THE PATHOLOGY OF HYPERPYREXIA
OBSERVATIONS AT AUTOPSY IN 17 CASES OF FEVER THERAPY*

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Heat in various forms is one of the oldest of therapeutic agents, although until recently it was employed only by local application.[1] Probably the first planned attempt to utilize increased body temperature as a therapeutic measure was made by Wagner von Jauregg in the malarial treatment of paresis.[2] Typhoid vaccine and other biologic substances have been used since, and various mechanical and electrical devices[3] have been constructed to serve the same purpose. Therapeutic hyperpyrexia has become an established means of treatment, not only for paresis, but for various forms of arthritis, chorea, asthma, sulfa-resistant gonorrhea, and other diseases.[4] As a consequence of its widespread adoption, numerous studies of the physiologic changes accompanying hyperpyrexia were undertaken. The results of some of these investigations are outlined briefly in the following paragraphs.

In the blood, hyperpyrexia produces leukocytosis; the red cell count and hemoglobin increase, the granulocytes exhibit a "shift to the left."[5,6] The sedimentation rate decreases,[5] and there is a reduction of the blood platelets.[7] Chemical studies show first a rise and then a fall of blood sugar.[6] Blood chlorides decline,[6] and values for nonprotein nitrogen[6] and lactic acid[8] are elevated. The plasma CO_2 content diminishes.[9,10] No changes are observed in values for calcium,[11] potassium,[11] or specific gravity.[12] Serum values for vitamin A decrease,[13] and there are conflicting reports regarding vitamin C.[14-16] Blood hormonal assays show increases of insulin, adrenalin, and of the antidiuretic hormone of the pituitary body.[17] Prothrombin[7,18] is diminished, and although there is no early change in plasma fibrinogen,[18] a late fall is observed. Miscellaneous findings include alkalinity of the urine and albuminuria[6]; both the heart and respiratory rates increase[5,19-21]; the blood pressure shows an early rise and late fall[5,19-21]; and counts of spermatozoa exhibit a reduction, lasting from 40 to 70 days.[22]

Experimentally, in rats, guinea-pigs, dogs, goats, and pigs,[23-27] the most common early changes are visceral congestion and disseminated focal hemorrhages in the internal organs; subendocardial hemorrhage is especially frequent. Dilatation of the right heart occurs and the blood is dark, fluid, and unclotted. There is pulmonary edema and

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hemorrhage. Later (12 to 24 hours), parenchymatous degeneration is apparent in the adrenal cortex, liver, and renal tubular epithelium. Occasionally, lower nephron nephrosis is observed.

It was recognized early that fever therapy is not without danger, and rigid controls were adopted both in the selection of patients and in the method of administration. The Council on Physical Therapy of the American Medical Association, by means of a questionnaire circulated in 1934, ascertained that 29 deaths had occurred following pyretotherapy.[4] Accounts of at least 20 additional fatalities have since appeared in the literature,[28-33] mostly as sporadic case reports with inadequately described pathologic findings. Doubtless, deaths from this cause are far more frequent than indicated in the literature, yet comparatively few attempts have been made to study the morphologic changes which occur in human beings. Although the incidence of fatality in large series of cases is admittedly low,[34,35] complications are not uncommon and indicate more widespread deleterious effects than are usually attributed to this form of therapy. Clinically, jaundice occurs in from 14 to 19 per cent of the patients,[36] circulatory collapse and transitory neurologic changes in a significant percentage,[37] and evanescent electrocardiographic changes are almost invariable.[38]

The meager evidence in the literature does not permit an adequate understanding of the pathologic effects of hyperpyrexia. Nonspecific changes reported by various authors in their efforts to avoid overlooking significant lesions further confuse the situation. Clarification is possible only by study of a relatively large group of cases.

The pertinent material at the Army Institute of Pathology consists of the clinical records and autopsy protocols together with fixed tissues and stained sections from 21 cases of fatal therapeutic hyperpyrexia. Four of these were not included in this study: the clinical information was inadequate in 2, and in 2 others there were intercurrent diseases which had produced significant modifications. Of the 17 remaining patients (all males, 3 colored, 14 white, with ages ranging from 18 to 35 years) 15 received this form of therapy because of sulfa-resistant gonorrheal urethritis. One patient had nonsuppurative arthritis, type unspecified (case 16), and one, gonorrheal urethritis treated in 1936 before the advent of sulfonamide medication (case 14). In only 2 cases was there evidence of sulfonamide intolerance or sensitivity (cases 5 and 8) and in each of these the drug had been discontinued 1 month prior to fever therapy and subsequent death. The interval between the induction of hyperpyrexia and death varied from 3 hours to 14 days. In 5 cases, fever therapy had to be discontinued because of the develop-

CASE AND A.I.P. ACC.	HIGHEST FEVER (F)	DURATION (HOURS)	LENGTH OF SURVIVAL	SULFA DRUGS RECEIVED	TRANSFUSION	"SHOCK" DURATION	JAUNDICE	RENAL FAILURE	NEUROLOGIC CHANGES	R B C	W B C	BLOOD SUGAR (mgm%)	NPN (mgm%)	ICTERUS INDEX	CO_2 CONTENT (VOL%)	CREATININE (mgm%)	ALB	URINE RBC	SEROUS EFFUSION	LIVER NON-FATTY VACUOLES	LIVER FATTY VACUOLES	LIVER CENTRAL NECROSIS	LIVER REGENERATION	KIDNEY PROXIMAL TUBULAR DEGENERATION	KIDNEY LOWER NEPHRON NEPHROSIS	BRAIN EDEMA	BRAIN NEURON DAMAGE	HEART FATTY DEGENERATION	HEART GRANULAR & HYALINE DEGENERATION	HEART EDEMA	TREATMENT
1 102894	106.5	3	3 HRS.	+		–			RESTLESS IRRATIONAL																						
2 99435	107.6	3	3 HRS.	+		–			RESTLESS IRRATIONAL										+											
3 93390	106	8	8 HRS.	+		–													+	+	+	+	+	+	+	+	+	+	+	+	
4 82251	106.6	8 1/2	8 1/2 HRS.	+		–													+	+		+		NOT EXAMINED							
5 225672	106.8	6	11 HRS.	+		–			STUPOROUS										+	+						+					
6 83533	106.7	11	11 HRS.						PUPILS UNEQUAL IRREGULAR REACTION										+	++			+			+					
7 93695	105	11	16 HRS.	+	PLASMA ONLY	–													+	++			++			+	++				
8 101069	106	8	16 HRS.	+		+ 1/2 HR.													+	+++	?		+			+	++		+		
9 99505	105.2	7	17 HRS.	+		+ 6 HRS.			UNRESPONSIVE PUPILS DILATED			36	100		7.1				+	++			+			++	++				
10 95801	107.8	3	20 HRS.	+		–																									
11 100659	106	7	49 HRS.	+		+ 6 HRS.										++++	++++														
12 100915	106.8	6-7	67 HRS.	+		+ 11 HRS.	+																								
13 96871	105	6 1/2	73 HRS.	+		+ ?	++					68	75		4.1																
14 51838	107	5	93 HRS.	0		+ 33 HRS.	++					186*	33		1.3	++	+														
15 89594	108	6	4 DAYS	+		+ 18 HRS.	+++	++	TREMORS OF ARM AND LEG	4.9 M	11,000 75% POLYS	95.2	154	100	29-49	3.6	+++	+++													
16 79906	109	DYSPROD VACCINE SYSTEMIC	7 DAYS	0		+ ?	+++	++		4.15 M	9,000		109	35			+++	+++													
17 30943	108	4	14 DAYS	+		+ 18 HRS.	+++	+++		5.4 M	25,000		308	90			+++	+													

* RECEIVED INTRAVENOUS GLUCOSE

TABLE I

Clinical and Pathologic Findings in 17 Cases of Hyperpyrexia

ment of such untoward symptoms as shock, coma, convulsions, or hyperexcitability. The remaining deaths occurred in cases in which symptoms developed from 2 to 36 hours following a fever treatment lasting from 3 to 11 hours. Fever had been induced by the Kettering Hypertherm Cabinet (13 cases), intravenous typhoid vaccine (3 cases), and hot baths (1 case), but the pathologic changes found at autopsy did not differ with the method of heat induction. The height of the fever and the duration of treatment are listed in Table I.

Clinical Features

All of the patients had been judged physically capable of enduring the treatment. The screening procedure included a complete physical examination, roentgenogram of the chest, blood count, chemical analysis of the blood, urinalysis, and electrocardiograms. Thirteen of the 17 patients were given a half-hour trial treatment which was well tolerated in each instance.

