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CAMPHOR POISONING

ANATOMICAL AND PHARMACOLOGIC STUDY; REPORT OF A FATAL CASE; EXPERIMENTAL INVESTIGATION OF PROTECTIVE ACTION OF BARBITURATE *

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A fatal case of camphor poisoning has presented the stimulus for investigation of camphor intoxication by raising certain questions concerning the pharmacologic and biochemical mechanisms of the action of camphor. In this case there were anatomical features not reported previously in man. These specific questions and features are considered in the following presentation.

CAMPHOR POISONING IN MAN

In medical literature, there have been reports of at least 130 non-fatal cases of camphor poisoning, the majority occurring in the nineteenth century. Selected source references of non-fatal cases are listed in the bibliography.[1-21] Only 18 fatal cases of camphor poisoning have been reported,[22-34] and in only two of them were necropsy studies made. Despite the fact that symptoms referable to the central nervous system had dominated the clinical picture, cerebral anatomical changes have not been reported for man.

The two earlier necropsy studies concerned a 16-months-old male infant dying 7 hours after ingestion of a teaspoonful of camphorated oil,[26] and an adult woman dying 3 days after intraperitoneal injection of camphor.[33] In the former case, there was a profuse hemorrhagic eruption over the body surfaces, subperitoneal petechiae of the stomach and bowel, and subcapsular hemorrhages in the kidneys. In the latter case, changes were limited to congestion of the peritoneal surfaces and swelling of the proximal convoluted tubular epithelium in the kidneys. The mildness of this renal injury is of interest in view of the urinary retention, albuminuria, and anuria sometimes encountered in non-fatal

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cases. To these cases may be added the following example of fatal camphor poisoning in which severe changes occurred in the central nervous system.

Report of Case

A previously normal 19-months-old male infant swallowed an estimated 1 teaspoonful of camphorated oil (20 per cent camphor in cottonseed oil) from a liniment bottle. He vomited within a few minutes but remained otherwise asymptomatic until onset of salivation and rigidity 3 hours later. He was taken then to a local physician, who administered 50 mg. of demerol, and caffeine and sodium benzoate with little effect. The infant was hospitalized. His temperature was found to be 41.5° C.; pulse, 150; respirations, 28; blood pressure, 75/55 mm. of Hg. The white blood cell count was 40,000 per cmm., with 93 per cent segmented neutrophils and 7 per cent lymphocytes; the count was 21,600 per cmm. the following day. There was albumin in the urine at admission.

Shortly after hospitalization, the infant vomited 300 to 400 cc. of coffee-ground material which smelled of camphor. The subsequent clinical course was characterized by coma, repeated tonic convulsions, spasticity, and generalized hyperreflexia. Penicillin, fluid by hypodermoclysis, intermittent sedation by phenobarbital, nasal oxygen, and sponge baths were given. Two days prior to death the right pupil was fixed and dilated, and the blood pressure rose to 150/100. The child experienced recurring periods of apnea which increased in severity, requiring artificial respiration. Tracheotomy proved of little value, and the infant expired on April 16, 1951, 5 days following the ingestion of camphorated oil.

At necropsy 5 hours after death, there was atelectasis and edema of both lungs, with severe congestion of both lower lobes. The right side of the heart was dilated. A 1 cm. agonal or post-mortem perforation of the esophagus was found 2.5 cm. above the cardia of the stomach. There was focal mucosal congestion of the gastro-intestinal tract, but no odor of camphor. Central zonal congestion was observed grossly and microscopically in the liver, and the spleen and kidneys were congested. No other alterations were observed in the kidneys or bladder, either grossly or microscopically.

The brain was swollen and soft. It weighed 1,350 gm., or about 350 gm. more than normal. Microscopic study disclosed extensive degenerative changes selectively involving neurons and sparing glial and vascular structures. These changes were found diffusely distributed in the cerebral cortex and in the basal ganglia, and were most severe in Sommer's sector of the hippocampus, where virtually every pyramidal cell was necrotic. There was a small focus of ischemic necrosis in the medulla. The cerebellar Purkinje cells were unaffected.

The injured neurons exhibited all degrees of chromatolysis and nuclear pyknosis. Dead and dying neurons had a characteristic faded, ghost-like appearance in Nissl preparations (Figs. 1 and 2), and an intense eosinophilia with the hematoxylin and eosin stain (Fig. 3). The ground substance was loose and the perivascular and perineuronal spaces were enlarged, indicating edema. There was no associated glial

or vascular injury, no reactive hyperplasia, nor any inflammatory exudative reaction. The neuronal changes were similar to those found in severe anoxia.[35,36]

Since symptoms referable to the central nervous system have dominated the clinical picture in previous cases of camphor poisoning, the finding of cerebral anatomical changes in this case was not unexpected. It is probable that the lack of human necropsy data accounts for the lack of previous descriptions of these brain lesions in man. For instance, in the two previous necropsy studies, the brain of the adult was not examined and the short survival period of the infant would not allow the development of necrobiotic changes in neurons. In all likelihood, the child we report survived 4 days only because of the therapeutic effect of barbiturates. This 4-day period was sufficiently long to allow irreversible neuronal changes to become manifest anatomically.

