SPECIAL REPORT

Cerebral Death and the Transplantation Era

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We all know that the cells which are more sensitive to acute anoxia than any other group of cells are those present in the central nervous system. When the central nervous system is damaged to a sufficiently high degree by, for instance, trauma, or has been completely deprived of its arterial blood supply for as long as ten minutes under normothermic conditions, there is no chance whatsoever that it will resume its function.

Looking back over the past two decades, I am entitled to say that what I predicted for the development of cardiac surgery, in my Martin Memorial Lecture in 1948, has really happened. We now have highly advanced teamwork and technical assistance from all branches of medicine and technology.

Before this era of technical assistance to different organ systems, as I mentioned previously, organ function could not be maintained for more than a very short period of time in patients with severe brain damage. In most instances, cardiovascular and respiratory function ceased within a few minutes, and within one-half to one hour, there was no possibility of detecting or reviving any function of organs such as the liver, kidney, pancreas and hormone-producing glands. The great step forward we have taken is that in all cases in which the primary brain damage has not been irreversible, we are now able to maintain blood circulation, respiratory function and cellular metabolism in every part of the body by artificial means for a prolonged period of time. During this time we may be able to decide if the function of the brain can be restored totally or at least partially.

This development has, however, brought in its wake many problems of a difficult nature. We can now keep alive decerebrated bodies which totally lack the ability to produce any spiritual life. They cannot be considered living human beings.

Throughout the centuries, it has always been members of the medical profession who have had to decide when a person is dead. Formerly, it was relatively easy to do so because the interaction between brain function and cardiorespiratory function could not be separated in time in the manner we can today. The easiest and most obvious sign for deciding that death has occurred has been cessation of the heart beat and respiratory movements. When both have ceased, the brain is irreversibly dead within five to ten minutes under normothermic conditions. Today we can keep the heart going artificially and the blood pressure on a sufficiently high level for total perfusion, and maintain the respiratory function with physiologically-acting respirators even if the brain is reversibly damaged.

We have known for a very long time that after cessation of respiration and circulation, life still continues in many different cell systems and organs for a variable length of time. Bone, muscle tissue, fat, skin and the gastrointestinal tract survive and can be reactivated after a considerably longer period of total lack of circulation than, for instance, the liver, kidney and pancreas. The reason why, for many centuries, doctors have selected cardiac and respiratory standstill as such predominant signs of death, is the fact that they are very easy to observe. Moreover, previously the brain—the organ that regulates the function of all the others in the body if not primarily damaged—also irreversibly died within a few minutes. However, both irreversible and severe reversible brain damage produce, within a variable but short length of time, cessation of circulatory and respiratory function, if no technical devices are applied to maintain these functions. In all these cases, it is the irreversibility or reversibility of the brain function that decides if death really has occurred or not. The importance of the heart beat and spontaneous respiration for deciding whether the patient is actually alive or dead is so deeply rooted in the mind of both primitive and highly civilized members of the human race that the alteration in these criteria of death has aroused worldwide discussion.

Unquestionably, an increasing number of people

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now understand that the life or the death of the brain is the factor which decides if a human being is living or not. However, there are still very many individuals who have the greatest difficulty in accepting the principle of the major difference between respiration and circulation regulated via brain centers, and artificially regulated respiratory and circulatory function without any connection with cerebral function. Even within the medical profession, mainly due to insufficient knowledge, there is some confusion and illogical thinking. This is expressed in an opinion that as long as we can keep circulation and respiratory exchange going with artificial, mechanically extraordinary means, a human being should not be declared as dead, with no consideration given to the fact of whether or not there is a completely nonfunctioning brain. The discussion related to these problems is not only a discussion of more or less academic interest, or merely of a moral and ethical nature. It is also a question of great practical consequences.

With the rapid and progressive development of our intensive care units for both postoperative and medical patients, we will always find certain patients in whom cerebral anoxia has prevailed for so long a time that irreversible, general anoxic brain damage has already taken place, before it has been possible to reinstitute total body perfusion, either by artificial means, or by restarting heart action and gas exchange. Such patients, as well as all others in whom it can be a question of whether irreversible or reversible brain damage is prevalent, are hospitalized and under highly skillful medical observation. In such a group of patients, I consider it to be not only justifiable, but very strongly indicated, not to base the determination of death on respiratory and circulatory function which—in the great majority within this group—are kept going by artificial extraordinary means. On the contrary, I think that it is cruel, and I would say almost criminal, to continue the use of artificial extraordinary devices when highly educated and skilled specialists in the fields of surgery, neurology, neurophysiology and radiologic diagnosis are in agreement that in the specific patient under treatment, damage to the brain is total and of irreversible nature.