During the course of fever therapy all patients showed an increase in the pulse rate (110 to 160 per minute) and in the respiratory rate (32 to 46 per minute). Respirations were shallow, and slight to marked cyanosis was observed. The blood pressures fell somewhat following an initial transitory rise. Most patients vomited watery material one or more times. In 5 cases it was necessary to discontinue therapy because of the advent of coma, convulsions, circulatory collapse, or irrationality.

Circulatory collapse occurred in 9 cases. In 3, shock did not supervene until 2 to 36 hours had elapsed following completion of pyretotherapy. Clinical symptoms of pulmonary edema were present in 6 cases and of cerebral edema in 1 case (case 7).

Icterus occurred uniformly in all patients surviving longer than 49 hours. In the 3 who survived 4, 7, and 14 days, respectively, urinary suppression, hypertension, azotemia, and other clinical features of renal failure appeared before death.

Laboratory Studies

Laboratory studies were recorded in only a few cases. The results are presented in Table I.

Morphologic Observations

The initial effects of hyperpyrexia are clearly metabolic and after early death there is little that can be seen in the tissues. With time, however, progressive morphologic changes occur which give evidence of relatively irreversible functional injury to the cells.

General

Perhaps the most common feature at autopsy was the presence of moderate to marked congestion of all viscera and the brain. Congestion was present grossly in 15 cases and microscopically in all. It was most pronounced in the early cases (3 to 10 hours post-hyperpyrexia), being described by the prosectors as "marked" or "extreme," and diminished with time, so that in the cases in which survival exceeded 3 days, congestion was "slight" on gross examination or evident only microscopically.

Hemorrhages constituted another striking feature at autopsy and were present in all but 2 of the cases (Figs. 9 and 10). Their approximate incidence in various locations is shown in Table II.

TABLE II

The Incidence of Hemorrhage in 17 Fatal Cases of Induced Hyperpyrexia

Heart	17	*Gastro-intestinal tract*	7
Subepicardial	10	Esophagus	2
Subendocardial	5	Stomach	3
Myocardial	2	Duodenum	2
Brain	4	*Kidney pelvis*	4
Pleura	3	*Miscellaneous* (Skin, mucous membranes of mouth, sclera, mesentery, perirenal fat)	5

The hemorrhages, for the most part, were petechial, but in 2 cases they were ecchymotic, and in one the hemorrhagic areas in the skin measured as much as 5 cm. The frequency with which the heart was involved is corroborated by the experience of others.[32,39] One author[32] postulated that death in many of these cases was due to destruction of the conducting system of the heart by hemorrhage, a thesis which receives no support from our observations.

Transudates into one or more serous cavities occurred in 5 cases, in 4 of which survival exceeded 3 days. Pleural effusions of yellow serous fluid occurred in all 5; they were more voluminous on the right side and ranged from 150 to 1200 cc. Ascites amounting to 2200 cc. occurred in case 17; the patient had survived hyperpyrexia for 14 days. Pitting edema of the legs was present in 2 patients (cases 15 and 17), both of whom had shown clinical evidence of renal failure. Excess pericardial fluid was not observed in any case.

Jaundice was evident invariably in patients (cases 12 to 17) surviving longer than 49 hours. Its occurrence was directly related to the extent of liver damage and will be discussed when the pathologic changes of that organ are described.

Intravascular thrombosis, reported by others,[39] was not observed. On

the contrary, in 3 instances the prosector commented on the persistent fluidity of the blood and the almost complete absence of clotting.

Marked sicklemia occurred in 2 (cases 1 and 10) of the 3 Negro patients in this series. Neither patient had anemia or a clinical history suggestive of the sickle cell trait.

Liver

The hepatic changes were the most striking of those observed. Their relation to the length of survival substantiates the assumption that the effects of hyperpyrexia are essentially physiologic and metabolic initially, and that it is only with time that morphologic alterations occur.

The livers in early cases were described as normal or congested, but in cases in which survival was as long as 8 hours post-pyretotherapy, the prosectors noticed "mottling" of the parenchyma with pale pink or gray areas. The size of the "mottled" areas increased with survival time; simultaneously the organ became less firm. The average weight of the liver when death occurred rapidly was 1850 gm. When the patient had survived 72 hours or longer, the liver was grossly enlarged (average weight, 1975 gm.), extremely soft, and uniformly yellow.

Microscopically, the earliest changes (3 hours), aside from congestion, were loss of glycogen and "cloudy swelling" of the liver cells. Cytochondrial swelling of the type described by Opie[40,41] was observed (Fig. 1). At 8 hours post-hyperthermia, tiny vacuoles appeared in the cytoplasm (Fig. 2), particularly in the cells of the centrolobular areas. The majority of the small vacuoles did not take the usual stains for fat and within many of them there were small eosinophilic inclusions, 2 to 5 μ in diameter. (This phenomenon of "watery vacuolization" has been produced experimentally in animals subjected to anoxia and increased hepatic venous tension.[42]) By 10 hours, small fatty droplets appeared in the cytoplasm (Fig. 3). These coalesced and became larger, obscuring the small non-lipid vacuoles still present. An occasional specimen showed nuclear vacuolization, but the nature of these vacuoles has not been determined. With further survival, liver injury became more manifest and necrosis was observed in the centrolobular zone. At 16 hours this was minimal but by 60 hours some 60 per cent of the central part of the lobule was necrotic (Fig. 4) and hyperemic. If survival was sufficiently prolonged, reparative changes became increasingly prominent. At 7 days, phagocytosis of cellular detritus by macrophages was conspicuous (Fig. 6); polymorphonuclear leukocytes played only a minor rôle in this process. The relatively undamaged cells at the periphery of the lobule underwent active regeneration as evidenced by mitotic figures,

multinucleated liver cells, nuclear enlargement, and prominent nucleoli (Figs. 5 and 8). Proliferation of biliary channels occurred simultaneously. Morphologically, such a liver may resemble those found in fatal cases of epidemic hepatitis,[43] but the sparsity of inflammatory cellular reaction and the lack of liver atrophy are helpful differential features. Since the liver damage in fatal cases is presumably greater than that sustained by survivors of pyretotherapy, changes of this magnitude would not be expected among the latter. No appreciable fibrosis was present even in the case of longest duration (14 days) (Figs. 7 and 8).

Jaundice occurred only in patients surviving longer than 49 hours; in each of these the centrolobular destruction involved 40 per cent or more of the liver lobule.

Central Nervous System

The brain was examined in 16 cases; weights ranged from 1260 to 1700 gm. and averaged 1480 gm. Conspicuous congestion of the blood vessels of the meninges or underlying brain was recorded in 13 instances, edema was considered a feature in 9, and a cerebellar pressure cone in 1. Petechiae or small ecchymotic areas were present in 4. They involved the corpus callosum, the caudate nucleus, the periventricular region (Fig. 10), and the white matter of the cerebral cortex in close proximity to the gray matter. Focal subarachnoid hemorrhages occurred over the cerebellar hemispheres.

Microscopically, perivascular edema (Fig. 11) was present in the majority of the brains and "ring" hemorrhages in 4 (cases 3, 12, 15, and 16).

The parenchymal damage incurred by the central nervous system was most striking and constant in the cerebellum. When death occurred in less than 24 hours, focal neuronal degeneration was present in the Purkinje cell layer (Figs. 9 and 14), but the molecular and granular layers were not appreciably altered. With survival beyond 24 hours, degeneration was progressively more severe and was featured by edema and moderate reactive glial proliferation. In the patients who died later than 7 days after pyretotherapy, most of the Purkinje cells had disappeared and the few remaining were deeply stained and pyknotic. The dentate nucleus showed neuronal changes similar to those in the cortex which are described in the following paragraph.

Changes in the nerve cells of the cortex were present even in the earliest cases, of 3 hours' duration. In all cases the alterations were widely scattered and affected small focal areas. While the majority of the neurones were well preserved in these, some were swollen, exhibiting chromatolysis and karyolysis, and others were shrunken, with deeply

staining eosinophilic cytoplasm and pyknotic nuclei (Fig. 13). At this stage there was no apparent reaction on the part of the glia. Subsequently, disappearance or disintegration of nerve cells was observed in the focally damaged areas (Figs. 14 and 15). Glial reaction was not observed in the cerebrum or brain stem; presumably degenerative changes were too sparse and too widely scattered. In case 10, in which small vessels were occluded with masses of sickled red cells, definite areas of ischemic necrosis were most prominent in the deeper layers of the cerebral cortex and in the periventricular part of the thalamus (Fig. 12).

