Pathological Effects of Hyperthermia in Normal Tissues

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Abstract

This is a brief review of the major pathological alterations produced by hyperthermia in normal tissues of humans and other mammals. Whole-body hyperthermia, spontaneous or artificially induced, can produce severe lesions that have been best described in humans: necroses, of fatal cases of heatstroke or of individuals treated in the 1940s by hyperpyrexia, have demonstrated important lesions in the central nervous system, liver, kidney, heart, adrenal, testis, and bone marrow. All cases have shown hemorrhagic diathesis affecting many tissues, and in some the hemorrhages may have directly contributed to death.

The information on the pathology of localized hyperthermia comes mainly from experimental studies in mammals. Pathology descriptions are available mainly for skin, mesenchymal tissues (skeletal muscle and adipose tissue), liver, small intestine, brain, kidney, urinary bladder, prostate, and cartilage. In several of these tissues, however, the morphological data are incomplete, and very few have sequential observations. Thus, the ultimate (delayed) result of the acute lesions of focal hyperthermia is unknown for most tissues.

Clearly, more information is needed in order to define the range of safety for clinical hyperthermia.

Introduction

Unquestionably, hyperthermia has an important role in cancer therapy today. Also, unquestionably, hyperthermia can affect the normal tissues adjacent to the treated tumor or, in the case of TBH, many normal tissues. Therefore, to apply this modality judiciously one must know, and weigh, these possible deleterious effects.

In this article I describe the pathological effects of both whole-body (systemic), and localized hyperthermia on tissues of several mammals, including humans. The scope of this publication does not allow an extensive review of "thermal pathology." Therefore, I limit it to outlines of the morphological findings in selected tissues. The descriptions of organs and tissues are organized not along conventional organ systems but according to the quantity of pathology data available (Tables 1 and 2).

Whole-Body Hyperthermia

This was the initial form of therapeutic hyperthermia. It was based on reports of spontaneous cures of tumors following high (erysipelas-associated) fever, in the mid-19th century. Clinical TBH is used nowadays only in carefully controlled trials at a few institutions (8, 43). In such clinical trials, fluid loss, hemodynamic alterations, serum enzyme abnormalities, and symptoms of variable severity have been described (7, 44) [see also article by L. H. Cronau in this issue (11)]. It appears that, by the current methods used for TBH, fatalities directly attributed to the hyperthermia are rare; autopsy descriptions are rather difficult to find.

What we know about the pathology of systemic hyperthermia comes mostly from observations made in fatal cases of heatstroke (30, 36), or from deaths in patients treated by "hyperpyrexia" for conditions other than cancer (23) (see Table 1). These 2 situations are somewhat different from current TBH (because of the methodology, intensive care, and careful monitoring in TBH), but the pathology of the fatal cases is probably comparable and, at the present, is the best material available. One of the most informative morphological studies was made during the 1940s in patients subjected to "systemic hyperpyrexia." In their publication, Gore and Isaacson (23) described meticulously the findings in 17 necropsies of individuals who died of TBH induced (by the Kettering cabinet, by i.v. injection of typhoid vaccine, by hot baths, etc.) in an attempt to treat gonorrhea, nonsuppurative arthritis, etc. The temperatures (p.o. or rectal) reached were 40.5-43°C, and the duration of hyperthermia was 3 to 11 hr (23).

Unfortunately, the total number (the denominator) of patients treated by such a method was not stated, and probably was not available to the authors. Thus, although stated as low (23), one cannot decide from their paper the incidence of complications or fatalities of that unusual treatment.

One other thorough and extensive clinicopathological study was made by Malamud et al. (36) on fatal cases of heatstroke. These pathologists described the findings in 125 necropsies of United States Army personnel who died between 1941 and 1944. In their series, the p.o. or rectal temperatures registered at admission to hospitals were 38-44°C; in 107 of these patients the temperature range was 41.5-44°C (36). In 70% of these cases death occurred in less than 24 hr, and in the rest between 1 and 12 days from initiation of illness (36).

The following is a description of the alterations observed in the most affected organs or tissues (in order of severity), following spontaneous (30, 36) or induced hyperthermia.

Liver

The most severe and consistent injuries observed in the Gore and Isaacson (23) series occurred in the liver: initially there was vacuolization of hepatocytes (8 to 16 hr after the end of therapy); then progressive necrosis of cells in the center of the lobules occurred, reaching a maximum ("60% of the central part of the lobule") by 60 hr. At 7 days necrotic debris was removed by macrophages. Regeneration from peripheral hepatocytes, and proliferation of bile ducts was active in those who died late;
fibrosis, however, was not seen in the longest (14 days) survivor. Jaundice (interpreted as a sign of liver failure) was observed in all patients surviving more than 49 hr (23).

