Aspects of Thermoregulatory Physiology Pertinent to Hyperthermic Treatment of Cancer

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Abstract

Local hyperthermia is relatively safe, while whole-body hyperthermia is potentially dangerous because the therapeutically effective elevation of body temperature is close to the tolerable limit to hyperthermia beyond which permanent damage may be caused. Here consideration is given to the most reliable index of body temperature during hyperthermia and the techniques for raising body temperature. The possibility of effecting local brain cooling and thereby increasing the margin of safety during whole-body hyperthermia is also considered.

Introduction

This consideration of some aspects of the physiology of thermoregulation which may be pertinent to the use of controlled hyperthermia in the treatment of cancer does not touch upon the question of the efficacy of such treatment, which is strictly a matter for clinical assessment, nor upon the cytology of normal and malignant cells which might account for the apparent differences in their upper lethal temperatures. Here I am concerned only with the practicalities of how, how far, and for how long body temperature can be raised in the course of such treatment.

In all probability, there is only a narrow gap between that abnormally high temperature which is lethal to malignant cells or which causes such damage as to render them more susceptible to adjunct drug or radiation therapy and the temperature at which irreparable damage is caused to the normal integrative functions of the body. Some navigational aids are necessary, therefore, if a safe course is to be found between the scylla of inadequate heat to achieve its therapeutic purpose and the charybdis of disastrous thermal damage to the whole organism. The sole object of this discussion is to search for those navigational aids. However, as the discussion proceeds, it will become evident that we are operating in waters that are to some extent uncharted by adequate experimental investigation. This means that the conclusions I am able to reach must be considered as tentative rather than established guidelines.

The Upper Lethal Temperature of Mammalian Cells and of Mammals

The constituent cells of mammals, like those of virtually all animals and plants, can survive temperature variations which extend from just below 0°C to about 45°C. The level at which the core temperature of most mammals is regulated, about 37°C, thus represents an acquired advantage to the whole animal in the context of its external environment rather than a condition of life imposed on the whole organism by the immediate environmental needs of its constituent cells. The supposed explanation for the level at which core temperature is regulated, which is some 8°C below the upper lethal temperature of a mammal’s constituent cells, is that this differential leaves room for the temporary rises in core temperature which occur during the high levels of activity involved in predation, the avoidance of predators, and perhaps also in mating.

Some reports indicate that the local heating of the cerebral cortex of the cat (28) and of the lung tissue (22), liver (24), and limb tissues (23) of the dog to 45°C for between 30 and 60 min may cause no permanent damage to these animals; most mammalian species, however, seem to be unable to tolerate whole-body heating to 43°C for that period of time (17), although constituent cells, tissues, and organs apparently can.

Thus, it would seem that the upper lethal temperature of an intact mammal is substantially below that of its constituent cells. This suggests that the thermal damage which the whole organ suffers relates more to the breakdown of the processes of interaction between cells, by which a multicellular complex functions as an integrated organism, than to the breakdown of the functions of the individual constituent cells. This would certainly explain the particular susceptibility of the central nervous system to damage during whole-body heating, since the functioning of the brain relies to a high and refined degree upon very specific relations between nerve cells.

There is, of course, no absolute upper lethal temperature. In all processes of heat-aided change, the duration of the application of the heat, as well as the degree of heat, is a factor in the extent of the change. This is as true of the effects of hyperthermia in humans as it is of any culinary or industrial process. Precise data are difficult to find, but the broad clinical experience of uncontrolled fever and accidental hyperthermia is that, whereas humans can tolerate a core temperature of up to 42°C for many hr or even days, he can tolerate 43°C for a much shorter period and 44°C for only a very brief period indeed.

The Level to Which Body Temperature Must Be Raised in Hyperthermic Therapy

Reports such as that of Cavaliere et al. (7) indicate that some types of cancer cells, at least, are selectively destroyed by a temperature of 42–43°C, while several other reports (25, 29) indicate that the minimum elevation of core temperature for effective cancer therapy is 42°C. This elevation in core temperature may need to be maintained for 6 to 20 hr (11, 12).