Similar but less severe neuronal changes were present throughout the basal ganglia and brain stem. No sections of spinal cord were available for study, but cellular damage in a fortuitously sectioned perivesical autonomic ganglion in one case suggested that the changes in nerve tissue might be widespread.

In 2 cases (10 and 12) the leptomeninges exhibited a very slight pleocytosis, the result of activation of histiocytes of the arachnoid trabeculae. According to Haymaker,[44] "similar changes have been observed in a great variety of disorders including anoxia of various types and toxi-infectious states."

Kidney

Renal changes were less constant than those already noted in the brain and liver. The kidneys were regarded as normal in those patients who died within 24 hours. Beyond this period, they were increased in weight, averaging 282 gm. each, and were described as pale, swollen, and somewhat softened. Petechiae were present beneath the pelvic mucosa in 4 (8 to 98 hours' duration) and in the perirenal fat in one.

Microscopically, congestion was marked if death occurred in less than 24 hours and slight interstitial hemorrhage was observed in one of these cases. With longer survival this feature was obscured by the more pronounced parenchymal changes. Parenchymatous damage was scanty in cases terminating rapidly. In the 7 cases in which death occurred within 12 hours, cloudy swelling of the tubular epithelium was the only consistent change and in places the swollen granular tubular cells occluded the lumen. In 2 of the 4 cases of 12 to 24 hours' duration, widespread karyolysis, karyorrhexis, and fatty degeneration involved the proximal convoluted tubules. Granular débris in the tubules appeared to have been derived from disintegration of the lining cells. Although absent in the early cases, in 5 of the 7 cases in which death was delayed for more than 48 hours the changes of lower nephron nephrosis[45] were apparent (Fig. 17). Pigmented casts were present within the lumina of distal convoluted tubules which showed progressive disintegration and detach-

ment of the lining epithelium. Concurrently, interstitial edema and cellular infiltration (largely lymphocytic) appeared. Numerous hyaline casts indicated a high degree of albuminuria and tubular stasis. Interstitial infiltrates were observed also in 2 of the earlier cases in which more widespread lesions indicated sulfonamides as the causative factor.[46,47] Three patients who survived 4, 7, and 14 days, respectively, died of renal failure with hypertension, azotemia, and oliguria.

Heart

The majority of the hearts in this series fell within the normal limits of weight; 2 showed an unexplained, probably pre-existent, increase to 460 and 510 gm. In 3 cases there was dilatation of the right auricle and ventricle. Hemorrhages were common (Table II) and occurred with equal frequency in the cases of short and long duration. The hemorrhages were petechial and occurred most commonly in the subepicardial tissues at the base of the heart. In 4 cases there were hemorrhages in the subendocardial layer of the interventricular septum, but microscopic examination revealed no involvement of the conduction bundles.

The microscopic changes in the heart were inconstant and, while more common in the cases of longer duration, were present also when survival was less than 24 hours. Focal degenerative myocardial changes were observed in 9 hearts: they were granular and hyaline in 5 (Fig. 18), fatty in 2, and lesions of both types were present in 2 others. Three hearts were the seat of slight stromal hyperplasia and cellular infiltration unrelated to the muscle lesions. These were considered results of sulfonamide administration, since infiltrates were present also in other organs.[46,47] Interstitial edema unrelated to renal failure occurred in 4 cases, fragmentation and rupture of muscle fibers in 2.

Lungs

The lungs usually were heavy, weighing together as much as 2560 gm. with an average weight of 1575 gm. In only one instance were the lungs of normal weight; in the others they were filled with edema fluid and blood. There were petechiae beneath the pleura in 5 cases. Microscopic examination merely substantiated the gross findings of edema, hemorrhage, and congestion. The changes of terminal bronchopneumonia were present in 2 cases.

Spleen

The spleen usually was enlarged, the average weight being 270 gm.; the range was from 160 to 530 gm. The spleen was soft and flabby with

an intensely congested, frequently diffluent pulp. In one case with sicklemia the perifollicular hemorrhages reported by Rich[48] were observed.

Adrenals

Grossly, the adrenals were unaltered except for post-mortem autolysis of the medulla in a few cases. Microscopically, engorgement of the cortical sinusoids was obvious in cases of early death. The earliest parenchymatous change was in the lipoid of the adrenal cortex. Normally, in the fasciculate zone, intracellular lipoid is present in the form of tiny uniform droplets, but as early as 3 hours after fever induction it was noted that these droplets had coalesced, appearing as large irregular vacuoles in the histologic sections (Fig. 20). The vacuoles increased in size progressively until the cells disintegrated (Fig. 21). The loss of these cells and their replacement by fluid resulted in the formation of "tubular" structures similar to those reported by Rich[49] in fulminant infections (Figs. 22 and 23). In cases in which survival exceeded 24 hours, the cortical cells had a homogeneous eosinophilic cytoplasm without lipoid. Small foci of acute necrosis in the cortex were evident in 3 of the cases of 1 to 3 days' duration. This "tubular" change was no longer exhibited in any of the 5 which had a survival period of more than 3 days after fever therapy, suggesting that it is a form of reaction to an acute injury.[50] The adrenal medulla appeared normal in every case, but the other changes, although nonspecific, contradicted the statements by others[89] that no significant injury to the adrenals is caused by hyperthermia.

Testis

Gross abnormalities of the testes were not observed, although the prosector in one case described "diminished consistency." Microscopic changes, not present if death occurred within 8 hours, were noted frequently. Spermatogenesis was greatly decreased and assumed an abnormal pattern. Giant multinucleated cells were formed in the walls of the tubules (Fig. 24) and subsequently found their way into the lumina (Fig. 25). Such cells are not a specific effect of heat injury since they have been reported in deficiencies of vitamin A or E and in inanition.[51-53] It seems reasonable to regard them as abnormal forms resulting from the failure of cytoplasmic cleavage to keep pace with nuclear division. With progressive impairment of spermatogenesis (Fig. 26), the testicular tubules may consist solely of Sertoli cells. In the majority of cases the intertubular stroma was edematous but the interstitial cells were unaffected and there was no evidence of inflammatory infiltration. Whether recovery of spermatogenesis occurred could not be ascertained in these

cases. A clinical study, however, indicates that the spermatozoa counts return to normal in from 40 to 70 days following hyperpyrexia.[22]

Other Organs

Gastro-intestinal Tract. Hematemesis had been observed in 3 patients prior to death, but the hemorrhages encountered in 7 cases at autopsy were punctate and confined to the mucosa (Table II). Edema of the submucosa was noted occasionally and congestion was prominent in virtually all cases. Ulceration of the esophagus was present in 2 cases; one of these patients had been subjected to repeated passage of a stomach tube (case 14).

Bone Marrow. Histologic study of bone marrow was limited to 5 cases and none of these showed essential alteration of hematopoiesis. In one case of sicklemia (case 10), foci of fat necrosis occurred in the bone marrow (Fig. 19). In view of the limited nature of the material, the absence of changes must not be regarded as a denial of injury to megakaryocytes as reported in heat stroke.[54]

Sections of *pancreas, thyroid gland, skeletal muscle, urinary bladder,* and *prostate* contained no significant lesions that might be attributed to hyperpyrexia.

A summary of the more important clinical, laboratory, and pathologic findings is presented in Table I.

Discussion

In fatal febrile conditions, it is impossible to segregate the morphologic effects of fever from those of the underlying process. As a consequence, the pathologic changes have never been clearly defined, although clinicians have long been aware of the danger of high body temperature, one of the commonest symptoms of disease. It seems particularly important, therefore, to report the observations in these 17 fatal cases which, although death was accidental, illustrate essentially the morphologic changes of controlled hyperpyrexia unmodified by other disease processes.