Similar but less striking liver alterations were described by Malamud et al. (36). Additional information comes from Kew et al. (30), who studied 18 liver biopsies and 8 necropsies from 39 Bantu miners afflicted by heatstroke. The biopsies showed usually mild lesions; 6 of the necropsies revealed structural alterations similar to those described above. Portal inflammatory infiltrate and fatty changes were also noted (30).

Pettigrew et al. (44) have described alterations of serum liver function tests in patients subjected to TBH by the paraffin bath method: patients who reached temperatures of 41.8–42.2° showed elevation of lactic dehydrogenase (2-fold), aspartate aminotransferase (25-fold), alanine aminotransferase (8-fold), and bilirubin (modest, to 1.56 mg/dl) (44). Higher levels of bilirubin have been reported by Wills et al. (54), up to 18.5 mg/dl 5 days after treatment of 42° for 8 hr. In vitro studies have indicated that increase in ammonia production by liver tissue (accumulation in the medium) is a sensitive indicator of hyperthermic injury and becomes detectable at 42° (9).

Central Nervous System

The entire brain was available for study in one-third of the cases of Malamud et al. (36). It showed strikingly severe lesions: congestion, edema (with increase in weight by several hundred g), extensive neuronal loss, and gliosis. The authors considered the neuronal damage to be a direct heat effect and the congestion and edema to be secondary to shock. Multiple hemorrhages, in the cerebral parenchyma and meninges, were interpreted as the neuronal damage to be a direct heat effect and the congestion and edema to be secondary to shock. Multiple hemorrhages, in the cerebral parenchyma and meninges, were interpreted as secondary to thrombocytopenia (36).

Almost identical lesions were noted in the Gore and Isaacson description of 16 brains (23). They observed the most severe alterations in the cerebellum, often with complete loss or damage of Purkinje cells (23).

Kidney

Renal lesions of variable severity were seen in 9 of 17 patients who died following therapeutic hyperpyrexia (23). Three of these patients, who survived 4, 7, and 14 days, died of renal failure. The lesions observed were progressive necrosis of tubular cells, edema and lymphocytic, rather than granulocytic, infiltrate (23).

Following heatstroke, renal lesions are also frequent and important. These consist of edema and congestion, and tubular necrosis (36). Of the 125 fatal cases reviewed in 1946, 19 had enough tubular damage to be classified as "lower nephron nephrosis," the old term used to describe acute tubular necrosis. The incidence of tubular necrosis increased with time of survival in these series (36).

Heart

The most conspicuous lesions in spontaneous (36) or induced (23) hyperthermia have been hemorrhages: subependimal, intramuscular, subendocardial, or even intravalvular. Some hemorrhages are massive (36), enough to produce ventricular failure. Various degrees of individual myocytolysis and myocyte necrosis have been described, from mild to extensive, but generally focal (23, 36). Fragmentation and fatty degeneration of myocytes have been observed (36).

Adrenal

Both heatstroke and induced hyperthermia produce adrenal lesions, limited to the cortex. Pericortical hemorrhage is common (36), but intraparenchymal hemorrhage is rare. Separation of cortical cells (artefactual?) from their basement membrane and from each other results in a tubular-like arrangement (23, 36). Focal necrosis is variable (23, 36). Gore and Isaacson (23) describe an early coalescence of lipid droplets in the zona fasciculata which results in large irregular vacuoles as early as 3 hr after heat induction.

Interestingly enough, no alterations of other endocrine organs are described in whole-body hyperthermia.

Testis

As expected, the seminiferous tubules are affected, although only in patients dying after 8 hr of induction of hyperthermia (23). The lesions consist of severe decrease in spermatogenesis, with formation of multinucleated cells in the germinal layers, which desquamate into the lumen. Later there is loss of germinal cells. Interstitial cells are not affected and there is no inflammatory exudate (23). These changes are similar to those seen after radiation (17), or in starvation, or in deficiencies of vitamins A or E (23).

Bone Marrow

Malamud et al. (36) studied 15 samples from their fatal cases of heatstroke. Depletion of granulocytes and erythrocytic precursors was present in patients surviving 35 hr or longer, but only in one was there significant hypocellularity. The most consistent changes occurred in megakaryocytes: karyopyknosis, karyorrhexis, loss of nuclei, and reduction in number of megakaryocytes (in one-half of the cases). In 3 cases there was evidence of regeneration, with many megakaryoblasts (36).