Whole-Body Heating versus Local-Tissue Heating

It is now evident that, whereas the degree of hyperthermia necessary for effective cancer therapy is probably not less
than 42°C core temperature for 12 hr, the maximum level of hyperthermia to which a patient could be subjected safely is probably not more than 43°C for 12 hr. Thus, there is, as was surmised in the Introduction, only a very narrow gap between effective total-body heating and dangerous total-body heating. However, since particular structures may be raised to 45°C without evidence of permanent injury, there is apparently a much greater safety margin between the necessary degree of hyperthermia and the maximum permissible hyperthermia when the heating is restricted to a particular structure containing a tumor. This clearly indicates that, all other things being equal, there is a distinct advantage in confining hyperthermic treatment to local tissues.

This clear indication of a preference for local hyperthermia over general hyperthermia is strengthened by the report of Yerushalmi (31) that, in experiments on mice inoculated with the Lewis lung carcinoma tumor, the appearance of metastases was advanced by whole-body heating but was delayed in animals receiving local hyperthermic treatment. However, some caution is needed in drawing the obvious conclusion that there is some qualitative difference between local and general heating; the difference could be only a quantitative one. The greater risk of metastasis after whole-body heating could be because the level to which the whole-body temperature can be raised is less than that to which a particular tissue can be raised. Thus, whereas the local heat treatment may have been sufficient to cause lethal damage to the cancerous cells, whole-body heating may have been less effective.

This note of caution, however, rests on a speculation, and the weight of currently available evidence is undoubtedly indicative of the clinical advantage of local treatment. However, the optimistic use of local hyperthermia alone would seem to presuppose that the known primary growth is the only one and that metastasis has not yet occurred. For this reason, whole-body hyperthermia as well as, or instead of, local hyperthermia will continue to be explored. Since any expertise which the thermoregulatory physiologist can contribute is pertinent only to the problems of whole-body hyperthermia, I shall confine myself to the selection of the best technique for whole-body heating.

**Core Temperature**

There are, as was pointed out by DuBois (14) and reviewed by Minard and Copman (20), many temperatures of the body. Practically all the heat of the body is liberated within the constituent cells, the liberation of free energy being one of the end products of the metabolic processes by which cells keep alive and contribute to the functioning of the whole organism. It is, of course, the temporary retention of this free energy, or heat content, of the body as it passes down thermal gradients from the points of liberation to entropy which determines the temperatures of the body.

The rate of heat production varies between different tissues, both absolutely and temporally, according to their rates of metabolism. The facility with which the heat can flow away from a tissue also varies both absolutely and temporally according to the thermal gradients to the immediate and more distant environments and to the resistance to heat flow. Thus, the temperatures of the different tissues also vary. However, while the temperatures of the "core" and "shell" tissues may differ markedly, the temperature differences between different parts of the core are not sufficient, at least under steady state conditions, to be of much more than academic interest. Under such conditions, the rectal temperature is a few tenths of a degree higher than that of the arterial blood leaving the left side of the heart which, being the mean temperature of the total venous return to the heart from all the tissues of the body, is probably the nearest that can be gotten to a definable and meaningful index of core temperature (2).

When the heat content of the body is changing, however, the rectum is subject to a thermal inertia such that its change in temperature lags behind that of the arterial blood leaving the heart. This "lag" is on the order of 5 to 10 min, and the extent of the enhanced difference between aortic arch temperature and that of the rectum is obviously a function of the rate of change in the heat content of the body. When body temperatures are changing rapidly as in induced heating or cooling of the body, this difference may be greater than 1°C and thus may be greater than the safety margin between the required and the dangerous levels of body temperature during hyperthermic therapy.

For this reason, rectal temperature is an unsatisfactory index of core temperature and should not be used, at least as the sole index of core temperature, when body temperatures are being caused to change rapidly or when core temperature must be regulated precisely at a displaced level. The measurement of temperature within one of 2 other "natural" orifices in the body is generally considered preferable. These are those of the deep esophagus and of the tympanic membrane.

Deep esophageal temperature is fairly close to the temperature of the blood leaving the left side of the heart and responds fairly rapidly to changes in the temperature of aortic arch blood (8). This measurement has been strongly advocated (9), is readily recorded, and is the least disputed temperature in terms of its meaningfulness. A comment (18) that the use of esophageal temperature as a single index of core temperature may be naive would appear to be based on a misunderstanding of what is claimed for esophageal temperature. It is meaningful as a reference temperature, not as a representative temperature. The venous return to the heart is thermally streamed in the vena cava as the blood from those tissues more concerned with heat production than heat loss, such as the muscles, brain, and liver, mingles with that from tissues more concerned with heat loss than heat production, such as the skin and the upper respiratory tract. There is negligible thermal exchange as the blood passes through the pulmonary vasculature; thus, the heart and lungs function as a thermal mixer, and the temperature of the blood issuing from the left side of the heart is essentially the mean temperature of the venous return to the heart. Obviously, therefore, some temperatures of the body will be somewhat above this value, and others will be somewhat below it. In general, however, core temperatures will be slightly above that of the aortic arch.