The explanation of the widespread effect of hyperpyrexia involves consideration of several factors. Kopp and Solomon[55] regarded shock as the sole pathogenic factor, and it is true that hemorrhages, serous transudates, focal myocardial degeneration, centrolobular hepatic necrosis, tubular degeneration and necrosis in the adrenal cortex, and lower nephron nephrosis have all been observed. But circulatory collapse occurred in only 9 of the 17 cases which we have studied. Moreover, their thesis merely substitutes one question for another, since the cause of

shock itself remains unexplained. We subscribe to Hartman's[56] view that anoxia constitutes the prime (but not the sole) injurious factor in hyperpyrexia, although we recognize that it may also occur in shock. Circulatory collapse, when present, serves only as an augmenting factor and adds anoxia of the stagnant variety to the anoxia already present. Hartman noted the similarity of the pathologic lesions following fever therapy and those due to prolonged asphyxia, as in carbon monoxide or nitrous oxide poisoning. He demonstrated experimentally that severe anoxia was produced constantly in animals by induced fever. Although oxygen determinations of the blood were not made in this series, the existence of significant anoxia was indicated by the constant occurrence of cyanosis, clinically, and by the presence of sickled red cells in the tissues at two of the post-mortem examinations. Since the routine laboratory studies had failed to reveal evidence of the sickle cell trait during life, we must infer a severe and prolonged anoxemia to account for the unmasking of the inherent cellular defect.

It is estimated that a body temperature of 106° F. increases the metabolic rate by 50 per cent,[57-59] and oxygen utilization proportionately. Yet the physiologic mechanisms for furnishing oxygen operate at reduced efficiency. At increased temperatures the oxygen-combining capacity of hemoglobin is diminished. Alkalosis induced by the hyperpnea of fever[58-64] results in an increased stability of oxyhemoglobin and impairs the release of oxygen to the tissues. Finally, the increased rate of blood flow reduces the time available for oxygen transfer.[19,65] Actual measurements by Cullen, Weir, and Cook[66] have shown that arterial oxygen saturation is decreased by approximately 25 per cent (comparable to that attained by ascent to an elevation of 17,500 feet) while venous oxygen saturation is increased to a fairly high level, thus demonstrating both a decreased supply and decreased utilization or delivery of oxygen. These conditions are not altered by oxygen administration and it is apparent that such therapy can only ameliorate,[60] and not prevent, deleterious effects. It is known that anoxia increases capillary permeability greatly (fluid passes through capillary walls at four times the normal rate after 3 minutes of anoxia[67,68]), and it seems likely that this accounts for the non-lipoid vacuoles in the cells of the liver and other organs. Similar changes have been produced experimentally in rabbits and occur with great rapidity.[69] They have been observed also in human material following accidental death from anoxic anoxia under conditions precluding survival for more than fractions of an hour.[42,69-75] The hydrostatic pressure of the blood, of major importance initially, becomes less essential as increase of survival time permits degradation of cytoplasmic

constituents. The latter process must certainly be associated with increased osmotic activity. It is to be expected that the changes would be most striking in the central portion of the hepatic lobule, considering that cells in that position are most remote from the arterial blood supply. Although the mechanism by which anoxia causes neuronal degeneration is not known, the sensitivity of the brain to oxygen lack is well established. It is logical to believe that identical lesions occurring in hyperpyrexia and in anoxic anoxia[74,75] are produced by the same mechanism. The site of the anatomic changes in the brain, though, may vary with the type of anoxia; according to Haymaker[44] the globus pallidus sustains the most severe damage in carbon monoxide poisoning, whereas the striatum bears the brunt of the injury in cyanide poisoning. The implication is that the metabolic injury producing cellular damage is more complex than simple oxygen lack.

Less measurable but none the less real alterations presumably occur among the cellular enzymes to explain the accumulation of fat in liver cells, myocardial fibers, and renal epithelium. The unraveling of the mechanism of carbohydrate utilization within the past decade has permitted an insight into the importance of complex interlocking and interrelated enzyme systems in cellular (and body) metabolism. Since enzymatic reactions are characteristically sensitive to alterations in temperature and pH, prolonged fever may be expected to have some influence on these vital activities. If sufficient damage is sustained, cellular metabolism will no longer be possible and necrosis will occur. With slighter degrees of injury the defect may become manifest as inability of the cell to utilize a material or materials which it ordinarily metabolizes. Using the conventional histologic technics, fat is the most readily demonstrable of these substances although there is no assurance that it is the only one. It seems likely that the inability of spermatogonia to divide properly represents another type of cellular metabolic inadequacy. The impaired capacity of the liver to form prothrombin and fibrinogen[18] is clearly attributable to a "bottleneck" in the cellular "production line." In this way the hemorrhagic tendency and decreased coagulability of the blood are aggravated. Other factors contributing to the latter are the direct destructive effects of heat on prothrombin,[76] platelets, and megakaryocytes,[7,54] increased capillary permeability,[67] and diminished capillary resistance.[77]

It is somewhat more difficult to explain the occurrence of lower nephron nephrosis in some of these patients. Transfusions or sulfonamides, either of which may cause kidney lesions of this type,[45] were given singly or together. However, since the transfusions were all compatible

and reactionless and the other viscera showed no morphologic evidence of sulfonamide sensitivity, it is probable that the renal injury was directly related to hyperthermia. Lower nephron nephrosis in 19 cases of heat stroke was unassociated with significant hypotension in 6.[54] Anoxemia must certainly be implicated in its causation as well as the cellular metabolic derangements more directly related to fever. Degradation products from quantitatively significant tissue necrosis, especially of the liver, are present to impose an additional burden upon renal function. Shock, should it supervene under such circumstances, would further diminish the likelihood of the kidneys escaping unscathed.

Finally, the similarity of the changes described to those occurring in thyroid crisis,[78-82] the postoperative liver-death syndrome,[83] and heat stroke,[54] all conditions in which hyperpyrexia is a prominent feature, would suggest a common mechanism of injury.

Summary

Seventeen fatal cases of therapeutic hyperpyrexia have been reviewed to ascertain the nature of any pathologic changes that might have occurred. The underlying disease in each instance was of a type not usually associated with more than local tissue changes. Therefore, except for the complicating factors considered in the text, morphologic alterations were regarded as the result of the controlled fever.

Congestion and purpuric hemorrhages were the rule. Patients who did not die within 48 hours after the fever also exhibited jaundice. Microscopically, necrosis of cells and other degenerative changes were observed in the brain, heart, liver, kidney, adrenal glands, and testes. The alterations, especially in the liver, were progressively more severe as the survival time increased. It is inferred that the absence of visible change when death is prompt merely expresses the limitations of current histologic technics.

Anoxia and deleterious effects of elevated temperature upon essential cellular enzymes and enzyme reactions are probably the essential factors in producing these pathologic effects. Fever in many conditions besides pyretotherapy may produce similar lesions.

