors but a description of the actual situation which may not be known to non-medical people. They also stress the largely neglected need for education of doctors in ethical reasoning and our duty to define the results and complications in medical practice.

How to avoid artificial prolongation of life

The responsibility for the occurrence of a situation which is experienced as a useless artificial prolongation of life, rests upon the patient's doctor. He decides if "extraordinary" means should be used to keep the patient alive. A well-trained and conscientious doctor will not introduce such methods if he knows that there is no chance at all that the patient will recover or regain consciousness. The therapy is usually started in an acute situation when the prognosis and sometimes also the diagnosis are unclear. The important issue then will be that the doctor must have the right, and probably also the duty, to withdraw the treatment when it is clear that its goals cannot be fulfilled. It is often argued that a life-sustaining treatment, once instituted, must continue. To my mind withholding and withdrawing treatment should have the same ethical significance. Admittedly it is psychologically more difficult for the doctor to finish a life-supporting treatment the sooner the deleterious effects will be seen. Nevertheless the intensive care doctor has the duty to reevaluate the therapy with every change in his knowledge of the disease of his patient. He must try to find a reliable prognosis for the individual patient. The medical society is obliged to provide a good scientific base for this.

If the principles indicated here are followed, there should be no artificial prolongation of life even if the treatment includes what might be called extraordinary means.

The determination of death

Death is a gradual process, whether it is defined for a cell, an organ or the whole organism. To see if it is possible to find an answer to the question about the moment of death, we have to discuss death on all these levels as well as on the human level.

Cellular and organ death

On the cellular level two different modes of destruction and dissolution occur: apoptosis and necrosis. (For a comprehensive review see Wyllies, 1981). Apoptosis is a physiological removal of cells in normal tissue turnover, embryokinesis, metamorphosis and endocrine-dependent tissue atrophy. Apoptotic cells are also seen in tumours together with

necrotic cells, especially in tumour regression. The effect of killer T-cells is apoptosis rather than necrosis. It may be enhanced by low doses of X-ray irradiation and radiomimetic cytotoxic agents, but also sub-necrotic degrees of hypoxia may have this effect. Apoptosis is characterized by shrinkage of the cell with nuclear changes, including chromatin fragmentation, condensation of the cytoplasm and separation due to destruction of cell-junctions. The apoptotic cells are excluded from the tissue surface or subjected to phagocytosis. The metabolism and membrane ionic pumps are working late in the process which seems to be an energy requiring one. Macromolecular synthesis seems to be necessary and endonuclease activation occurs. The course and mechanism of apoptosis are incompletely known, but are believed to be under remote kinetic control. New gene expression may also be involved.

Necrosis occurs under pathological circumstances such as hypoxia, inhibition of oxidative phosphorylation, glycolysis or Krebs cycle enzymes, exposition to hyperthermia, complement and toxines. The first morphological changes seen are reversible with slight swelling of cytoplasm, mitochondria and endoplasmic reticulum combined with some chromatin condensation and disaggregation of polysomes. These changes progress to irreversibility if the pathological condition prevails. The irreversible changes are characterized by severe mitochondrial swelling and rupture of internal cristae, progressive dissolution of other cell organelles, endoplasmic reticulum dilation, plasma membrane rupture and dissolution of the cell nucleus. The rupture of lysosomes occurs late. The main mechanism for necrosis is a loss of volume control of the cell and the organelles in hypoxia and ischemia due to energy failure or with regard to the central nervous system sometimes also excessive neuronal discharge. A cascade of metabolic events occurs in which loss of calcium homeostasis seems to be a common deleterious mechanism responsible for irreversible cell damage.

Cell death thus occurs either as a predetermined apoptosis or an acute ischemic cell destruction when the vital functions of the whole organism are failing.

Loss of function and revival possibilities

Brain cells lose many of their physiological functions within seconds in acute ischemia and are energy depleted within a few minutes. Brain cells require continuous oxidative glycolysis, while cells from other

organs can survive for a long time on anaerobic glycolysis. The revival time is the period of ischemia during which restoration of circulation still can revive the cell. Brain cells may have a revival time of 60 minutes under ideal experimental conditions. Clinical experiences speak more in favor of revival times of 4-10 minutes for the brain. Brain cells are also known to have a selective sensitivity to hypoxia. Other organs like cornea are viable enough for transplantation even after 48 hours. Other cells, like erythrocytes, can be stored in a deep frozen state for a very long time.

Irreversible loss of the function of all cells and organs will not give a useful definition of the moment of death of an organism but will describe a gradual process over several days. Medical progress has made this definition of death definitely obsolete when transplanted organs can continue to function in other bodies a long time after the donor is declared dead. Furthermore cell lines from malignant tumours in patients may reproduce for an unlimited time in tissue culture.

The death of a human being

In defining human death it becomes evident that we have to discuss the organism as a whole and that we also have to try to define what is specific to human life. I refer to the concept of death given in 1984 by the Swedish Committee on Defining Death, which says as follows: "A person is dead when he has suffered total and irreversible loss of all capacity for integrating and co-ordinating the functions of the body — physical and mental — into a functional unit". However, it is empirically evident that the brain is the organ which effects the essential part of this co-ordination and regulation, all other organs being possible to replace by drugs, artificial devices or transplantation for shorter or longer times without loss of the identity of the person.