These megakaryocyte alterations do not appear to be artificial and were not seen in appropriate controls, including cases of anoxia (36). Furthermore, thrombocytopenia was present in the majority of the patients having platelet counts (36), and it is known to occur in induced hyperthermia (23).

Thrombocytopenia, therefore, could be explained by what may be a selective effect of hyperthermia on megakaryocytes. This, however, does not explain the severe and widespread hemorrhages seen on multiple sites in fatal cases; the recorded platelet counts were not below 22,000/ml and most were above 40,000/ml (36). Such levels ordinarily do not lead to hemorrhagic diathesis, unless other factors contribute to it. Such factors may include deficiencies in soluble coagulation factors, especially if...
there is severe liver injury. An important mechanism of hemorrhage may be injury to capillary endothelial cells by heat. Evidence for thermal sensitivity of endothelial cells has been found recently in our laboratory.4

Other Tissues

The striking alteration common to most organs and tissues, including serosal membranes, skin and mucosae, both in spontaneous (36) and induced (23) hyperthermia, is hemorrhage. The importance of this finding has been discussed for the individual organs, and its possible mechanisms have been mentioned under "Bone Marrow."

Localized Hyperthermia

On the basis of human and experimental observations, one would expect that local hyperthermia at 40–50°/30 min would cause major injury in skin (42, 52), mesenchymal tissues (40), liver (23), intestine (28), testis (23), and tissues of the embryo. In addition, important lesions may occur in tissues (organs) such as kidney (36), endocrine glands (especially adrenal) (23, 36), lymphopoietic organs, and various structures of the eye. The central nervous system and the bone marrow, which are affected in systemic hyperpyrexia (see above), are less likely to suffer from local hyperthermia because of the poor heat conductivity of bone, unless the hyperthermia is designed to treat precisely such organs (see "Central Nervous System" below). The heart, major blood vessels, and lung would be least affected by local hyperthermia because of very effective heat dissipation by convection.

Clearly, there is a need to study systematically the effects of therapeutic hyperthermia in many of the tissues mentioned above (and in others not mentioned), as well as in normal cell lines. Radiobiologists have already begun this task. The thermal sensitivity and (conversely), the induced thermotolerance of several normal cell lines is already known (21).

The scope of this publication does not allow an extensive review of "thermal pathology." Therefore, I limit it to brief descriptions of the morphological findings in selected tissues (see Table 2). Some descriptions are based on studies performed in our institution (38, 40).4,6 Many have been obtained from data of other investigators. Notice that most morphological observations of the effects of localized hyperthermia have been made in mammalian species other than humans. In some instances, only gross pathology is available, and sequential observations are lacking for most tissues.

Skin

Although the skin has been perhaps the normal tissue most often studied in therapeutic hyperthermia (there are many more publications than those listed here), relatively few clinical or experimental protocols have included detailed morphological descriptions.

The careful sequential observations by Moritz and Henriquez (41) in 1947, on porcine and human skin, were aimed at studying the effects of burns, and therefore included a range of temperatures (44–52°) and exposure times (e.g., 6 hr) not used in therapeutic hyperthermia. They devised a grading system (hyperemia, focal necrosis, and complete epidermal necrosis) based on gross changes (41). They found similarities in the responses of human and pig skin: complete epidermal necrosis occurred in both at 45° for 180 min, but times were different for higher or lower temperatures (e.g., 30 versus 45 min, respectively, at 47°) (24, 41).

One of the few studies including systematic histological examination of the skin was performed by Thomsen et al. in swine (48). These authors compared the lesions produced by electricity (59 to 100,000 Hz) with those produced by heat, in sequential biopsies. They noted detachment of epidermis after heat, but not after electrical injury, with fibrillary or granular cytoplasm in the necrotic epidermocytes. Thomsen et al. (48) were successful in distinguishing thermal burns from electric lesions (their aim was to diagnose the effects of electrical torture), but unfortunately their findings are difficult to apply to the different levels of heat used in clinical hyperthermia.

The skin of mice appears to be more thermosensitive than human or porcine skin; in the latter, 45° for 1 hr does not seem to cause permanent damage (24, 41). The mouse ear has been used to quantitate thermal skin response (19, 31). From various experiments it appears that injury occurs after treatment at 44° for 1 hr, or higher. Complete epidermal necrosis is seen in all animals with doses of 45.5° for 45 min, and this occurs in 4 days (19, 24). These lesions appear earlier than those produced by X-radiation (e.g., 3000 rads) (19). Recovery from this thermal necrosis is slow or may not occur. Below 44° for 1 hr, lesions are mild (mostly hyperemia), and recovery is usually complete within 2 weeks. These time-dose data generally agree with the observations of Okumura and Reinhold (42). Anderson et al. (1) have shown that the mouse ear lesions can be potentiated by exposure of the animals to ethanol.