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DESCRIPTION OF PLATES

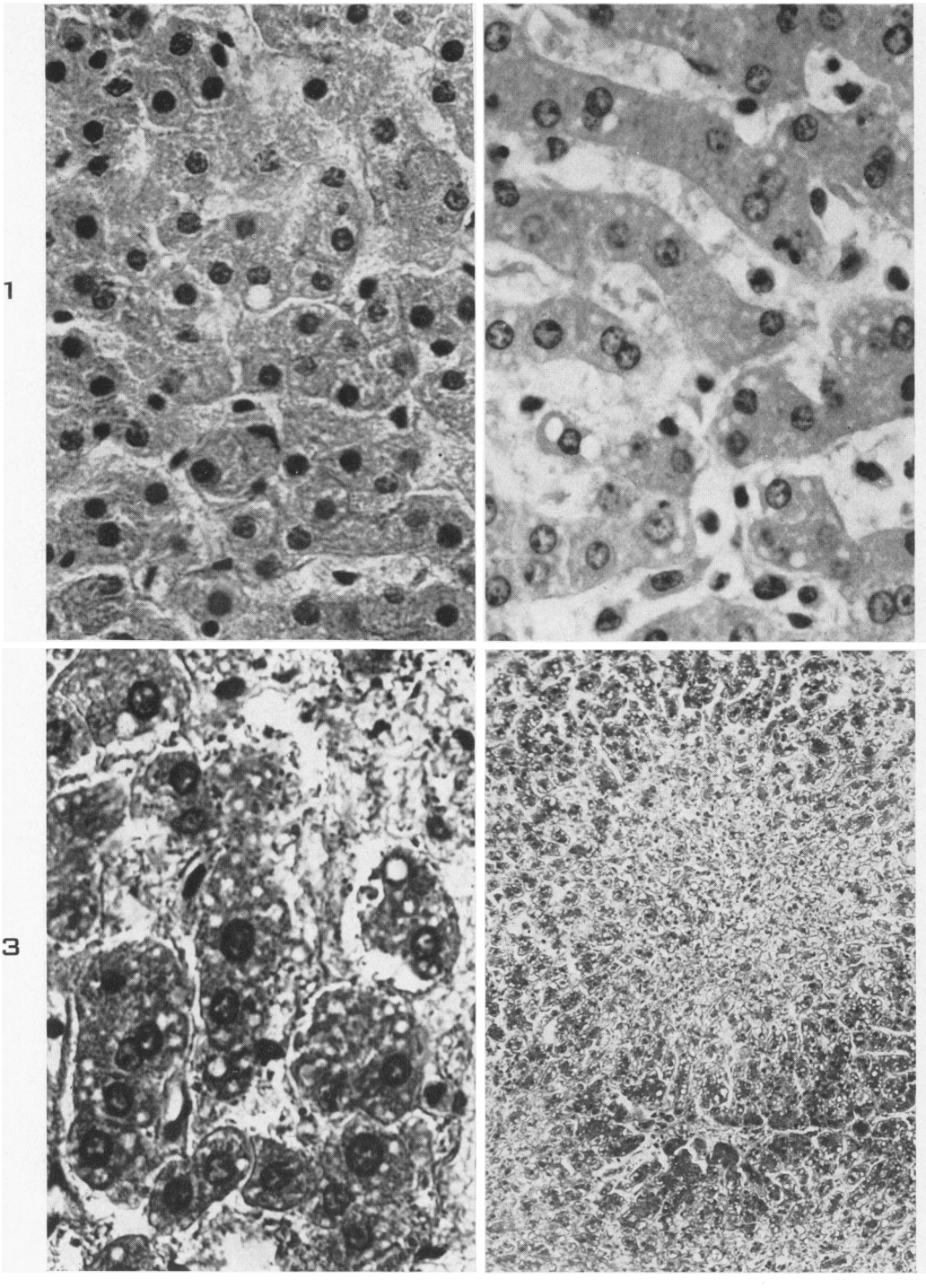
PLATE 165

FIG. 1. Case 1, Army Institute of Pathology accession no. 102884. Liver, demonstrating cellular granularity (cytochondrial swelling) after 3 hours of hyperpyrexia. × 435. Negative no. 103922.

FIG. 2. Case 3, A.I.P. acc. 93390. Non-lipid vacuolization of liver cells 8 hours after onset of hyperpyrexia. × 515. Neg. 103909.

FIG. 3. Case 8, A.I.P. acc. 10169. Large fatty and small non-lipid vacuoles of the liver cells. × 600. Neg. 103722.

FIG. 4. Case 15, A.I.P. acc. 89594. Centrolobular degeneration of liver 100 hours after onset of fatal hyperpyrexia. × 100. Neg. 74693.



Gore and Isaacson Pathology of Hyperpyrexia

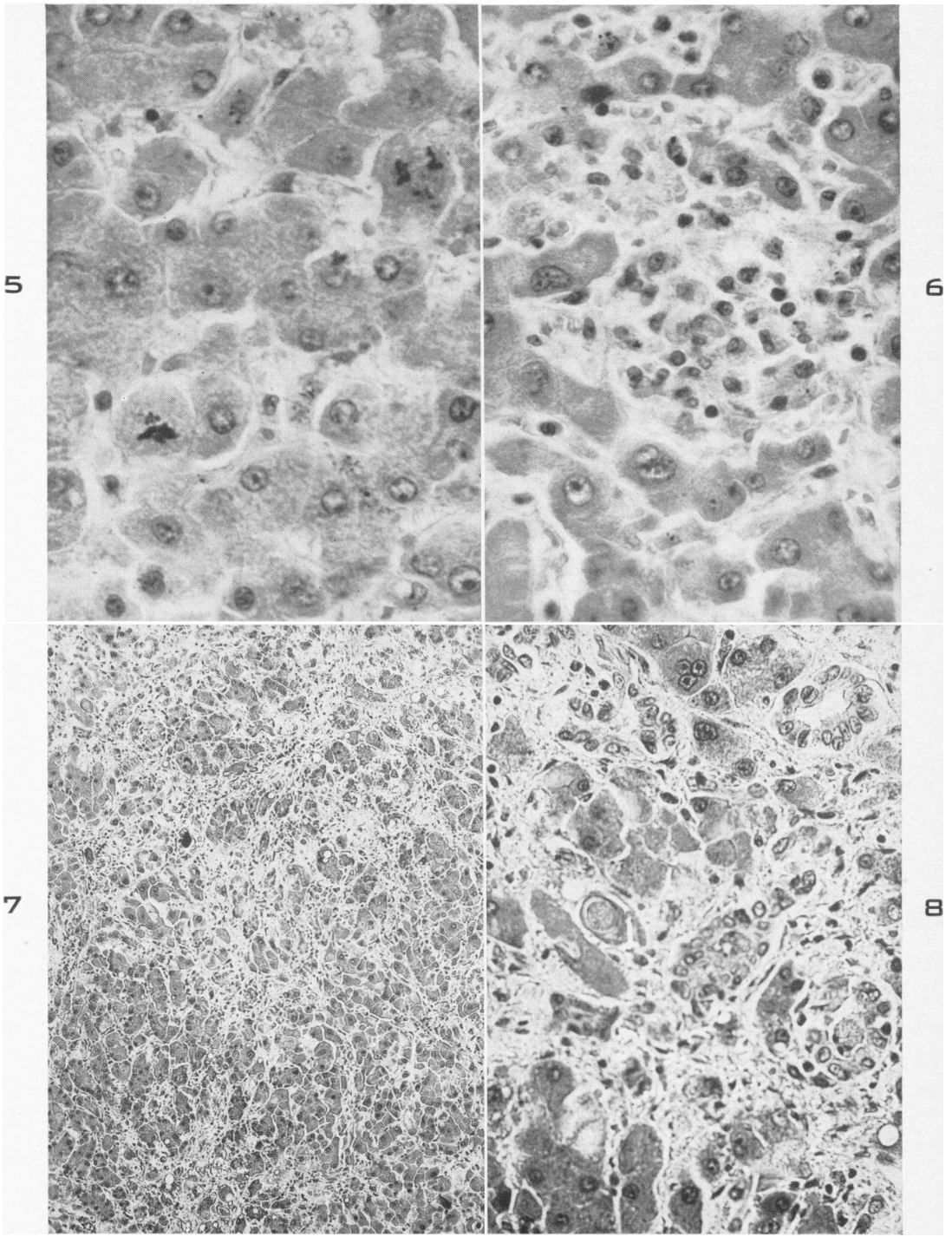
PLATE 166

FIG. 5. Case 16, A.I.P. acc. 79906. Mitotic figures in liver showing regenerative activity 7 days after therapeutic fever. × 475. Neg. 103706.

FIG. 6. Case 16, A.I.P. acc. 79906. Focal accumulation of macrophages replacing liver cells. × 395. Neg. 103705.

FIG. 7. Case 17, A.I.P. acc. 130943. Considerable loss of liver cells, stromal collapse, and hyperplasia of the residual cells have occurred. × 70. Neg. 103925.

FIG. 8. Case 17, A.I.P. acc. 130943. From the same section as Figure 7, but at a higher magnification. Of note are the mononuclear character of the leukocytic response, the proliferating bile ducts, and the bile "thrombi." × 275. Neg. 103926.



Gore and Isaacson Pathology of Hyperpyrexia

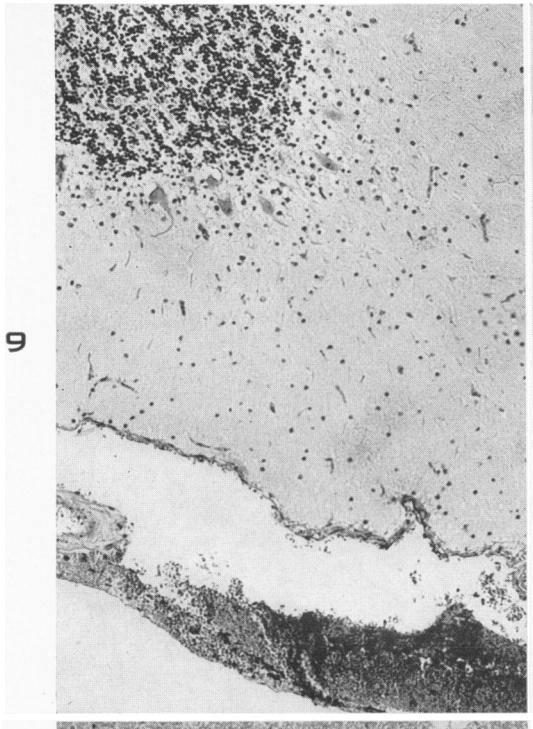
PLATE 167

FIG. 9. Case 15, A.I.P. acc. 89594. Cerebellum 100 hours after fever therapy. Subarachnoid hemorrhage and degenerative changes are seen in the Purkinje cell layer. × 75. Neg. 103724.