The only conditions under which such artificial extraordinary technical devices should be permitted to carry on for body perfusion and gas exchange are if there is, in fact, any doubt about the irreversibility of the brain damage, or if through such treatment organs can be kept alive (in this already lost human being) for so long a time that they can, with some prospects of success, be considered for transplantation.

Naturally, before a transplantation is performed, there must be either previous consent by the patient himself, before his brain damage occurred, or by the nearest relative. There has been much talk and heated discussion about so-called human integrity and the respect which is due a dying individual. How then do we define a dying patient? As long as conscious or unconscious brain function persists, the patient is dying, but when there is no further brain activity, we no longer have a dying patient—we have a corpse. How people feel and think when they try to envisage themselves as being in a state in which one of their organs could be used for the benefit of another suffering human being, is naturally variable. From my own experience I know, however, that a very great number of individuals would not hesitate to donate surviving organs or tissue to somebody sick and in real need of a transplant. Even when people are fully active and in normal health, we have many instances when, for example, consent is willingly given to the removal of one of their kidneys for the benefit of a relative, or even of an unrelated person.

In surgery, the transplantation sector will, without doubt and within the relatively near future, be not merely at an experimental stage, but an established method of treatment. We even have a law in Sweden since 1958 that gives the medical profession the right to take tissue for transplantation from a dead body, even if no permission has been given by the donor or his relatives, provided that no objections have been expressed. This law was passed at a time when grafting of the cornea, which is composed of avascular tissue, had been shown to be both practical and of lasting nature. For the successful outcome of such a graft and also transplantation of, for instance, bone, there was no urgency in removing the organ. It could be done at a routine but accelerated autopsy, and has never been subject to any general discussion.

When it is a question of transplantation of the liver, pancreas, heart or, in my opinion, also a kidney, it is of utmost importance for the organ to be in the best possible condition as regards its cell metabolism. In all such instances, the organ to be transplanted should be removed and implanted in the recipient patient as close as possible to the moment when death of the donor can be established. This fact makes transplantation surgery more dramatic, and gives rise to much more emotional thinking and discussion than any other field of surgery has done.

DIS. CHEST, VOL. 55, NO. 2, FEBRUARY 1969
In every human being who dies, it is the irre-
versible brain damage that gradually stops the life
of all other cell systems. This occurs regardless of
whether the brain damage has occurred prior to
cessation of circulation and gas exchange, or
whether it arises as a sequel of primary inhibition
of heart and lung function. It is therefore funda-
mentally wrong to speak of a new definition of
death. Under all ordinary circumstances which are
present in the majority of deaths, it will—as before
—be the practicing physician who will declare a
patient to be dead when circulatory and respira-
tory function have ceased. Thus, it will be in only a very
small minority of patients—treated in highly spe-
cialized hospital departments, with access to all
scientific, clinical and technical expertise—who will
be pronounced dead in connection with irreversible
brain damage. This may then apply even if circu-
latory and respiratory function have never ceased
completely, or if they have been arrested, and then
restarted, and kept going with the aid of extra-
ordinary technical means; for short or even rela-
tively long periods of time.

It is, unquestionably, the technical advances in
vascular surgery that have laid the technical
foundations for transplantation surgery. As I see it, it
is (as so many times in the past)—the activity of
progressive, bold surgeons that has driven represen-
tatives of theoretical sciences—in this case, the
immunologists—into frenzied action, and great
progress has been made rapidly. This already es-
tablished progress, as well as that to come, will, I
am certain, in the very near future incorporate
transplantation surgery as a well-established
branch.

The proper development of transplantation sur-
gery requires an internationally accepted agree-
ment. In Geneva, a two-day meeting was held in
the middle of June, 1968. It was arranged in the
headquarters of WHO by the Council for Inter-
national Organizations of Medical Sciences. All
together 24 medical scientists from different fields
in medicine—such as surgery, cardiology, immu-
nology and neurology—met together with represen-
tatives of WHO and UNESCO. The main topic
was heart transplantation. In the beginning of Au-
gust, 1968, the WMA (World Medical Association)
met in Sydney, Australia, where it was agreed that
a close study of the question of when death takes
place was strongly indicated by two developments
in modern medicine. The first of these is that we
can now, by artificial means, maintain circulation
and oxygenation even without the aid of the cen-
tral nervous system and also after cardiac arrest
and respiratory standstill. The second is the use of
organs from dead individuals for transplantation.
The death of the brain as a basis for issuing a death
certificate in a given case was one of the most
important matters for discussion. Nevertheless, it
was stressed in both meetings that all clinical symp-
toms, including the case history and the results of
technical examinations, should be taken into con-
sideration. In both meetings, it was concurred that
at least two doctors with no connection with the
patient/recipient should be in agreement that the
donor patient was dead.