The following precision of the definition of death was given by the Swedish Committee: "A man is dead when all functions of the brain have totally and irreversibly disappeared". Other definitions including only parts of the brain, e.g., cortex, have been discussed as prerequisites for human life. Although it can be argued that complete decortication precludes mental activity, so-called vital functions of the brain stem will still remain, keeping the person alive without extraordinary means. In exceptional cases a total, isolated, irreversible loss of cortical function may be possible to verify with modern investigative techniques. However,

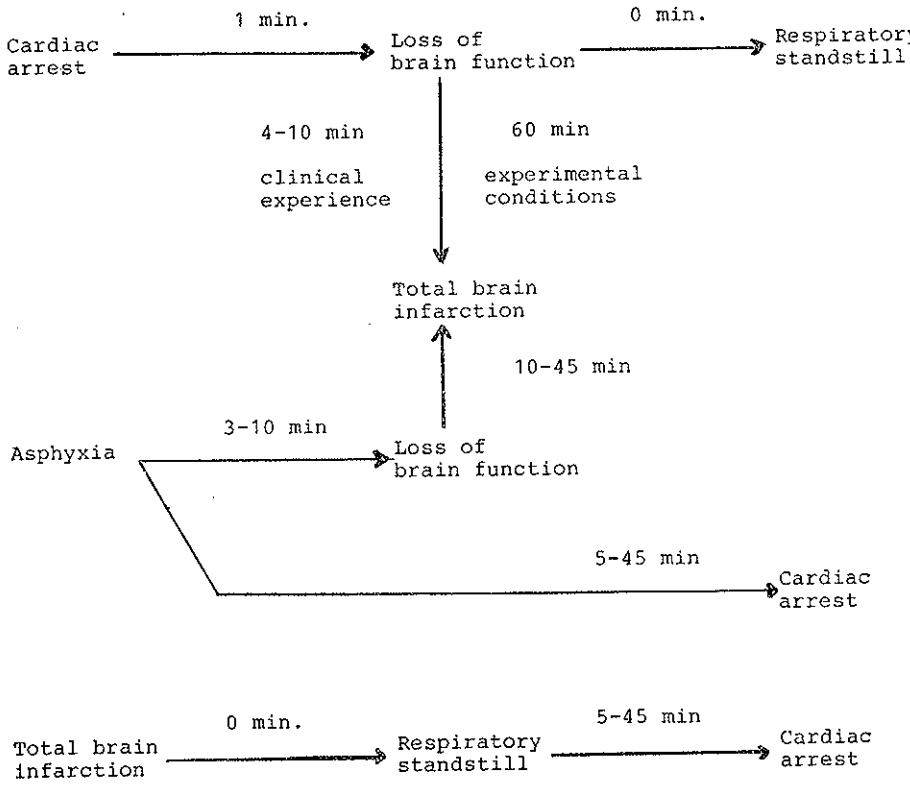
the increasing knowledge of possible plasticity of the central nervous system makes it difficult to determine the irreversibility of such lesion with complete confidence. Only if a total and irreversible loss of all cerebral functions is used as the definition of human death can the determination of this state be made with complete reliability.

It is very important to have a completely unambiguous definition of death which also can be diagnosed with complete accuracy. This holds for total brain infarction. Furthermore, the Swedish Committee states, about the cause of the condition, that it "must be known to be one which can entail such heavily increased intracranial pressure as to obstruct the flow of blood to the brain". It is very important that no confusion will exist between death and poor prognosis. If there are any signs of remaining function or circulation anywhere in the intracranial space the person should not be declared dead, although in most instances he certainly has a completely pessimistic prognosis. It could be argued that small remaining islands of circulated brain tissue can by no means represent function in the brain and thus human life. However, the diagnosis of brain death has to be completely reliable, and rigid criteria have to be used.

Criteria of death

The classical criteria for human death are cessation of respiration and cardiac arrest. When no movement of the chest is seen and no flow of air in and out can be recognized, the pulse no longer can be felt or the heart-beats heard, a person can be declared dead. A certain time lag is necessary, however, to make sure that the respiration cannot be started again or the heart resuscitated. These time lags essentially mean that we are waiting for an irreversible stop of heart and brain functions. The old criteria of death thus can be taken as indirect criteria for brain death, as was done by the Swedish Committee.

As shown in the figure, there is a close temporal connection between the loss of cardiac, respiratory and brain functions. If one of these functions fails in the non-supported state, the others will follow within the very limited time spans which are indicated in the figure. When the brain function is lost, respiration immediately stops. However, when the respirator is turned off from a brain-dead person it takes 5-45 minutes before the heart stops. The usual time-span for heart activity after brain death with on-going respiratory treatment is a few days. With supportive



Temporal relations between cardiac, respiratory and brain functions

intensive care the heart may go on beating for several weeks after the total brain infarction. It may be possible to prolong this time even further.