FIG. 10. Case 15, A.I.P. acc. 89594. Hemorrhages beneath the subependymal cell plate of the third ventricle 100 hours after fever therapy. × 15. Neg. 74071.

FIG. 11. Case 17, A.I.P. acc. 130943. Cerebrum 14 days after fever therapy. There is perivascular edema of the subcortical white matter. × 75. Neg. 103711.

FIG. 12. Case 10, A.I.P. acc. 95801. Focal degeneration in the caudate nucleus 20 hours after artificial fever. Sicklemia had not been recognized during life. × 65. Neg. 103698.



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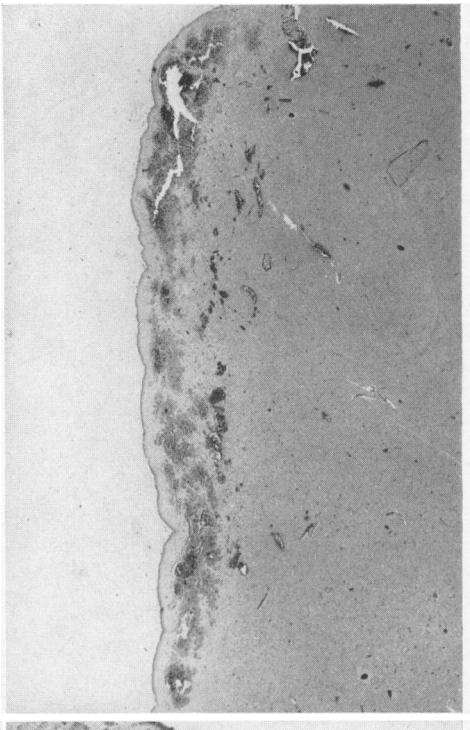

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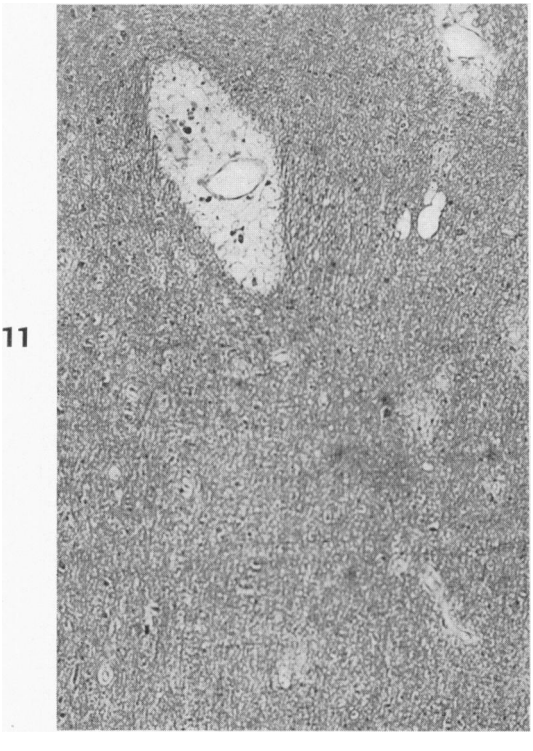

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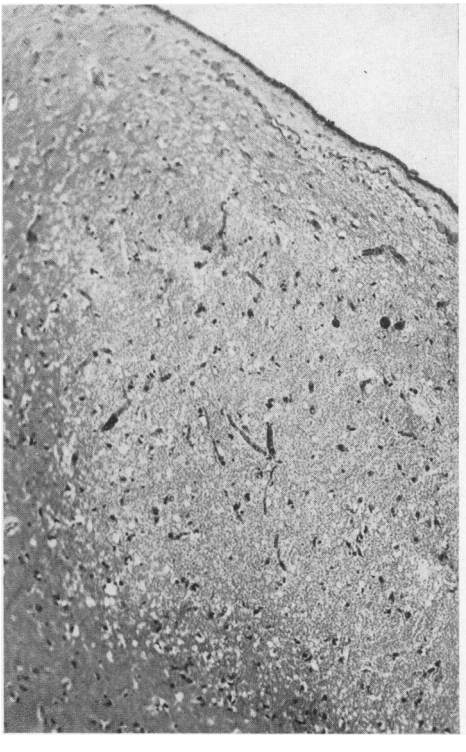

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Gore and Isaacson Pathology of Hyperpyrexia

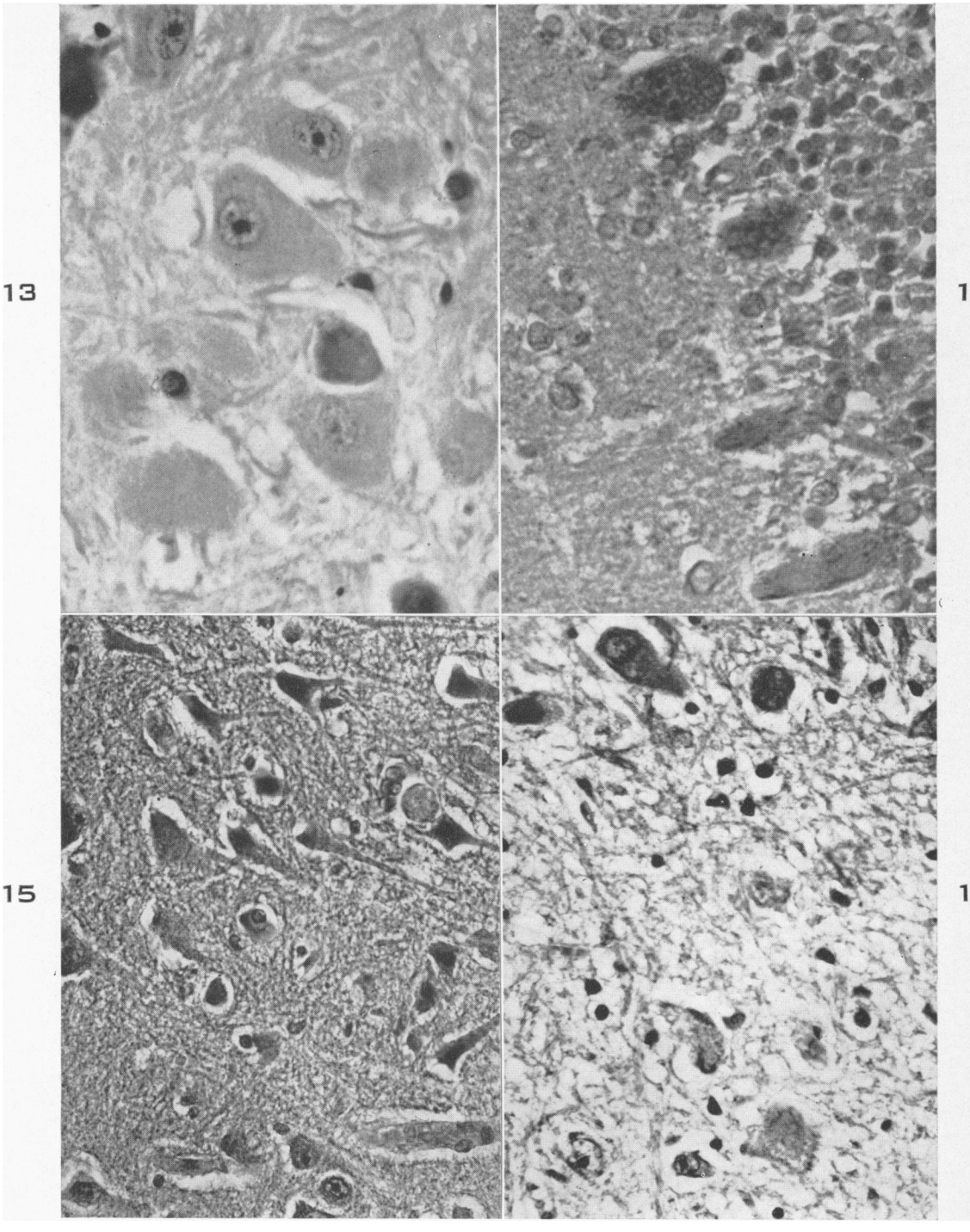
PLATE 168

FIG. 13. Case 1, A.I.P. acc. 102884. Inferior olivary nucleus, medulla, 3 hours after the onset of artificial fever. A few of the nerve cells exhibit karyolysis, others are pyknotic. × 475. Neg. 103729.