In non-steady state conditions, the important factor is not the representativeness of aortic blood temperature but its rapid responsiveness to changes in the rates of heat production and heat loss. Because esophageal temperature is the best available index of aortic arch blood temperature, this probably the best temperature to monitor when core temperature is generally changing or when it needs to be closely controlled at a displaced level.

The other candidate is tympanic membrane temperature.
Benzinger (1) emphasized the closeness of tympanic membrane temperature to hypothalamic temperature, but it is also a close approximation of the temperature of the arterial blood enroute from the heart to the brain. Like esophageal temperature, it is rapidly affected by any change in the balance between heat production and heat loss. In the absence of any local thermal influence on it, tympanic membrane temperature closely follows esophageal temperature and might therefore be considered a satisfactory alternative core temperature. However, the acute discomfort that can be caused in a conscious subject when a thermometric probe is caused to rest on the tympanic membrane, coupled with the risk of damage to the membrane, may mitigate against its preference to deep esophageal temperature, which can be readily monitored in both the conscious and the anesthetized subject.

Possible Local Influences on Brain Function

The extent to which deep esophageal and tympanic membrane temperatures are equally representative of that of the blood when it reaches the brain has not been thoroughly tested, largely because of the difficulty of measuring brain temperature. Cabanac and Caputa (5) have recently shown that the tympanic temperature of a hyperthermic exercising human is significantly lower than the esophageal temperature during face cooling, although these 2 core temperatures are similar when facial cooling is prevented. A possible explanation for this finding is that tympanic membrane temperature is determined not only by arterial blood supply to the brain but also by jugular venous blood draining from the face and passing only a few mm from the membrane within the temporal bone. Cabanac and Caputa (5) concluded that tympanic membrane temperature may be an undefinable intracranial temperature.

In a subsequent study, however, Cabanac and Caputa (6) have produced strong, though indirect, evidence that facial cooling during exercise-induced hyperthermia results in brain cooling. Part of their evidence is that, whereas under normothermic conditions peripheral vasomotor tone and heart rate correlate fairly well with both deep esophageal and tympanic membrane temperatures, during exercise-induced hyperthermia with facial cooling when tympanic membrane temperature falls below that of the deep esophagus, peripheral vasomotor tone and heart rate then correlate only with tympanic membrane temperature. This interpretation is consistent with the view that in humans the core temperature is sensed predominantly in the hypothalamic region of the brain and that heart rate is a function of the regulated core temperature.

These findings do not constitute definite evidence that facial cooling during hyperthermia results in local brain cooling. However, the possibility clearly exists and cannot be ignored. The extent of the lowering of brain temperature relative to the general core temperature may not be as great as that of tympanic membrane temperature, which can be on the order of 1°C, but even if the difference between esophageal and brain temperature is only half that between esophageal and tympanic membrane temperature this would still represent a significant widening of the gap between the effective core temperature for hyperthermic treatment of cancer and the maximum safe elevation of core temperature.

The suggestion that facial cooling may make whole-body hyperthermia a safer clinical procedure rests on the premise that the tolerable limit to whole-body hyperthermia is fixed by the thermal effects on the central nervous system. Opinions differ about this, but the residual damage caused by excessive but nonfatal hyperthermia is almost always limited to the central nervous system. The purpose of this discussion, however, is not to argue the correctness of this thesis that facial cooling may render whole-body hyperthermia safer, but simply to point out the possibility and to suggest that the proposition may be worthy of further investigation.

The Induction of Therapeutic Hyperthermia

Fever induced by the injection of the lipopolysaccharide extract of a fever-producing organism has been used in cancer treatment with apparent success (21). Such pyrogenic extracts of microorganisms are obviously preferable to the use of live or even dead bacteria. However, even these extracts are general cellular toxins rather than specific pyrogens. Thus, there are many other effects on the systems of the body, the consequences of which will depend upon the amount administered and the condition of the subject. In addition to these unwanted and unpleasant side effects, Dickson (12) has pointed out that the fever thus produced can be unpredictable in occurrence, degree, and duration. This may be partly because these bacterial preparations have not been standardized for potency as pyrogenic agents but also because the response to a bacterial pyrogen rapidly diminishes with repeated application. So far as is known, the response to all bacterial pyrogens may depend on whether the recipient has suffered recently from a fever due to an infection.