A primary cardiac arrest will lead to irreversible brain damage if efficient circulation is not restored within 4-10 minutes according to common clinical experience. However, it has been possible to resuscitate animals under well controlled experimental conditions after up to 60 minutes of complete cerebral ischemia. Thus, the classical death criteria will give strong indications that the brain functions are totally and irreversibly lost within less than an hour, probably in almost all cases within 15 minutes. This delay is very seldom of any practical consequence. However, deep hypothermia and deep anesthesia may prolong this time considerably.

Medical progress, especially intensive care including respirators and artificial circulatory devices as well as organ transplantation, has broken up these close functional connections between brain, heart and respiration and made it necessary to find direct brain-related criteria for death in man. It is important that these criteria also define a total and irreversible loss of all brain functions, i.e., total brain infarction.

The principles for diagnosis of total brain infarction are well documented and not controversial. I will only comment upon a few points.

Poikilothermia due to loss of temperature regulation is a very reliable sign. Usually it leads to a decrease in rectal temperature down to 32-35°C with the ambient temperature around 20°C as is usually kept in an intensive care ward.

Separate brain stem lesions may give a symptomatology which is very close to the direct brain-related criteria for death. This stresses the importance of carefully documenting the underlying condition with regard both to its character and to its extent, and it also implies that the neurological examination has to be complete and carefully performed. In all doubtful cases angiography should be performed.

The diagnosis of brain-related death criteria requires special knowledge in intensive care and neurology, especially with regard to diagnosis of the underlying cause. In my opinion the clinical diagnosis of direct brain-related death criteria should only be performed by doctors with special training and competence in the field. Since these patients are always dependent on respirators and intensive care, competence of this kind should be available.

Conclusions

An exact determination of death is possible by using brain-related criteria — either the indirect criteria as has been done for centuries or the direct criteria based upon modern knowledge of brain functions or recent developments in brain investigative technology. If the use of the direct criteria is restricted to determine total brain infarction, the risk of declaring a person dead by mistake is minimal, probably less than by using the indirect criteria.

The determination of the exact moment of death is more difficult due to our incomplete knowledge of the possible revival times in general and in the individual case. However, if we define the moment of death as the time when the cerebral function is totally and later irreversibly

lost, it can be determined in retrospect with great accuracy in some cases. The intensive care charts often directly or indirectly indicate the final intracranial pressure increase which leads to a permanent cessation of the cerebral blood flow. However, a reliable diagnosis cannot be made immediately, before the revival time has passed. Two investigations are requested both for clinical and angiographic diagnosis, with a time interval of at least 30 minutes for angiography and 2-24 hours for clinical diagnosis according to regulations in different countries. In most cases this does not matter. When necessary, the exact moment of death has to be determined in court, according to available circumstantial evidence.

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THE PROLONGATION OF LIFE AND THE CRITERIA OF DEATH

E. J. ZERBINI
Facultade de Medicina, Universidade de São Paulo
São Paulo - Brasil

A) *Actual Criteria of death*

Biological death means the complete cessation of life for all the organic tissues and cells corresponding to the somatic death. Clinical death precedes total body death. After the confirmation of irreversible brain death, a gradual and progressive deterioration of the organic cells and tissues takes place according to its resistance to anoxia.

The fundamental criteria is that brain death is a nonreversible cessation of all brain activity, with no evidence of any brain stem or cortical function and without the possibility of survival in spite of intensive treatment.

It is necessary to emphasize the difference between the two situations connected with the concept of cerebral or neurological death: the concept of cortical brain death and the concept of brain stem death. Even after destruction of the cerebral hemispheres with no cortical function at all, the patient may remain responsive. By contrast, lesions of some areas of the brain stem result in permanent coma, even if the hemispheres are intact.

The flat or isoelectric electroencephalogram (EEG) though not essential to the diagnosis of irreversible coma, is a valuable indication in the determination of brain death. There is a high correlation between isoelectric EEG and loss of brain stem function, but the EEG represents the activity of cortical neurones which may act independently from the brain stem. The EEG does not identify the irreversible loss of brain stem function. Moreover the flat EEG is not always a reliable test, considering the pos-

sibility of poor documentation due to inadequate recording and the possibility of considering as cerebral other signs generated from respirators, dialysis machine, people walking in the ward, and even from technicians wearing nylon underwear and the accepted 3% variance in the reading of the records. The mentioned circumstances must be excluded during the obtention of a reliable tracing. Nevertheless, the EEG is a relevant graphic documentation of the brain death and should not be omitted. It is a supplement to the clinical diagnosis of brain death. It would also provide a permanent record of the absence of brain activity in the event of questions being asked later on.

The EEG is irrelevant to the diagnosis of brain stem death and is not essential to the diagnosis of irreversible coma. The clinical signs of the interruption of the brain stem are unambiguous and a neurologist or a trained physician can recognize them.

In the management of brain-damaged patients, the prognostic importance of the EEG and clinical signs of brain stem function cessation are relevant. It could be suggested that the irreversibility of the coma could be accepted when both the isoelectric EEG is recorded and the clinical signs of cessation of brain stem function are certified by a neurologist.

Brain death is a state in which cortical, subcortical and brain stem functions are permanently lost.