A popular method for the study of hyperthermic injury has been the immersion of a mouse foot in a water bath (52). The subsequent "foot reaction" has been quantitated by a scoring system of gross changes that include edema, epilation, wet desquamation, and may be as severe as complete loss of the foot (52). This foot reaction includes, of course, damage to several tissues aside from skin, and hopefully it has been interpreted as such (49–51).

The mouse foot reaction has been quite useful in several respects. Urano et al. (51) have used it to demonstrate enhancement of the hyperthermia effect: Corynebacterium parvum given to the animals several days before hyperthermia enhanced the effect of heat in tumors and, to a lesser degree, in the normal tissues. Glucose (i.p.) also enhanced the tumor response and produced a lesser enhancement in the foot (50). The phenomenon of "step-down heating" (sensitization to low-temperature heat by a prior shock of high temperature) was shown to occur

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4 L. F. Fajardo, A. Schreiber, N. Kelly and G. M. Hahn, unpublished observations.
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in the mouse foot as well as in a transplanted tumor (49). There was no therapeutic advantage in this model (49).

The enhancement effect (TER) of hyperthermia on the effect of ionizing radiation has been studied in skin, as well as in other tissues. One of such studies (with ultrasound-induced hyperthermia and X-radiation), performed by Baker et al. (2), has shown that the TER was independent of the sequence of the 2 treatments for intervals up to 1 hr in rodent skin.

Recently, a modified Fowler scale has been used to quantitate the gross skin reaction in 80 patients treated by radiation (3395 rads, mean total dose) and microwave hyperthermia (mean value, 42.3°) (33): 17% of patients developed only desquamation; erythema occurred in 24%; blisters occurred in 7%; and ulceration occurred in 18% (33).

Perhaps the thermal sensitivity of skin is only of minor importance in clinical hyperthermia, especially when using electromagnetic sources; the skin can be effectively cooled during therapy, sparing it from any thermal damage (38, 40).

Soft Tissues

Localized radio frequency-induced hyperthermia for superficial or deep-seated tumors often requires deposition of energy in skin or in mesenchymal tissues. Damage to skin can be minimized by cooling of the electrodes (38). The mesenchymal (soft) tissues, such as skeletal muscle and adipose tissue, cannot be effectively cooled by external means. The adipose tissue has a relatively high electrical resistivity which causes greater power absorption from radio frequency sources. The muscle has greater electrical conductivity and will absorb energy from microwave heating sources. Because of its low blood perfusion rate, adipose tissue removes heat poorly. Additionally, the fat-muscle interface causes wave reflections leading to high-energy absorption in the adipose tissue at some frequency ranges.

All of the above, and other considerations (38), indicate that damage to adipose tissue and skeletal muscle may be a limiting factor in hyperthermia.

A systematic study of thermal injury has been performed in the superficial skeletal muscle and adipose tissue of swine (38, 40). Hyperthermia was induced by radio frequency currents passed through electrodes placed symmetrically on the skin of opposite sites of the flanks of pigs. Water circulating through the hollow electrodes cooled the skin. Fifteen sites were sham treated (controls), while in 102 sites the temperature was increased, during 30 min, to levels of 40–48° (40). Some sites were subjected to 43° for 30 min, 4 hr before the final, preselected treatment, testing for thermotolerance (40). Large samples of the adipose and muscle layers were obtained 18 to 24 hr later in some sites, and 28 to 31 days later in other sites (40). The lesions were examined histologically, using a specially developed scoring system (40).

The early (acute) samples revealed edema, focal hemorrhage, necrosis, and granulocytic infiltrate. The latter 2 (particularly necrosis) were more severe in muscle. In general (but not in all samples), the severity of these acute lesions increased with dose, but it never reached the levels of the delayed lesions (40). Thermotolerance was not observed in these early samples (38).

The delayed samples revealed important lesions: chronic lymphohistiocytic infiltrate in both fat and muscle; evidence of fat necrosis, with lipophages; persistent muscle necrosis and foci of muscle regeneration; abscesses (only at highest temperatures) in the deep muscle layers; and fibrosis. The latter lesion was by far the most important in severity (extent) and affected especially the adipose tissue; thick bands of collagen and fibroblasts replaced and deformed many of the normal adipocyte lobules (40). There was a clear dose response in these delayed lesions (38, 40). Thermotolerance was demonstrated in both adipose tissue and muscle, and it was most remarkable in the former (38); in the sites that received the initial conditioning dose, the scores were reduced by 76 to 86% at 45–48°. This induction of thermotolerance in vivo provided an overall advantage of 2° for the protection of these normal tissues (38).