FIG. 14. Case 7, A.I.P. acc. 93695. Purkinje cell layer of the cerebellum 12 hours after the onset of hyperpyrexia. There is loss of nuclear structure in all of the Purkinje cells in this field. × 515. Neg. 103716.

FIG. 15. Case 10, A.I.P. acc. 95801. Hippocampus 100 hours after fever, showing acute degenerative changes in the cells of Sommer's sector. × 275. Neg. 104346.

FIG. 16. Case 15, A.I.P. acc. 89594. Hypoglossal nucleus showing both cellular lysis and pyknosis 100 hours after artificial fever. × 355. Neg. 103735.



Gore and Isaacson Pathology of Hyperpyrexia

PLATE 169

FIG. 17. Case 15, A.I.P. acc. 89594. Distal nephron nephrosis 100 hours after onset of hyperpyrexia. × 350. Neg. 74686.

FIG. 18. Case 10, A.I.P. acc. 95801. Focal hyaline and granular degeneration of myocardium 20 hours after onset of hyperpyrexia. × 400. Neg. 103701.

FIG. 19. Case 10, A.I.P. acc. 95801. Focal area of fat necrosis in the bone marrow 20 hours after onset of hyperpyrexia. The sickle cell trait had not been recognized during life. × 150. Neg. 103695.

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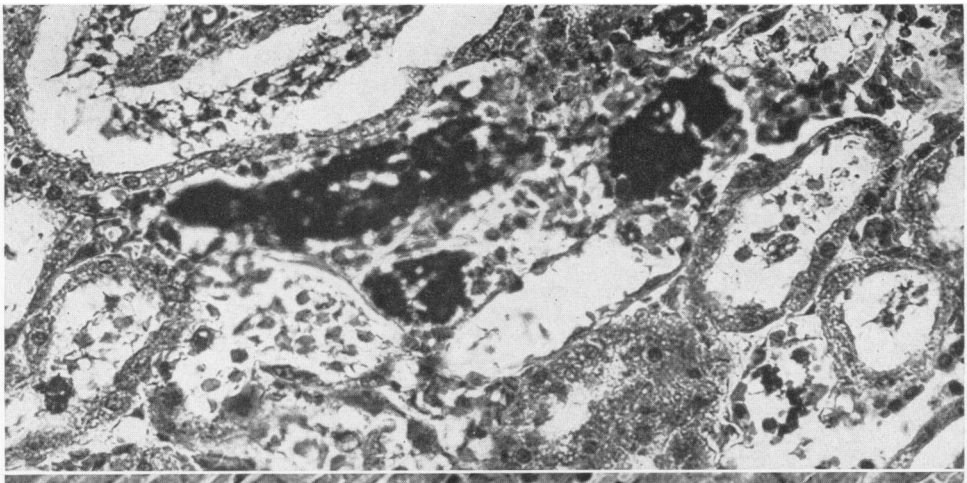

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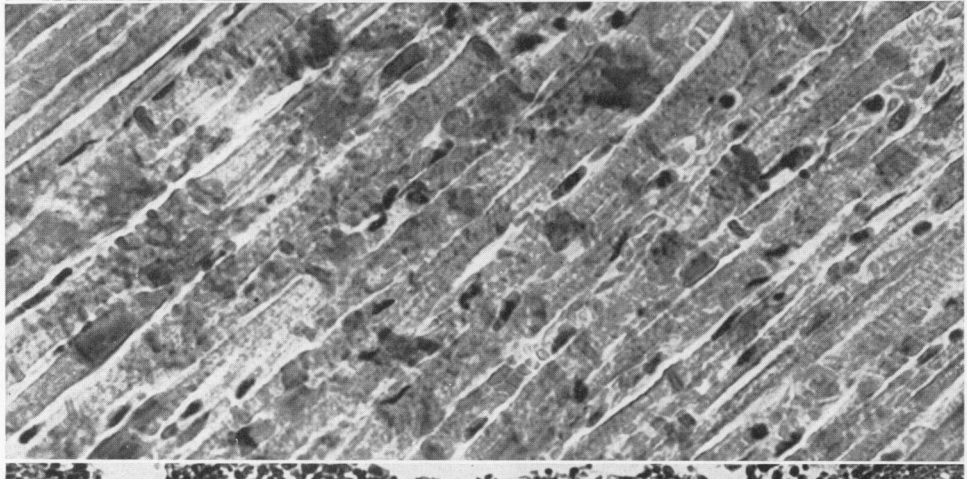

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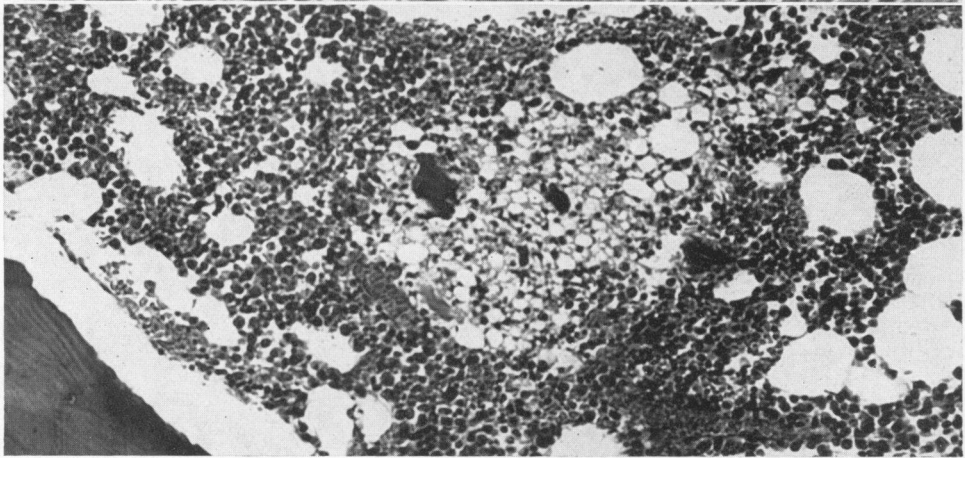


Gore and Isaacson Pathology of Hyperpyrexia

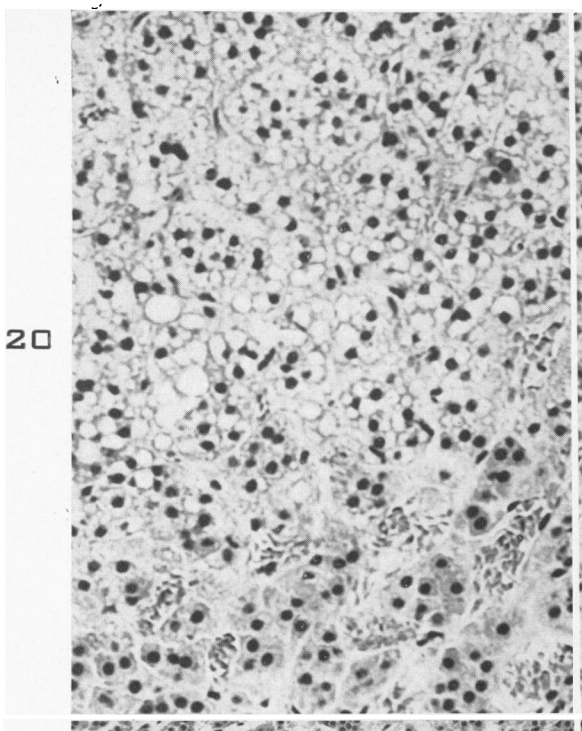
Plate 170

Fig. 20. Case 11, A.I.P. acc. 102884. Adrenal cortex 3 hours after the onset of fatal hyperpyrexia. The normally small lipoid droplets have coalesced to form large, irregularly sized vacuoles. Of note are the sickled red cells in the vessels. × 214. Neg. 103728.

Fig. 21. Case 2, A.I.P. acc. 99435. Early stage of "tubular" degeneration, 3½ hours after onset of fatal hyperpyrexia. Necrotic cells are visible in the spaces. Adrenal cortex. × 214. Neg. 103726.

Fig. 22. Case 3, A.I.P. acc. 93390. Adrenal cortex 8 hours after onset of fatal hyperpyrexia, showing "tubular" degeneration and depletion of lipoid. × 90. Neg. 103712.

Fig. 23. Case 13, A.I.P. acc. 96871. The adrenal cortex exhibits "tubular" degeneration; cortical lipoid is depleted. × 125. Neg. 103912.