In the Finnish code no confirmatory investigations, such as electrical activity or blood-flow studies, are needed when the absence of brain stem functions has been verified by clinical examination. Similarly, the British criteria do not include EEG or other investigations such as a cerebral angiography or cerebral blood flow measurements. In USA, the Harvard criteria for brain death requires:

1. Unreceptivity and unresponsivity;
2. No movements or breathing;
3. No reflexes;
4. Flat encephalogram.

The criteria for cerebral death (brain death) proposed by the Collaborative Study of Cerebral Death requires:

a) Prerequesite: all appropriate diagnostic and therapeutic procedures have been performed;

b) Criteria (to be present for 30 minutes at last 6 hours after the onset of coma and apnea):

1. Coma with cerebral irresponsitivity;
2. Apnea;
3. Dilated pupils;
4. Absent cephalic reflexes;
5. Electrocerebral silence;

c) Confirmatory test: absence of blood flow.

Brain death is a state of irreversible destruction of virtually the entire brain from which survival has never been seen. Several investigations showed that brain death, when confirmed by rigid criteria, is always followed by somatic death. It can predict inevitable biological bodily death.

B) *The exact moment of death*

The classical definition of death requires that the heart no longer works and *rigor mortis* has set in in the subject. Under the actual criteria of brain death an important philosophical question may be raised: should the patient presenting cranial nerve areflexia and other requirements of brain death, "properly tested and found virtually certain to die within a few days" be equated with "dead"?

An extensive literature has been published, with the experience of a great number of authors confirming the value of combined clinical and instrumental investigations in the declaration of brain death, and demonstrating that when all functions of the brain have permanently and irreversibly ceased, this condition is always statiscally followed by somatic death. In between the two events (brain death and somatic death) the function of many organs can be maintained artificially with proper assistance. But even if mechanical ventilation is maintained, the progressive dissolution of the brain and other organs proceeds.

The interruption of this assistance will be followed by biological death, or cessation of that "assisted life". The ventilators and instrumental assistance can "mimic" life but the human being must be regarded philosophically as dead.

The person's life, as a person, requires the complete capacity for consciousness, and its cessation deprives the individual of his spiritual capability of decision. He is deprived of his mind, of his liberty of decision between good and evil. The body deprived of its volitional faculties is spiritually dead. Brain death equates spiritual death; it is the loss of the power to will.

C) *The artificial prolongation of life*

After brain death the body is a mass of alive tissues depending on artificial assistance. We have no more right to maintain such an individual, who is essentially a heart-lung preparation. The decision to stop the support systems is strictly clinical. To maintain an artificial life we are refusing treatment to another patient, considering the limitation of intensive care units. The distress of the relatives is needlessly prolonged and failure to make a decision to withdraw the ventilation from a brain-dead patient gives no credit to the medical staff involved. A clearly written protocol for management of brain-dead patients could minimize the uneasiness of the situation.

According to the Ad Hoc Committee of the Harvard Medical School, in the address "The Prolongation of Life" (1957), Pope Pius XII concludes: 1) In a deeply unconscious individual, vital functions may be maintained over a prolonged period only by extraordinary means. Verification of the moment of death can be determined, if at all, only by a physician. 2) It is incumbent on the physician to take all reasonable, ordinary means of restoring the spontaneous vital functions and consciousness, and to employ such extraordinary means as are available to him to this end. It is not obligatory, however, to continue to use extraordinary means indefinitely in hopeless cases. It is the Church's view that a time comes when resuscitative efforts should stop and death be unopposed.

After the declaration of brain death and during the maintenance of artificial life, tissues and some organs can be recuperated and used to prolong the life of other patients. At the present moment, after the introduction of new and more active immunosuppressive drugs, the transplantation of organs has been reactivated and deserves the support of legislation, the medical profession and the population in general.

D) *Legislation*

The legislator must take into consideration that the actual interest in the technical and ethical problems related to brain death and artificial prolongation of life was stimulated by the acceptable results of the program of organ transplantation. The donation of organs to seriously ill patients is more frequent now, and the family of a brain dead individual accepts today the fact that an organ of his beloved member

will make life possible for another person who might otherwise be condemned.

The text of the law must be simple in order to facilitate the removal of organs after the certification of brain death.

The following recommendations should be emphasized:

1. Rigid criteria for the declaration of brain death should be observed.

2. The permission of the family for the removal of organs should not be indispensable, as is the case in Spain and France.

3. The permission should be signed by the physician considering the dead brain as a patrimony of society.

4. In cases of suspicion of crime, the participation of a medical examiner (coroner) should be required in the permission for organ removal.

5. A worldwide campaign should be promoted to motivate humanity to accept that the donation of organs is an act of love and charity.

DEUX CAS EXEMPLES

JEAN-FRANÇOIS LEMAIRE
Expert près Tribunaux
Collaborateur médical du « Point »
Rédacteur en chef de « La Pratique Médicale Quotidienne »
97 Rue du Bac, 75007 Paris (France)

Comparés aux éminentes personnalités réunies autour de cette table, mes titres sont de peu de poids. Mais lorsque le Président Carlos Chagas m'a précisé les deux raisons pour lesquelles il me confiait à m'asseoir parmi vous, je me suis rangé à son avis. Si je n'ai pas la responsabilité thérapeutique des malades, il me revient, comme expert près les tribunaux, celle d'informer la Justice française sur la qualité et l'opportunité des soins donnés.