The fever itself, whether induced deliberately by the injection of a pyrogenic bacterial extract or occurring in the course of an infection, is probably not harmful (19) and is only rarely the cause of fatal damage to the organism. This is because fevers produced by live or dead organisms or by pyrogenic extracts from organisms seldom rise above 41.3°C (13) which, as we have already seen, is a degree of hyperthermia which the body can well tolerate. This limit to infectious hyperthermia is still not understood. Indeed, it is almost a forgotten clinical phenomenon because the fever pattern is now almost invariably attenuated by antibacterial and antipyretic drugs. However, DuBois's (13) statement that fevers seldom exceed 41.3°C is wholly consistent with the temperature records of Wunderlich (30), who was one of the first clinicians to make systematic use of the clinical thermometer and the chart at the end of the bed. The highest levels to which the body temperatures of his patients rose in the course of various infectious illnesses were remarkably constant at about 41–41.5°C, although the durations and patterns varied with the type of infection. Wunderlich was able to use these variations as aids in both diagnosis and prognosis.

During fever, body temperature is raised by the combined effects of an increase in heat production by shivering and a decrease in heat loss by peripheral vasoconstriction and the nonoccurrence of sweating. There is one distinct advantage in raising body temperature by means of an induced fever: the subject does not oppose the rise in body temperature either physiologically or behaviorally. Indeed, if conscious, he actively collaborates by demanding additional warmth during the rising phase of fever. This is because in the fevered state the thermoregulatory functions are as if the body is hypothermic and
needs to store heat in order to reach the regulated level. In other words, the condition of fever is exactly as if the set point of thermoregulation has been raised. This advantage, however, is offset by the quite serious disadvantages discussed earlier: the uncertainty of the occurrence or extent of the fever response to a bacterial endotoxin; the general toxicity of such injectates; and the limit to the maximum rise in body temperature which can be caused in this way.

Despite earlier reports of the clinical success of fever in bringing about the regression of cancer growths, other studies cited above indicate that an elevation of body temperature to 41–41.5°C is insufficient to be effective against cancer cells and may, indeed, precipitate their dissemination.

From this brief summary, it might seem that pyrogen-induced hyperthermia is unsatisfactory for the treatment of cancer. However, it is noteworthy that knowledge of the sequence of the chemical processes by which fever results from an infection is growing rapidly (16), and it is at least conceivable that the present assessment of the value of pyrogen-induced hyperthermia may become invalid.

There is a delay of 1 hr or so between the injection of a bacterial pyrogen and the onset of fever, which suggests that the action of the pyrogen on thermoregulation is indirect. Indeed, the bacterial endopyrogen has been shown to act on reticuloendothelial cells, especially the leukocytes, causing the production and liberation of a proteinaceous endogenous pyrogen. This substance can be produced in vitro by incubating leukocytes together with an inoculation of a bacterial endopyrogen. When the leukocytic pyrogen is injected into a mammal, there is then an almost immediate onset of fever, and with successive injections on succeeding days there is no attenuation of the fever. This lack of attenuation with repetition, together with the probability that it is not a general and potent cellular toxin like the bacterial endopyrogen, may render a leukocytic pyrogen a more suitable agent for the therapeutic or experimental induction of fever. However, leukocytic pyrogen has not been produced in sufficient quantity for clinical use, so its efficacy remains undetermined.

Whether the endogenous leukocytic pyrogen has a direct effect on central processes of thermoregulation is uncertain. The fevers induced by both bacterial and leukocytic pyrogens can be reversed or largely prevented by antipyretic agents such as aspirin and indomethacin. These drugs prevent the breakdown of arachidonic acid into several substances including thromboxanes, which are involved in blood clotting, and prostaglandins, which are apparently involved in many modulatory functions in the body. The prostaglandins of the E series are pyrogenic, and this action is unaffected by aspirin-like drugs, which indicates that the antipyretic action of aspirin-like drugs occurs by the prevention of the conversion of arachidonic acid into its derivatives.