Camphor Poisoning in Animals

Somatic changes reported in chronic experimental camphor poisoning in animals have included fatty alteration in the liver and kidneys.[37] Focal gastric ulcers, presumably secondary to contact points of concentrated solutions, have been observed following administration of camphor by stomach tube. Production of these ulcers has been connected theoretically with decreased glycuronic acid in the liver, due to conjugation with camphor and excretion by the kidneys. The decreased glycuronic acid was thought to be associated with hyposecretion of mucin by the stomach, thus exposing it to acid digestion.[38] Despite the report of a leukemoid reaction in a human patient who received camphor, no camphor effect on blood leukocytes in animals has been reported.[39]

Cerebral changes have been produced in animals by repeated toxic doses of camphor. Petechial hemorrhages, chromatolysis of nerve cells, focal zones of neuronal necrosis, and a reactive focal gliosis have been observed.[40] Other neuronal alterations, consisting of sclerosis (shrinkage, hyperchromatism, and clumping of the Nissl substance) also have been described.[41] However, these changes are of questionable nature, since they were found within a few hours following lethal doses of camphor. Furthermore, the latter changes appear identical to those described by Koenig and Koenig[42] as artifacts resulting from necropsy trauma, autolysis, and immersion fixation.

Experimental Camphor Poisoning of Animals

In an attempt to clarify the nature of the cerebral changes recorded in animals and to correlate these findings with those in our human

case, we studied the effect of camphor upon animals. Particular care was exercised to evaluate correctly the artifacts described by Koenig and Koenig,[42] which were regularly observed in our control animals as well as in rabbits or mice receiving camphor. These changes were found in animals dying in convulsions hours after administration of camphor as well as in those sacrificed several days after recovering from the convulsive episodes. The effects of single dose injections of camphor were studied in rabbits, and of single and multiple injections in mice.

Rabbits. The minimum lethal dose for rabbits is 2 gm. of camphor per kg. of rabbit.[43] Accordingly, 8 rabbits were given varying doses of camphor as camphorated oil (20 per cent camphor in cottonseed oil) by oral tube. Doses were 1/2, 2/3, 7/10, 8/10, 9/10, 1, 1½, and 2 MLD. In addition, 2 rabbits were given 25 per cent camphor in alcohol by gastric tube in doses of 8/10 and 9/10 MLD, and 10 control rabbits were given nothing. All rabbits receiving camphor had tonic and clonic convulsions within 5 to 40 minutes of ingestion. The tonic convulsions were characterized by rigidity and hyperextension of the forelegs, and the clonic by violent shaking motions of the entire body. Masticatory motions of the jaws, salivation, great hyperactivity, and violent jumping also were observed. Convulsions began later in the animals receiving the smaller doses. Those animals that died had convulsions intermittently until death; those that lived recovered from the convulsions within 4 hours and thereafter appeared normal. One rabbit receiving camphor in alcohol lived only 4 hours, but death was due probably to the aspiration of this material.

The brains were removed as soon as possible and were fixed by immersion in 10 per cent formalin within 30 minutes after death. Nissl preparations and celloidin and paraffin, hematoxylin and eosin preparations were studied. Other tissues were fixed in Helly's fluid.

Mice. An attempt was made to produce lesions of the central nervous system in mice by single injections of camphor and then by multiple injections. The LD/50 for mice was found to be approximately 30 mg. of camphor per 100 gm. (Mice nos. 13 to 32, Table I). All injections were given intraperitoneally. The results of these experiments are summarized in Table I. Mice nos. 1, 13 to 17, and 23 to 34 were necropsied and studied grossly and microscopically. Techniques for fixation and staining were similar to those used with rabbits.

All mice that had convulsions exhibited similar hyperactive behavior patterns, which consisted of marked clonic convulsions with some tonic elements, and running and jumping. One of the first signs to appear was rigidity of the tail, which would point straight up, such as is seen in the mouse in morphine poisoning.

Results

There were no significant lesions of the brain or spinal cord in the rabbits. The brains of all rabbits, including the controls, showed the artifacts described by Koenig and Koenig.[42] The esophageal and gastric mucosa of many of the rabbits was congested and showed small focal hemorrhages, but it was not certain whether these changes were due to camphor or trauma from the stomach tube. The kidneys of every rabbit were normal, as were the lungs, heart, liver, pancreas, and spleen.

In all of the mice listed in Table I, including both the ones that received single doses and those that received multiple doses, there were no significant lesions, other than those in the brain, attributable to camphor. All brains showed the pyknosis (hyperchromatism, sclerosis) of the neurons of the cortical layers described as a fixation artifact.[42] Mice nos. 13, 31, and 32 showed *bona fide* neuronal changes. The lesions consisted of necrosis of neurons in the brain stem, basal ganglia, medulla, hip-

pocampus, and cerebral cortex. These neuronal changes were virtually identical to those seen in the human case we report, as they were characterized by chromatolysis and nuclear pyknosis. Dead neurons exhibited an intense eosinophilia of the cytoplasm in the hematoxylin and eosin stains. In the Nissl preparations, necrotic cells were characterized by marked vacuolization of the cytoplasm and a loss of the cytoplasmic staining reaction.