Although fibrosis and possibly deep abscesses are potentially serious, chronic complications of therapeutic hyperthermia, these lesions were usually significant at 46° and above. Therefore, by extrapolation, serious fibrosis and abscesses should not be expected in treatment protocols using doses of 45° for 30 min or less. Furthermore, the demonstration of thermotolerance in vivo provides a possible therapeutic advantage.

Liver

From the data of TBH (see above), the liver appears to be at risk for significant injury from localized hyperthermia. Indeed,
lesions are consistently found, but their ultimate clinical effect may not be as important as expected.

A systematic study of liver lesions produced by localized hyperthermia has been completed recently. Using radio frequency currents, individual liver lobes in dogs were subjected to temperatures of 43–47.5° for 30 min. Several sites were heated first with a conditioning dose of 41–43° for 30 min, 4 hr before a final predetermined dose, in order to test for thermotolerance. Temperatures were measured with thermocouple sensors. Twenty-eight days later, large samples were obtained for light microscopy. The earlier stages of these lesions, however, might be better observed by electron microscopy. Wills et al. (54) have studied by electron microscopy biopsies of human liver obtained before, and within 2 days after 40–42° for 65 to 495 min. Evidence of ultrastructural damage in some hepatocytes was observed immediately after therapy (when no histological lesions were evident), and became progressively worse. By 2 days, there were numerous autophagic vacuoles, dilatation of Golgi cisternae, massive distension of rough endoplasmic reticulum, flocculent deposits in mitochondria, dilatation of bile canaliculi with loss of villi, and increase in bile granules. Most prominent were large vacuoles (as much as 12 μm in diameter) (54).

Presumably, these alterations result in necrosis of the damaged cells and extrusion from their plates in less than 4 weeks. In mice treated for tumors located in the flank by radio frequency (44° for 30 min), we have observed focal necrosis of liver, kidney, and intestine adjacent to the treated area (37).

Additionally, we have observed foci of hepatocyte necrosis in mice subjected to TBH for 1 hr (rectal temperature of 41–41.5°) within 3 hr of termination of treatment.

Long-term studies are needed to determine if these alterations will result in permanent or even progressive, physiologically important lesions, such as postnecrotic cirrhosis, with portal hypertension. Hopefully, fibrosis will be limited to the portion of the liver parenchyma within the area of energy deposition.

**Alimentary Tract**

Potentially all segments of the digestive tube could be damaged by therapeutic heat. Morphological studies, however, have been almost exclusively limited to the small intestine.

Indeed, the enteric mucosa appears to be rather thermosensitive (26, 28, 29). Field et al. (20) and Hume et al. (27–29) have shown a dose-dependent loss of epithelial cells in crypts and villi, following hyperthermia (by immersion) of exteriorized loops of jejunum. Following doses of 42.3–44.5° for 30 min, the lesions are apparently characterized by necrosis of epithelial cells of both villi (first) and crypts (later), with cessation of mitotic activity (28). These authors observed an all-or-none effect; either the crypts were well preserved, with dividing cells, or the crypts were totally necrotic (28). Edema was also noted, immediately after cessation of hyperthermia. Crypt loss was always more severe, and sometimes occurred only, at the wall of the intestine opposite to the mesentery. These authors have used the “crypt survival assay” devised (for radiation effect) by Withers and Elkind (55) to quantify hyperthermic injury in the small intestine (28).

More recently, experiments using incorporation of [3H]thymidine indicate that the nonproliferative epithelial enteric cells, closer to the lumen, are more sensitive to thermal injury than are the crypt cells (29).

The effects of thermal injury in the intestine have been compared with those of ionizing radiation (10, 28, 45). One study used transmission and scanning electron microscopy to show that while radiation (X-rays; 1000 rads) injures mainly the proliferative pool of crypt cells, an already well known fact, heating
Both agents produced conical villi (10). As could be suspected, hyperthermia enhances the effect of radiation on the small intestinal mucosa (20). This has been well demonstrated in the mouse by a study of Merino et al. (39). The maximum TER was quite significant, 4.7° for a dose of 44° for 30 min prior to radiation (total body single dose of 400 to 2000 rads) (39).

Thermotolerance has been demonstrated in the mouse jejunum, both by crypt-survival assay (27), and by using death (LD$_{so/7}$) as the end point (26). Heating of exteriorized enteric loops is often fatal to mice because sepsis develops, presumably due to penetration of bacteria through the denuded mucosa. The LD$_{so/7}$ is around 6 min of heating at 45° (26). This LD$_{so/7}$ is independent of the length of the intestinal loop, prior feeding of animals, and fluid replacement postheating (26). Gentamicin administration increases the LD$_{so/7}$ to more than 9 min/45° (26).