Par ailleurs, responsable de l'information médicale, tant au sein d'organes de presse dirigés vers le grand public que vers les milieux professionnels, il me revient, dans des cas similaires à ceux qui ont été exposés aujourd'hui, de traduire le pourquoi et le comment des choses. De même, de faire remonter vers ceux qui assument la responsabilité d'agir ou de s'abstenir, le courant profond de la conscience populaire.

Je voudrais m'interroger avec vous sur deux exemples que j'ai eu récemment à connaître:

— un vieillard de 83 ans est tombé progressivement, sinon dans le coma, du moins dans une vie purement végétative. Sa communication se limite en un murmure incohérent; il ne reconnaît plus les siens et pleure en regardant fixement le mur de sa chambre. Mais il accepte les aliments, accomplit ses fonctions et dort. Sa femme est morte, ses enfants ailleurs, l'assistance est permanente.

La sécurité sociale ne prend en charge qu'une partie des charges. La solution serait l'hôpital, mais chacun est conscient que, s'il quitte le décor familial, c'est la mort à brève échéance.

— Un enfant de 10 ans est depuis quatre ans dans un coma léger. A six ans, il est tombé dans une piscine et est demeuré vingt minutes immergé. Sorti de l'eau, il a pu être réanimé, mais présentait des lésions cérébrales irréversibles. Il est perpétuellement alité, trachéotomisé et suppose des soins constants. Il ouvre parfois les yeux, n'accroche ni les gestes, ni les regards, ni les objets — on pense qu'il perçoit la musique.

Ses parents sont français, résidant aux Etats-Unis. Les assurances américaines ont payé, mais ne s'exercent que sur le seul territoire américain. Or, son père doit professionnellement regagner la France. Aucune assurance privée, ni la Sécurité sociale, n'accepte d'y prendre en charge un sinistre déjà ancien et qui s'est produit à l'étranger.

Cet enfant a un jeune frère, âgé de 5 ans, qui, depuis qu'il marche, tourne sans comprendre autour de son lit. Pour les psychologues, cette situation entraine, chez ce deuxième enfant, un début de désordre psychique.

Reprenant les propos du Prof. Lejeune, je dirai, si monstrueux que cela puisse paraître, que le vieillard se situe dans le cadre d'éventuels traitements, alors que l'enfant ne légitime plus que des soins.

Le vieillard vit. Il est possible d'interrompre cette vie, facile même. Il suffit, par une nuit froide, de laisser entrebaillée la fenêtre — mais ce serait alors le tuer.

L'enfant survit. Il ne peut rien espérer et, sans le vouloir, il détruit: la vie sociale de ses parents, et l'équilibre mental de son frère.

Mais c'est là que se situe l'essentiel. A partir de ces deux schémas authentiques, combien de situations qui leur paraîtront semblables et ne le seront pas. Seule la conscience du médecin saura faire le tri, mais cette conscience n'est pas innée et le médecin n'apprend plus à en explorer les abysses. Il est urgent d'en prendre la mesure.

En mon âme et conscience — le mot revient — choisir entre traitement et soins n'est pas un niveau de compétence médicale, mais de formation: une formation éthique, une fois admis qu'aucun cas ne ressemble à un autre.

CONSIDERATIONS ETHIQUES SUR LA PROLONGATION ARTIFICIELLE DE LA VIE ET LA DETERMINATION DELIBEREE DE LA MORT

SOPHIE DION et GEORGES MATHÉ
Service des Maladies Sanguines et Tumorales et ICIG
Hôpital Paul-Brousse
14 avenue Paul-Vaillant-Couturier - 94804 Villejuif cedex France

La plupart des morales et l'éthique prescrivent *le respect de la vie* de tous les êtres humains et leur reconnaissent le *Droit* à celle-ci sans prévoir la moindre exception. Ce n'est pas en tant que droit, mais en tant que *fait* que certains cas d'irrespect sont tolérés.

Le fait de tuer toujours toléré, et le droit de tuer récemment légiféré

Ils concernent *les tueries* à l'échelle des organisations de populations, notamment les Etats, ceux-ci évoquant pour les justifier, la « Défense » de leur existence et indépendance et celle de leurs populations dans la liberté qu'ils leur offrent. Ainsi, l'armée peut-elle tuer les étrangers qui ont « attaqué » son pays et le soldat de l'un, celui de l'autre. Mais le terme de défense peut s'entendre à titre préventif, et un pays en attaquer un autre, ce qui est le cas de la moitié des pays en guerre.

A l'intérieur même des pays, le policier et le magistrat peuvent aussi tuer un ou plusieurs individus pour défendre les autres. Mais chacun de ces deux tueurs potentiels peut se tromper respectivement de cible et de culpabilité.

En France, un magistrat a défendu l'idée de l'assassinat de l'embryon. L'idée, transformée en loi contre l'opinion de la majorité de l'Ordre des Médecins, donne aux chirurgiens gynécologues ou non le droit d'homicide.