Thus, it has been supposed that an endogenously produced prostaglandin is the terminal pyrogen which acts directly on the thermoregulatory structures in the brain, that this is formed from arachidonic acid under the influence of the endogenous (leukocytic) pyrogen, and that this is formed and produced in response to the presence of a bacterial endotoxin. This is probably not the whole story since drugs which block the pyrogenic action of prostaglandin E do not prevent the fever caused by a bacterial or a leukocytic pyrogen, although aspirin-like drugs do modify the response. This indicates that more than one of the products of arachidonic acid is pyrogenic, and recent studies have confirmed this suspicion (10).

Whether the use of any of these substances, which are linked in the chain of events by which an invading microorganism causes fever, will change the assessment of the use of fever in hyperthermic therapy remains to be investigated. In particular, it is necessary to know whether substances such as E-series prostaglandins have appreciably fewer and less harmful side effects than those of a bacterial pyrogen and whether there is the same limitation to the height of the fever which can be induced. Thus, while at present there is no reason to suppose that pyrogen-produced hyperthermia is a commendable and effective way of inducing therapeutic hyperthermia, there is the possibility that this judgment will need to be revised as the chemistry of fever becomes better understood.

Other Chemical Means of Changing Body Temperature. So far as is known, no substances other than those involved in the natural processes of fever act precisely as if to raise the set point of thermoregulation. However, a great many studies have been made in recent years on the modifying effects on thermoregulation of putative transmitter substances and other synaptically active substances when injected into or close to the hypothalamic structures concerned in homeostasis (3, 4, 15, 16). These studies are not only yielding tentative knowledge of the neural processes by which thermoregulation is effected, but are also suggesting pharmacological means by which the balance between heat production and heat loss can be temporarily disturbed, such that upward or downward shifts in body temperature can be engineered. Since in these studies the application of the substances is almost invariably central, there are no immediate prospects of clinical application of this new knowledge to cancer treatment. Some of these substances, however, may still exert their effects on the central regulation of body temperature when injected extracranially without introducing additional and interfering extracranial actions. Future research may, therefore, result in a satisfactory means of shifting body temperature pharmacologically.

Physical Means of Causing Hyperthermia. There is no means of increasing the rate of heat production without the use of pharmacological agents or pyrogens, except by the performance of a high level of work, as on an exercise machine. While this may be feasible in some cases, it is obviously unsuitable as a general technique in the induction of therapeutic hyperthermia. The only other way of raising body temperature by purely physical means is to cause heat to flow down a thermal gradient into the body or otherwise to inject energy into the body, as by nonionized radiation techniques. At the same time, heat loss from the body down a thermal gradient or by the evaporation of fluid from its external surfaces or the respiratory tract must be prevented.

In conscious and undrugged man, any attempt to induce heat storage will be countered by the activation of the sweat glands, and if the sweat can freely evaporate any substantial change in body temperature becomes virtually impossible. Thus, we are concerned with 2 problems: how best to transfer heat from the environment to the body; and how best to prevent evaporative heat loss from the body.

There would seem to be little doubt that the simplest means of achieving both maximum heat transfer into the body and minimum transfer of heat out of the body by evaporation is to immerse the anesthetized subject in water at the highest tem-
perature that can be tolerated without damage to the skin (45°C). In this circumstance, the rate of rise of body temperature would be determined by the sum of heat production and heat transfer. When causing hyperthermia with this technique, as with any other, there is the need to be able to exert a fine control on core temperature once it has been raised to the predetermined level. The hot water bath must, therefore, be suitably plumbed so that the water temperature can be rapidly changed to and accurately maintained at whatever temperature is necessary to maintain a stable elevated core temperature.

Other techniques, such as the use of a high-temperature/high-humidity chamber in which the whole subject is placed or a cabinet which does not encase the head, will be less effective than a water bath in effecting the rise in body temperature but may be more readily varied to maintain the stability of the raised body temperature. Variation in the humidity of the heated air will be sufficient to achieve this if sweating is not prevented by an anesthetic agent or other drug, but in almost all cases where whole-body hyperthermia is used in the treatment of cancer the patient will be anesthetized. Apart from the avoidance of additional discomfort and distress, a possibly important aspect of anesthesia is that it largely eliminates any physiological counter to hyperthermia. The reduction or absence of sweating may thus be a factor in the selection of heat treatment. A possibly efficient and effective means of inducing hyperthermia has emerged from studies of the treatment of accidental hypothermia. Shanks and Sara (27) suggested that breathing heated and humidified air might be a way to add heat to the thoracic viscera. The basis for expecting a high rate of heat transfer to the body from heated and humidified inhaled air is the large surface area of the alveoli. Since the inhalation of very hot or very cold air does not cause tissue damage at the level of the alveoli, while much other evidence indicates that inhaled air is brought to core temperature and becomes fully humidified high in the respiratory tract, the extent to which heat is transferred into the body at the alveolar level may be doubted. However, Shanks (26) has given evidence of the efficacy of this technique. He raised the body temperature of a hypothermic patient from 26 to 36°C in 12 hr. The average rate of increase in core temperature was thus 0.83°C hr⁻¹. The heating and humidification of the air inhaled by an intubated anesthetized subject might thus be used as the principal or the auxiliary means of raising body temperature to the normal level.