The membrane labilizer retinol did not enhance gross damage to mouse small intestine, although it did enhance lysosomal membrane permeability in the spleen, as measured by histochemistry (45). These findings were interpreted by Rogers et al. (45) as suggesting that lysosomal membrane injury is not a primary event in hyperthermic cell killing. Our morphological study of a thermosensitive mouse neoplasm supports the same view (18).

Since microwave heating is a more likely method than water bath for abdominal neoplasms in clinical hyperthermia, one should also be concerned with the possible effects of microwaves on intestinal motility. A study of the effects of low-level microwave irradiation (5 and 7.5 milliwatts/sq cm at 2.45 GHz) was made in the intestine of rats (47). Acceleration of slow waves and inhibition of action potentials were shown in this model, using chronically implanted electrodes (47).

Most experiments have ignored the possibility of delayed injury in the intestine. In one study, the rectum of rabbits was examined histologically up to 3 months following 43° for 30 min delivered by a coaxial probe (56). In these experiments the authors found no injury of the rectum in most of the animals (56).

Hahn (24) has suggested that intestinal heat lesions may be more severe when there are lumenal masses of undigested material that may overheat and do not cool effectively. If so, colonic lesions would be worse in the presence of fecal masses, and these could be ameliorated by fasting (24).

We have not seen morphological descriptions of intestinal lesions following therapeutic localized hyperthermia in humans. Considering the increasing clinical use of this modality, and the obvious sensitivity of the small intestine, we would not be surprised to find such lesions.

Central Nervous System

The possibility of treating cerebral neoplasms by local hyperthermia (either microwave or ultrasound induced) has great potential (4, 6, 34, 46). In preparation for clinical trials, studies of the thermal response of various normal brain structures have been made by several investigators (3, 25), particularly the group of Britt et al. (4, 6, 34).

Ultrasound, applied to the exposed dural surface of cats during 50 min, caused acute lesions detectable at temperatures above 42.5° (4). Such lesions were sharply demarcated and consisted of edema of the white matter, pyknosis and loss of neurons (especially at 44–45°), and destruction of myelin. Coagulative necrosis was observed at 47° (4).

Single or multiple intracerebral microwave antennas were used to generate temperatures of 40–47° during 50 to 75 min in 3 groups of dogs: normal adults, normal growing animals (5 to 6 weeks old) and dogs with SR-Rous sarcoma virus brain tumors (34). The animals were terminated at the end of the thermal exposure. As in the cats, the acute lesions consisted of edema of white matter, pyknosis of neurons, and damage of white matter tracts. Neuronolysis was seen above 43°. Necrosis and hemorrhage of tumor were noted (no control tumors were described) (34). It was concluded that the threshold of irreversible damage occurred at 42.2° for 50 to 60 min.

Earlier observations of Harris et al. (25) in regionally perfused dogs also indicated absence of lesions below 42° and significant lesions above 44°, edema, focal hemorrhage, and infarct.

A physiological study in cats subjected to TBH (5) (via cardopulmonary bypass) confirmed the above morphological observations: the critical temperature for evoked potential responses was calculated, by Arrhenius equations, to be 42.2° per 1 hr (5).

Physiological observations in humans during TBH (electroencephalogram and somatosensory-evoked responses) suggest functional impairment at 41.8–42°, which is reversible (13). There is concern about the combined effects of ionizing radiation and hyperthermia on the spinal cord (22). Sudden myelopathy occurred in 3 patients treated by spinal irradiation and TBH (12). Studies in mice suggest enhancement of the functional deficit when the 2 modalities are applied to the spinal cord within a short time interval (22).

Hopefully, brain neoplasms may respond to hyperthermia doses below the apparent threshold of 42° for 60 min.

Kidney

Because of its high blood flow rate the renal parenchyma has not been considered by some investigators as a likely site of hyperthermic injury. Some studies, however, suggest that this is not the case.

A well-described histological study in mice was published by Elkon et al. (15). After unilateral nephrectomy, the contralateral kidney was shielded from adjacent organs and heated intraoperatively by ultrasound, reaching temperatures of 40.5, 42.5, and 44.5° for 35 min, as measured by 4 thermocouples inserted in the kidney. The kidneys were systematically examined by a pathologist 1, 7, or 28 days later (15).