Le médecin n'achève pas les hommes

En-dehors de cette condition, non seulement, *le médecin ne rentre*, selon aucune des morales ni selon l'éthique, *dans aucune de ces catégories de tueurs*. Elles le lui interdisent même absolument. Le médecin s'est donné, avec son maître à penser, Hippocrate, une éthique singulière et remarquable par son exigence absolue à cet égard et à d'autres, que Cornelius Celsius a prolongé jusqu'à la notion du « medicus amicus », qui lui retire non plus seulement le droit de le faire, mais toute raison puisqu'on ne tue pas son ami, ce qu'est pour lui chacun de ses patients.

La lutte pour la vie

Toutes les morales et éthiques propres au médecin lui ordonnent, au contraire, même s'il oeuvre dans l'armée ou la prison, d'appliquer à tout être humain menacé dans son existence (même au soldat ennemi et au condamné à mort dont le cou sera tranché dans les prochains moments), tous les moyens disponibles de sa science et de son art pour lui donner le maximum de *chances de prolonger sa vie* dans les *meilleures conditions* somatiques et psycho-mentales possibles.

En danger de survie

La réponse théorique à la question des *traitements acharnés* à prolonger la durée de la vie dans le cas des états certainement désespérés, n'est donc aucunement ambigue: le médecin doit la prolonger autant que possible, et cela d'autant plus qu'aucun praticien ne peut affirmer, sauf « in extremis », qu'une vie est certainement condamnée à court terme.

Une zone d'ambiguïté

Et pourtant règne, en effet, une totale confusion dans la définition des états qui vont du cas désespéré à celui « d'état avancé ». D'où l'existence d'une *zone floue*, sur laquelle les morales confessionnelles et culturelles se taisent et dans laquelle se sont engoufrées des pseudo-morales idéologiques, qui s'expriment au nom de pseudo-cultures au seul service d'ambitions politiques ou sectaires, voire d'intérêts financiers. La contradiction y règne à plaisir. Les meneurs n'hésitent pas à recourir à la manipulation de l'opinion, et le risque en est grand qu'ils manipulent aussi les pouvoirs au point d'aboutir à la réglementation de leurs opinions.

En danger de mort

Toute l'hypocrisie de la législation et de la juridiction est dans l'art de recourir le moins souvent possible à la notion de *Droit,* et le plus souvent possible à celle de *fait,* via la jurisprudence. Le résultat en est qu'aucune frontière n'est fixée a priori aux pratiques, d'autant que la marge de manoeuvres des tueurs est large, et que ce n'est qu'a postériori que les défenseurs d'une victime peuvent se plaindre, au sens juridique du terme, de malpratique. Sauf quelques cas de faits, dont le modèle est considéré par tous comme scandaleux, la plupart des actions seront ou masquées par les techniciens ou masquables par la technique, et les moyens de jugement, échappent au juge.

Le « droit à la mort »

Plus grave est le fait que des snobocrates, comme F. Sarda, demandent le « droit à la mort », (comme si les médecins voulaient ou même pouvaient la leur confisquer), approuvent les para-médecins de se vanter, au seul profit souvent du best-sellering, d'avancer pharmacologiquement la mort sous le prétexte que la vie du patient est pénible, voire seulement inconfortable.

Le danger d'extrapolation

Le danger réside dans l'extrapolation, à laquelle n'ont pas manqué de procéder ceux qui considèrent qu'appartenir à telle race, est anormal, qu'être dans l'opposition ou dans la minorité l'est aussi. Il est curieux que les théoriciens du « droit à la mort » appartiennent souvent aux minorités culturelles, qui se livrent dès lors au viol moral de la majorité.

D'où la nécessité d'une *approche par l'éthique et non par les morales* de la question qui nous est posée. Ces dernières sont en effet multiples et possiblement contradictoires, tandis que l'éthique est unique et universelle, puisqu'elle est la morale de la seule Nature. Elle indique les frontières à l'intérieur desquelles l'homme peut agir avec le maximum de sécurité de survie, ou tout au moins avec le minimum d'insécurité que lui laisse la Nature, selon son mode de multiplicité symbiotique et compétitive pour la survie de l'espèce.

Les chrétiens de culture et de foi doivent non seulement défendre leurs concepts moraux. Ils peuvent recourir à ceux du Shintoïsme qui respectent ceux-là et leur foi, mais prétendent n'obéir qu'à l'éthique, cette morale de la Nature.

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EUTHANASIA: WHY WE SHOULD REJECT IT

CORRADO MANNI
Head of the Department of Anesthesiology and Resuscitation
Università Cattolica del Sacro Cuore, Rome, Italy

The arguments to be found in the text, according to the intentions of the author, are independent of any ideological reference. Rather, they belong to the language and experience of a doctor, of any doctor.

It is no accident that euthanasia is the object of general attention today and arouses suspicion and mistrust. Euthanasia is seen as the most appropriate treatment to put an end to the sufferings of the terminally ill patient and to favour gently his passing away without violating the natural course of events. I am obviously referring to what is generally called passive euthanasia. It cannot be held to be a matter of opinion that direct and active intervention to accelerate the death of a terminally ill patient is illicit.