Whether, during such treatment, esophageal temperature would remain a valid index of general core temperature would have to be investigated, as would the efficacy of concurrent facial cooling as a means of restraining the rise in brain temperature to increase the safety of the procedure.

Conclusions

Individual tissues of the intact mammal can be raised to 45°C for periods of hr without causing irreparable damage to the particular tissue or to the whole animal. Mammals are, however, less tolerant of whole-body heating, apparently because of disturbances to the processes of interaction between cells. Thus, the body temperature of humans cannot be allowed to rise above 43°C, even for 1 to 2 hr, without fatal consequences. The extent of the hyperthermia necessary to destroy cancer cells is not firmly established, but it appears to be below that which destroys healthy cells. Available evidence indicates that a temperature of not less than 42°C for several hr is required for successful treatment and that a lesser degree of heating may facilitate dissemination of the cancerous cells rather than induce regression of the tumor.

It thus seems that local hyperthermic treatment of the structure containing a tumor is technically preferable to whole-body hyperthermia because of the greater safety margin between the temperature which is effective and that which causes general and irreversible damage to normal tissues. In whole-body hyperthermia, the safety margin between the temperature necessary for effective treatment and that which damages the integrity of the organism is very slender indeed. Whenever there is the possibility of undetected or widely disseminated secondary growths, however, whole-body heating may still be considered a necessary procedure despite the technical difficulties of achieving the fine control of body temperature which is essential if the risk of hyperthermic trauma is to be avoided. The problem, then, is how to maintain core temperature at a stable level nearer to 42 than 43°C for several hr.

Rectal temperature is an unreliable index of core temperature in such an endeavor because of the thermal inertia of the rectum. Deep esophageal temperature is a good measure of the temperature of the arterial blood leaving the left side of the heart. The temperature of the blood as it leaves the heart is a rapidly responding index of changes in the balance between heat production and heat loss and, therefore, of body temperature. Thus, it is concluded that, during hyperthermic treatment, deep esophageal temperature should be monitored continuously and used as the controlled quantity.

Fever is the classical means of raising core temperature therapeutically and has been reported to have resulted in the regression of cancer growths. The limitation to the level of core temperature which occurs during fever (about 41.5°C), together with the general toxicity of bacterial pyrogens, indicates, however, that this means of inducing hyperthermia is unlikely to be satisfactory. On the other hand, from recent research into the chemical sequence by which microorganisms cause fever it would seem possible that some of these intermediary substances may prove satisfactory as inducers of therapeutic hyperthermia.

Other means of raising body temperature are essentially physical and consist of changes in the environment whereby heat loss from the body is largely prevented and heat flows into or is otherwise injected into the body from the environment. The simplest and most rapid means of raising body temperature is to immerse the whole body in the water at 44–45°C. In this way, the heat flow into the body is maximized while evaporative heat loss from the body is largely eliminated. A general environment of heated and humidified air will also eliminate heat loss; heat is thus stored in the body and core temperature will rise at a rate determined by that of heat storage. The heat flow into the body, however, will be negligible.

Once the predetermined level of hyperthermia has been achieved, there must be sufficient control of the ambient conditions to hold deep esophageal temperature steady for the required length of time. This may be more readily achievable with an environment of heated and humidified air than with a water bath, but in neither case is the engineering particularly difficult.

Since the patients will probably be anesthetized for hyper-
thermic treatment, the use of heated and humidified air in the anesthetic machine may greatly facilitate both the elevation of core temperature and its control at the required level of displacement.

Recent evidence from studies on humans during exercise-induced hyperthermia indicates that local facial cooling during hyperthermia may bring about local brain cooling. If this is so, local facial cooling during therapeutic hyperthermia may increase the safety of the treatment.

References

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