Sharply demarcated, subcapsular areas of necrosis occurred, involving only the tubules in minimal lesions, or tubules, glomeruli, and even vessels in large lesions. The extent of the necrosis did not increase in time (i.e., it had reached maximum by 24 hr), but segmented neutrophils were maximal at 7 days and had disappeared by 28 days. Calcium deposits increased with time. Even at 28 days, there was no collapse of the framework of the tubules, although the epithelial cells had disappeared within the first day, and fibrosis was only minimal and peripheral (15).

In kidneys heated to 40.5°, lesions did not reach 5% of a given section of the renal parenchyma; of those kidneys receiving the higher doses (42.5° and 44.5°), one-third had lesions ≥5% of the parenchyma. Based on these observations, the authors
conclude that the mean renal temperature at which necrosis developed was 43° for 20 min (15).

In a different study, exteriorized rabbit kidneys were treated by brief (15 sec) exposures to ultrasound beam of total acoustic power of 30 watts (approximately 900 watts/sq cm at center) (14). The kidneys of 45 rabbits so treated were examined 10 min to 1 year later. The progression of the sharply defined histological lesions ranged from acute injury at 10 min (lysis of erythrocytes, early necrosis of tubular cells, karyolysis, edema, etc.) to established, progressive necrosis between 1 and 10 days: tubulorrhexis, glomerular necrosis, areas of coagulation necrosis, neutrophilic infiltrate, and later calcification. Between 1 week and 1 year, there was removal of cell debris by macrophages and progressive fibrosis which eventually resulted in a scar. Apparently some tubular regeneration occurred (14). Unfortunately, no temperature measurements were obtained in the kidneys, although the authors estimate that these exposures could have resulted in temperatures of 60–70° (14). Such exposures are difficult to compare with those used in clinical hyperthermia. The histological observations, however, serve to corroborate the findings of sharply defined lesions observed later by Elkon et al. (15). Furthermore, the long sequential study indicates that ultimately fibrous scars should be expected from early lesions, quite similar to those occurring at lower temperatures (15).

Lower Urinary Tract

Damage to these structures could occur in the course of therapy, either to adjacent organs or to the urinary tract itself. In rabbits, heating of the rectum at 43° for 30 min by means of a coaxial probe did not produce gross or histological damage of the bladder examined sequentially at 16 time points, 1 day to 3 months following exposure (56).

Hyperthermia of the bladder wall can be achieved by continuous irrigation with warm fluid. Using water, Linke et al. (32) treated 20 dogs with exposures at 35–69° (measured by thermistors) during 8 min. The urine was diverted and the animals were killed 6 weeks later. Neither gross nor microscopic alterations were noted between 35 and 44.5°. Patchy destruction of the mucosa, and focal necrosis of the muscularis were seen between 46.5 and 61.5°. The muscularis lesions were often severe, of full thickness, and did not necessarily coincide with the mucosal lesions.

Complete destruction of the bladder wall occurred between 59 and 69°; by 6 weeks the bladder was replaced by a fibrous scar. Occasional thrombosis of small vessels was noted but no damage was observed in the adjacent organs (32).

Thus, it appears that, at least in dogs and rabbits, the urinary bladder can tolerate temperatures of up to 44.5° for 8 min (and perhaps longer) without significant damage.

Prostate

In 2 interesting experiments (35, 56), the thermal sensitivity of the normal prostate has been assayed histologically; by means of a coaxial probe located in the rectum, microwave hyperthermia was induced, reaching temperatures of 42.6–43° for 30 min in the prostate, as measured by thermocouples (56). The 32 rabbits thus treated were examined histologically at multiple times from 1 day to 3 months after exposure(s). Only minimal alterations of the rectum (focal karyopyknosis, edema, etc.) were observed in a few animals (56). The authors found no prostatic lesions after one or two 43°/30-min exposures (56).

The above report contrasts sharply with (but does not necessarily contradict) that of Magin et al. (35). These authors treated intrasurgically the prostate of 8 dogs with microwaves (60° for 15 to 22 min, controlled by thermistor) after shielding the rectum and some of the adjacent muscles. At the end of this severe therapy, the prostate was edematous and dark; 1 week later (4 dogs), although its volume was not decreased, there was coagulation necrosis of the entire organ with some foci of neutrophilic infiltrate and/or liquefactive necrosis. Six months later (4 dogs) there was no recognizable prostate; the organ had been replaced by a fibrous scar. Minor lesions were seen in the bladder and the vasa deferentia, but not in the (shielded) rectum (35).

These separate observations may, or may not, be pertinent to the human prostate. If applicable, they would indicate a threshold of thermal injury in the normal prostate, somewhere between 43° for 30 min and 60° for 15 min. Hopefully, carcinomas will respond at lower doses.

As indicated above, the systemic temperatures reached by these patients were not always documented, and obviously the renal temperatures were unknown (1).