The reason for the reserves just mentioned lies in the fact that, without wishing to deny sincerely human intentions and an apparently noble end to the upholders of euthanasia, they seem to lack the awareness of the presuppositions, explicit or implicit, of any measure aimed at legalizing euthanasia. If one does not consider the person to be helped and the profound changes undergone by him in the course of time and which he will certainly continue to undergo, one does not realize how complex it is to presume to dictate judicial norms in this field. The terminally ill patient, in fact, cannot be reduced to a single well-defined category, even though he reflects historically different situations. And this without mentioning that principle of totality which refuses to look at the specific pathology while not considering the integrality of the human person. It is to this "historicity" of the subject that reference must be made for any consideration of euthanasia. This

"historicity" blocks its prefigured evolution and warns us against making suggestions and establishing legal norms which would regulate euthanasia almost as if it were justifiable and acceptable. To appreciate the meaning of this reservation completely, it is necessary to go back over certain situations which could be described as typical.

Perhaps the cases which most obviously solicit euthanasia are patients suffering from acute diseases; for example, patients in a state of shock, for whom doctors are often inclined to give clinical assistance indefinitely even though they know that the results are not always positive. The state of shock is a condition whose salient characteristic is irreversibility. This was absolute until the American surgeon G. Crile, at the beginning of our century, studied its effects on animals. He discovered that one of the most obvious processes was the fall in blood pressure. And so he indicated the treatment. Lather, the apyrogenous preparation of saline solutions, the determination of blood groups and the consequent transfusions of blood (its derivatives or its substitutes), and a better knowledge of the processes at work enabled doctors to save the lives of many patients, even though today the prognosis still remains uncertain and their fate is known only *a posteriori.* In fact, in spite of considerable progress many patients — perhaps one in ten — do not get over the state of shock. And so the question arises whether it is better to treat all patients with the aim of saving only a few, or to abandon all of them to their destiny.

The question could, in fact, appear captious since the aim of euthanasia is not that of sacrificing someone but of simply helping those who are certainly destined to die by sparing them the suffering which some continue to consider useless. Often the greatest protests against therapeutical perseverance are made with reference to the assistance given to political personalities. These, precisely because of their position, have been subjected to protracted and useless surgery and intensive care treatment. New reports in recent decades have concluded by favouring — from considerations suggested also by these cases — a movement of opinion against indefinite medical assistance. However, it is sometimes forgotten that even in these cases, the prime motive was that acute complications could arise, especially as a result of surgery. The treatment of these complications is obligatory for those who have the responsibility of assisting the patients. Even if the result of these efforts is often negative, it is not always so. There are not a few cases, largely unknown to public opinion, with a totally positive result. For proof of this it is

sufficient to carry out an inquiry in hospitals; it results that the patients saved from clinical death, thanks to deeply committed intensive care carried out *in extremis,* are numerous.

In fact, euthanasia is not proposed for acute patients; the course of their illness is, in general, brief. It is proposed rather for patients afflicted with chronic diseases; these, even if they have got over the acute phase of the illness, still remain in pathological conditions which are completely without hope of a definitive cure. Among these are numbered, above all, those who suffer from chronic renal insufficiency. Until a few decades ago they had an inexorable destiny. Today, the picture is completely changed. Few people remember that the merit of the change goes to a young Dutch doctor. During the Second World War, he was working in a small provincial hospital and he was moved by the sufferings of a despairing mother because of the slow but inarrestable decline of her son affected by renal insufficiency. Rather than cultivating sentiments of euthanasia, he engaged in the study of terminally ill patients suffering from acute or chronic renal insufficiency. He discovered a method of restoring them to life. Today these patients form a large group and, thanks to the blood-purifying apparatus assembled by Dr Kolf, they are able to live and, in many cases, to carry on an adequate working activity.

Clearly, today no one would propose euthanasia for patients suffering from acute or chronic renal insufficiency but only for those for whom any treatment which would have a minimal effect is precluded. The reference is here especially to patients suffering from terminal cancer. For these, valid therapies do not exist which would guarantee any probable recovery. The only therapies that exist are those which prolong the agony in the midst of grave suffering.

The problem can be put in these terms: in the face of a patient suffering from terminal cancer is it appropriate to practice euthanasia and shorten, with his life, the inevitable suffering, or, to resist this temptation and let the disease run its course limiting oneself to giving the patient those palliatives which his condition demands?

There is no doubt that whoever must face this question responsibly, cannot find an excuse in agnosticism or abstain from giving himself a reasonable code of behaviour. However, to reply to the question under consideration, one must keep in mind the clinical chart and the objective situation to be faced.

An obligatory consideration is that the evolution of a disease, even

in its terminal phases, is not generally gradual. Rather, it is characterised by a multiplicity of acute episodes, one of which becomes the ultimate and decisive cause of death. The image of the cancer patient tormented by serious suffering corresponds to the truth, but these sufferings can be explained by the fact that they are caused by complications which set in later. Sometimes they are caused by the compression or irritation of a nerve; more often by intestinal, urinary-hepatic or lung complications, etc. In the face of a patient suffering pain with a specific cause, have we the obligation to remove the cause or shall we let him suffer? If another patient has difficulty in minction, even though it is in the terminal phase, can we refuse to give him the necessary assistance? And still: before a patient affected by intestinal occlusion who is vomiting and who cannot feed himself and who asks us to relieve him from his sufferings, can we refuse to consider a possible treatment even if this is exclusively symptomatic? If a lung infection appears, can one withhold the administration of a suitable drug solely because the patient is already destined to a short existence?