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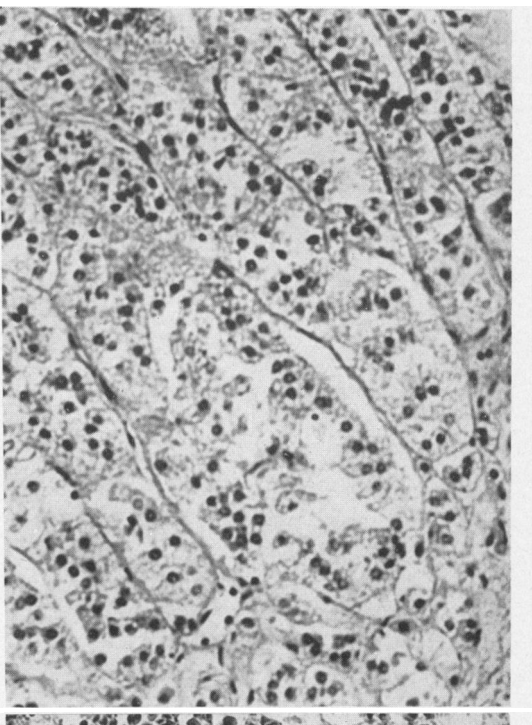

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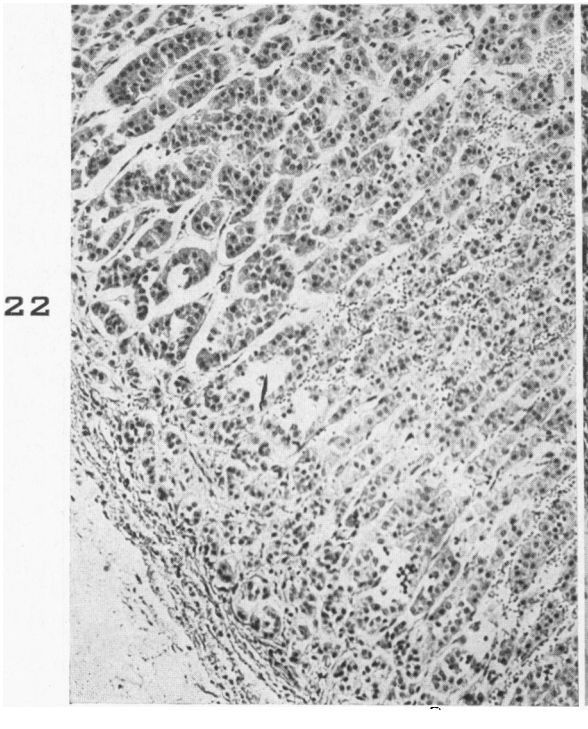

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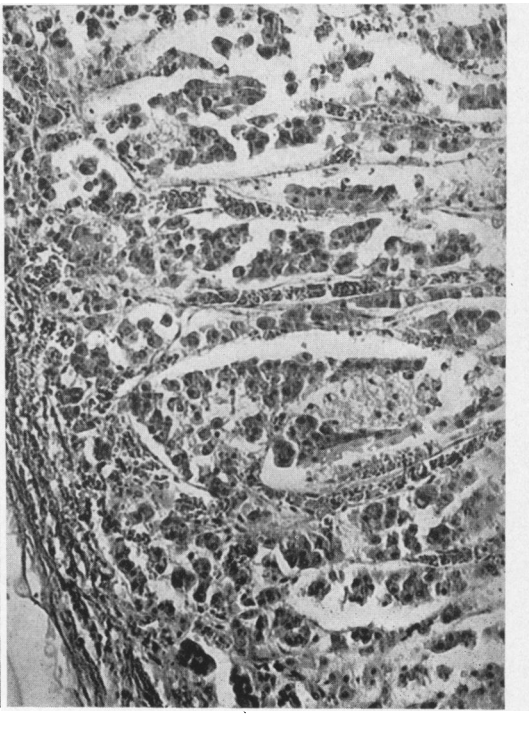

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Gore and Isaacson

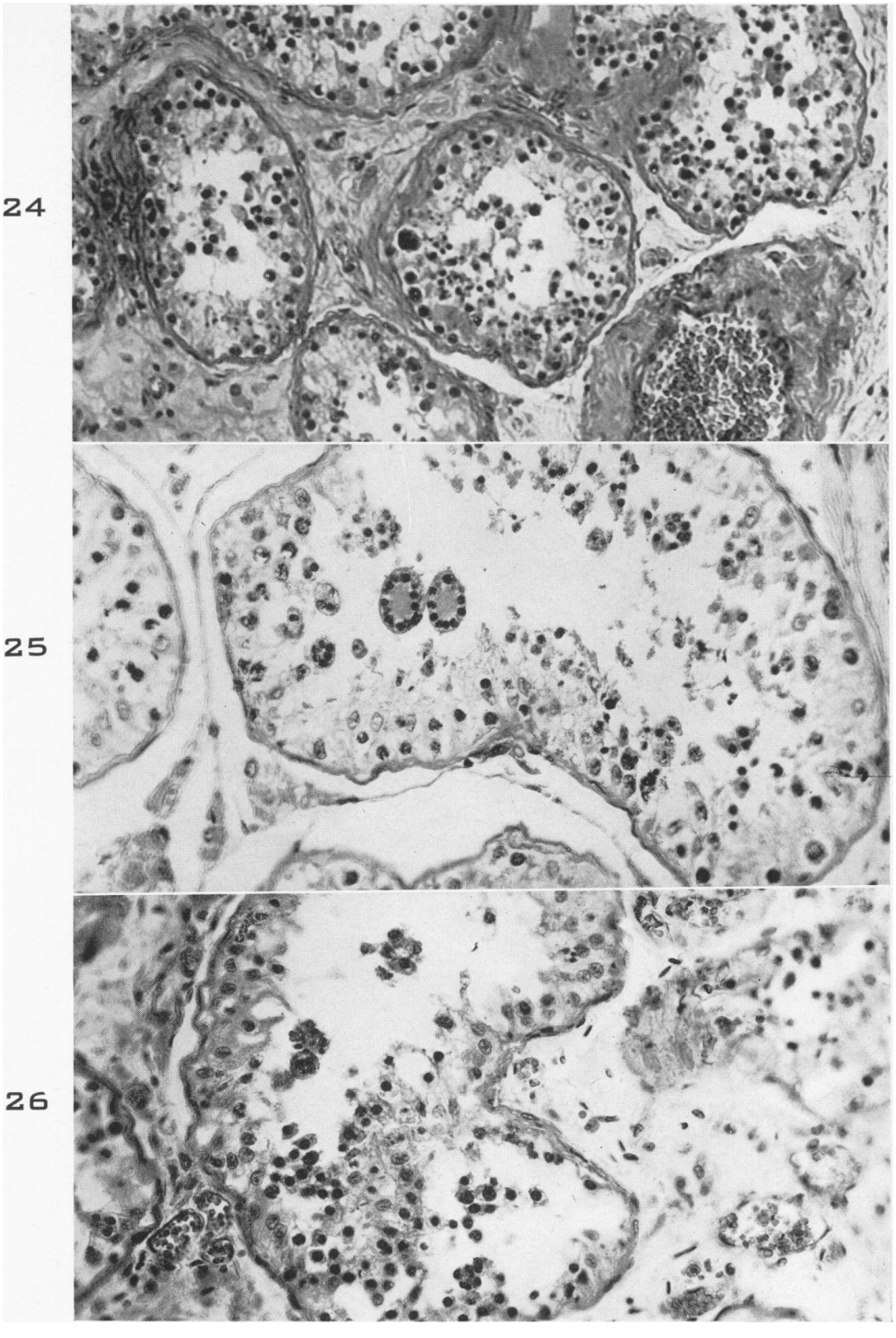
Pathology of Hyperpyrexia

PLATE 171

FIG. 24. Case 4, A.I.P. acc. 82251. Seminiferous tubules 8½ hours after hyperpyrexia. Spermatogenesis is reduced. A giant cell form is visible within the wall of the tubule at the center of the field. × 187. Neg. 103733.

FIG. 25. Case 5, A.I.P. acc. 125672. Seminiferous tubule 11 hours after hyperpyrexia. Spermatogenesis is greatly reduced. Four giant cell forms are present within the lumen. × 275. Neg. 103717.

FIG. 26. Case 15, A.I.P. acc. 89594. Seminiferous tubule 100 hours after hyperpyrexia. Spermatogenesis past the stage of primary spermatogonia has ceased. The latter are greatly reduced in number. Of note is the intraluminal giant cell, the nuclei of which have the same characteristics as the adjacent spermatogonia. × 235. Neg. 103703.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