Skeletal System

It is rather difficult to find studies of the osseous pathology produced by therapeutic hyperthermia. There seems to be more interest in the effects of high-speed drills and other surgical instruments.

An interesting device, designed for vital microscopic observations during local bone heating, is the “thermal chamber” (16). This titanium chamber is implanted for an indefinite time in a bone, allowing multiple observations of various in vivo responses, especially vascular, to a thermal insult. Using this device in the tibia of rabbits, Eriksson et al. (16) studied the effects of 53° for 1 min; blood flow became sluggish and stopped 2 days later. The original vessels gradually disappeared and were replaced by new ones. Adipocytes decreased in number, and bone remodeling started 3 to 5 weeks postinjury (16). Although these data are not too pertinent to clinical hyperthermia, the thermal chamber is potentially a very useful tool for the study of the effects of therapeutic heat, ionizing radiation, etc.

The effect of hyperthermia on cartilage has been measured in terms of its ability to inhibit the growth of the tail in baby rats and mice (24). The tails are partially immersed in heated water at 7 days of age. Several months later, the heated caudal vertebrae are compared radiographically with the unheated ones, and a quantitative index of stunting is obtained (24). In addition, necrosis occurs within a few days after exposures in the higher range.

From these observations, Hahn et al. (24) and Field et al. (19) have shown a dose-related stunting effect; 43° for 1 hr resulted in 10% growth inhibition, but did not cause necrosis; 44° for 1 hr caused necrosis in 50% of the animals; if the time at 44° was reduced to 50 min or less, the necrosis was prevented (24). Thus, in this system the limit of tolerance for growth inhibition is below 43° for 1 hr, and the limit of tolerance for acute damage in the various soft tissues of the tail seems to be 44° for 1 hr.
Embryo

Of great concern are the effects of temperature elevation on the embryo. Retardation of brain growth has been documented in guinea pig embryos exposed to maternal temperatures of 41.8–43.9°F for 1 hr (in an incubator) on the 21st day of gestation (53). Such exposures resulted in a dose-related microcephaly of 41.8-43.9° for 1 hr (in an incubator) on the 21st day of gestation. The experimental system showed that an elevation of 1° produced a deficit in brain weight equivalent to the effect caused by a dose increment of 42.5 rad (53). Obviously, this information refers only to maternal temperatures; the embryonal temperatures are assumed to be equal, or at least to change parallel, to the maternal ones, but this assumption may be wrong.

Other studies of the effects of systemic or local hyperthermia on the embryo are available, but their review is beyond the scope of this article. In any case, the possible teratogenic effects of hyperthermia should be considered in the therapy of abdominal neoplasms, and even in the diagnostic use of ultrasound.

References


Fig. 3. Focal loss of hepatocytes is illustrated in the midzonal area of a lobule whose thickened central vein appears in the left upper corner. Normal, continuous plates of liver cells are present in the right upper and left lower areas, while in the center the hepatocytes do not form plates but are separate from each other, due to the loss of multiple intervening liver cells. Treatments were at 43° for 30 min and 47.5° for 30 min. Gomori’s trichrome, × 176.

Fig. 4. Focal loss of liver cells is shown in the center of this photograph from a canine liver treated at 43° for 30 min and 47.5° for 30 min. In the center, and below a portal area, hepatocytes have disappeared, leaving delicate reticular-vascular framework. Compare with the normal hepatocytes plates and sinusoids in the right and left portions of the field. Neither this nor Fig. 3 show cells in the process of necrosis, such as “acidophilic bodies.” In this experiment, individual cell necrosis presumably occurred during the first weeks after hyperthermia, followed by removal of cell debris by macrophages. Gomori’s trichrome, × 320.

Fig. 5. Massive area of liver necrosis (after 41.2° for 30 min and 45.3° for 30 min), involving more than one lobule. With this stain necrotic hepatocytes are pale and devoid of nuclei, although the continuity of the plates is preserved. A large portal area, with thrombosis of the vein and artery, is present in the right upper corner. A margin of inflammatory reaction (neutrophils) is seen at the lower edge. Unlike individual cell necrosis, massive necrosis did persist to 28 days. H & E, × 100.

Fig. 6. Early scar in area of massive necrosis, after 41° for 30 min and 44.5° for 30 min. The persistent necrotic liver plates appear dark with this stain, at the bottom of the figure. Invading collagen bands occupy the top. Although the ultimate result of these areas of fibrosis is unknown, probably localized hyperthermia affecting portions of the liver will not result in significant functional impairment of this organ. Gomori’s trichrome, × 100.
Pathological Effects of Hyperthermia in Normal Tissues

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