The clinical problem, the one which offers the image of the terminally ill patient, is the synthesis and expression of these inescapable motivations. If the terminally ill patient is today destined to die in a short time, this is due to the fact that too many aspects are and will remain unknown until such time as, by means of incessant attempts, this medical problem is finally solved. It is not, in fact, rhetorical to recall that many diseases have found their remedy through the efforts made to bring aid to the terminally ill. However, reference is made to the hypothesis of euthanasia not only because of the existence of cancer patients but also because of the condition of old age, when this is accompanied by extreme conditions of serious disability.

Old people who are still lucid and assist helplessly at the loss of their various organic functions, would they not perhaps prefer a dignified death to this humiliating condition? No one, I believe, apart from the person himself, can give a sincere answer to this question and it cannot be excluded that some people are disposed to give an affirmative answer. On the other hand, I would like to observe that, subjectively, it is entirely permissible to *desire* that death put an end to one's sufferings. Quite different is the problem of wanting to cause or favour it. In any case, the task of society is that of examining in depth old age itself and of seeking in it the glimmer of a different evaluation. Certainly, old age can be a condition of extreme gravity also because no one can

escape it. The problem has reached enormous social proportions since the progress of medical science has raised considerably the average human life span. And this is a curious paradox of our times. The absolute good of the promotion of life is accompanied by the increase of particular problems to which medical science is not yet able to give an answer.

In the face of the rising number of patients and their increased needs, our civilization is faced with two opposing choices: either to privilege the strong by ensuring greater benefits for them and by emarginating the weak, bringing the terms of their existence towards forms of greater degradation, or, by increasing efforts to arrive at a different solution to present-day health problems.

Euthanasia, birth control — obtained even by infanticide — and many other manifestations which modern life privileges, depend on one of these two choices. There is, however, an alternative and that is the choice of solidarity with those who find themselves in greatest difficulty, like the sick, the weak and the emarginated. This solidarity is accompanied by the commitment to greater scientific progress which will enable us to find the true solution to the chronic diseases which afflict mankind today. Unfortunately, those who had foreseen less organic deficit with the lengthening of life have been proved wrong. The concept remains always valid that most of chronic diseases are not the result of multiple causes but of one only, which lies at the base of all the diseases of old age. If it turns out that a single genetic defect can have multiple effects, the perspectives of old age are modified without having recourse to means which have no justification.

A loyal faith in research and commitment is needed to give greater support than nowadays appears to be the case to biomedical strategy. It has as its objective not so much that of lengthening life as that of preventing the beginning of innumerable debilitating diseases. Euthanasia is not situated along this line, but along that of surrender.

CONCLUSIONS

At the invitation of the Pontifical Academy of Sciences, a Working Group met on the 19th, 20th and 21st of October 1985 to study « the artificial prolongation of life and the exact determination of death ».

After having reviewed the recent progress in reanimation techniques and the immediate and long-term effects of cerebral damage, the Working Group discussed the objective criteria of death and the guidelines in facing a persistent state of apparent death. On the one hand data obtained from experiments undertaken in mammals reveal that the resistance of the brain to absence of cerebral circulation can permit recoveries previously considered impossible.

On the other hand, it is established that when the whole brain has suffered an irreversible damage (cerebral death), any possibility of sensitive and cognitive life is definitely abolished, while a short vegetative survival can be maintained by artificial continuation of respiration and circulation.

I. Definition of Death

A person is dead when he has suffered irreversible loss of all capacity for integrating and coordinating physical and mental functions of the body.

Death has occurred when:

a) spontaneous cardiac and respiratory functions have irreversibly ceased, or

b) there has been an irreversible cessation of all brain function.

From the discussion it appears that cerebral death is the true criterion of death since the definite cessation of cardio-respiratory functions leads very rapidly to cerebral death.

The Group thus analyzed the various clinical and instrumental methods to ascertain this irreversible cessation of cerebral functions. In order to

be sure, by means of the electroencephalogram, that the brain has become flat, that is, that it no longer shows any electric activity, the observation must be made at least twice within a six-hour interval.

II. Medical Guidelines

By treatment the Working Group understands all the medical interventions, however technically complex, which are available and appropriate for a given case.

If the patient is in permanent coma, irreversible as far as it is possible to predict, treatment is not required, but care, including feeding, must be provided.

If some prospect of recovery is medically established, treatment is also required or pursued.

If treatment may bring no benefit to the patient, it can be withdrawn, care being pursued.

By care the Working Group considers the ordinary help due to bedridden patients, as well as compassion and affective and spiritual support due to every human being in danger.

III. Artificial Prolongation of Vegetative Functions

In case of cerebral death, artificial respiration can prolong cardiac function for a limited time. This organ survival thus produced is indicated when organ explantation is regarded in view of transplantation.

This is possible only in case of cerebral lesion, total and irreversible, occurring in a young subject, essentially after a brutal trauma.

Taking into consideration the important progress of surgical techniques and of the means to increase graft tolerance, the Working Group considers that transplantation of organs deserves all the support of the medical profession, of legislation and of the population in general. The donation of organs must, under all circumstances, respect the last will of the donor or the consent of the relatives if they are present.