As I stressed previously, it is fundamentally
wrong to speak of a new definition of death. Form-
erly, as I pointed out, the cessation of circulatory
and respiratory function was not clearly related to
the fact that either very shortly before or shortly
after irreversible brain damage took place. This
irreversible brain damage could equally well have
been responsible for the cessation of circulation and
oxygenation, as secondary to circulatory and respira-
tory arrest produced by some other cause.

Now, when, with extraordinary technical means,
we are able to separate in time the complete ces-
sation of brain function and complete perfusion and
oxygenation of the body, the refinement in diag-
nostics must be centered on the brain. When can a
definite brain death be assessed, and what is re-
quired for this to be done?

1. In the first place, there must be the most de-
tailed case history possible. One must, however,
realize that one often cannot be absolutely cer-
tain about the case history. A patient with a
traumatic skull injury may, at the same time,
have an intoxication. Conversely, a patient with
definite intoxication may, because of respiratory
arrest, also have developed irreversible anoxic
brain damage.

2. In the second place, one must perform a de-
tailed neurologic examination, subsequent to a
detailed general examination. In cases of brain
death, the neurologic examination shows com-
plete loss of consciousness. There is a total lack
of responses. All cerebral and spinal reflexes are
absent. A certain degree of spinal automatism
can, however, appear after a varying time. We
also have cessation of sufficient respiration for
adequate oxygenation. Furthermore, regulation
of the blood pressure is unsatisfactory, and nor-
mal regulation of the temperature is lacking.
3. Thirdly, an electroencephalogram is recorded. In brain death, it shows extinguished cortical activity, that is, an isoeletric EEG. This must be evaluated by an expert, as sources of error exist.

The fact is that even for a relatively long time, a flat EEG can be present and despite this be reversible. This happens, for instance, in certain cases of intoxication, such as intoxication with barbiturates or other soporifics, as well as deep hypothermia. If the previous history and examinations can exclude such causes, one should, when a transplantation is being considered, as soon as possible after extinction of the EEG, perform cerebral angiography. This is an examination that has been very little discussed, but which, as an objective method of diagnosing irreversible brain death in a certain group of patients must be considered to be of the utmost and decisive importance. We have within the neurologic field a not too uncommon group of patients in whom intracranial pathologic changes suddenly produce very high intracranial pressure. In many of them this pressure rises to such a high level that it considerably exceeds the arterial pressure. Such conditions can also be found in a group of injuries to the skull. It is quite easy and very simple to understand that if no arterial blood has been pumped up into the intracranial arteries, the brain is irreversibly dead after a very short period of time, from five to ten minutes in adults, somewhat longer in children.

In the South Hospital in Stockholm, one of our biggest and most modern municipal hospitals, it was shown in 1956 in isolated cases that patients invariably died if arterial cerebral angiography showed that no dye, together with arterial blood, entered the skull at repeated injections of dye during 10–15 minutes (Fig 1 and 2). This observation was published at that time and a new paper with some more cases was published in 1959. Since then, 50 cases have been examined by this method, and none of them survived, even if extraordinary means for perfusion, oxygenation, blood-pressure elevation and nutrition (intravenously or by gastrointestinal

**Figure 1.** Aortocervical angiography in a case of cerebral death. Following injection into the aortic arch, no intracranial arteries are filled, from either the internal carotid or vertebral arteries. Only branches of the external carotid artery, i.e. the temporal and occipital arteries, are seen projected into the calvarium. Normally branches from the internal carotid artery will fill prior to those of the external carotid. These films and those in Figure 2 were all taken 1–2 seconds after the completion of the injection. Serial filming was made over a period of 15 seconds and no contrast medium entered the cranial cavity. (B and C [center and lower] are subtraction films, taken 1–2 seconds after injection, C same phase as A [upper]).

DIS. CHEST, VOL. 55, NO. 2, FEBRUARY 1969
tube) were continued. The longest so-called survival time with these means has been a few weeks, and autopsy of all such cases have demonstrated a brain mass that was necrosed and liquefied.

The fact observed at the Stockholm hospital, namely that brain necrosis always takes place when arterial blood supply to the brain has been absent as demonstrated by cerebral angiography for 10–15 minutes, has been confirmed by a similar report in 1963 of 26 cases from Finland and other recent, smaller series from the Karolinska Hospital of between 40–50 cases. Brain necrosis was present in every autopsied case and in these series only odd isolated cases were not examined postmortem. This was shown in every autopsied case. Without artificially maintained circulation of oxygenated blood, all other signs of cell life would disappear within a brief period. By artificial means, different organ systems can be kept in a fairly good functioning state for a considerable time. I do in fact consider that it is such dead individuals with partly living organs who form one of the largest groups which are the best to select as organ donors. This applies from all points of view, including religious, ethical, moral and medical.

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