The Mechanism of Camphor Action

The Pharmacologic Action of Camphor

The outstanding pharmacologic effect of camphor is stimulation of the central nervous system with excessive doses producing convulsions. The exact mechanism of the excitatory effect, the precise site of action,

Table I

The Effect of Camphor upon Rabbits and Mice

Animal	Camphor/kg.	No. of doses	Interval between doses	Length of life following first injection	Neuronal damage
	In cottonseed oil:				
Rabbit 1	1.0 gm.	1		5 days*	o
Rabbit 2	1.3 gm.	1		5 days*	o
Rabbit 3	1.4 gm.	1		5 days*	o
Rabbit 4	1.6 gm.	1		5 hours	o
Rabbit 5	1.8 gm.	1		40 hours	o
Rabbit 6	2.0 gm.	1		5½ hours	o
Rabbit 7	3.0 gm.	1		4 hours	o
Rabbit 8	4.0 gm.	1		45 minutes	o
	In 95% alcohol:				
Rabbit 9	1.6 gm.	1		4 hours	o
Rabbit 10	1.8 gm.	1		4 days*	o
Rabbits 11–20	o	o		o	o
	In 95% alcohol:				
Mice 1–5	1.8 gm.	1		5 minutes	o
	95% alcohol without camphor:				
Mice 6–10	0.6 cc.	1		5 minutes	o
	In cottonseed oil:				
Mouse 11	1.2 gm.	1		2 hrs., 15 minutes	o
Mouse 12	1.8 gm.	1		20 minutes	o
Mouse 13	0.30–0.40 gm.	3	24 hours	4 days*	++
Mice 14–17	0.30–0.40 gm.	3	24 hours	4 days*	o
Mice 18–22	0.30–0.40 gm.	1		1–3 hours	o
Mice 23–24	0.30–0.40 gm.	2	24 hours	25 hours	o
Mice 25–30	0.30–0.40 gm.	1		1–2 hours	o
Mouse 31	0.30–0.40 gm.	2	24 hours	36 hours*	++
Mouse 32	0.30–0.40 gm.	3	24 hours	56 hours*	+++
Mice 33–34	0.30–0.40 gm. +3 cc. Ringer's solution	2	24 hours	3 days*	o

* Animal sacrificed at specified time.

and the metabolic pathways involved are unknown. However, reactions are alike in man and other mammals in which the behavior patterns are known. The action of camphor upon frogs differs from that upon mammals by producing such rapid paralysis in frogs that convulsions do not occur.[44]

The action of camphor upon the circulation has been studied extensively.[1,45,46] Camphor, when given as a weak solution, causes vasodilatation of the coronary and peripheral arteries. Hence, convulsions, if caused by cerebral vasoconstriction, must be mediated through a mechanism other than that operating on peripheral arteries when camphor has been given as a weak solution.

Camphor has a carminative, as well as a rubefacient effect, and it induces several side reflexes, such as acceleration of the heart rate due to local irritative action on the oral mucous membrane. The drug is employed today as a liniment and insect repellent. It has been tried without real success as an abortifacient,[10,19,20,21,32] contraceptive,[14] cold remedy,[14] aphrodisiac,[21] anti-aphrodisiac, suppressor of lactation,[6] cardiac stimulant, and antiseptic.[1]

Camphor unites with glycuronic acid, perhaps in the liver, and is rendered inert. It may appear subsequently in the urine as camphoglycuronic acid.[45]

The fatal dose for man has been as low as 0.7 gm. in infants, but 15 gm. have been taken by adults without lethal effect. The oral MLD for rabbits is 2 gm. per kg.[43] and for guinea-pigs, 180 mg. per 100 gm.[43,47] Our tests indicated an LD/50 for mice of 30 to 40 mg. per 100 gm. when camphor was given intraperitoneally (Table I).

Cerebrovascular Mechanisms of Action of Camphor

Careful studies have been made of the possible vasoconstrictive actions of camphor. For example, study of data on cerebral blood flow obtained by inserting a thermorecorder into a cat's brain has revealed no general diminution in the flow during convulsions induced by camphor.[48] Studies of cerebral blood flow in animals given diodrast and similar convulsants have indicated early vasodilatation rather than constriction.[49] These facts provide experimental proof that vasospasm and anoxia are not requisite for the production of neuronal necrosis. Nevertheless, available experimental data are somewhat conflicting. Finesinger and Cobb[50] found, by direct observation of pial arteries, that homocamfin convulsions were preceded by slight constriction of the pial arteries, a drop in systemic arterial blood pressure, and a decrease in pressure of the cerebrospinal fluid. They found also that monobromated camphor convulsions were preceded by dilatation of the pial arteries, and, as a rule, an increase in pressure of the cerebrospinal fluid.

We have attempted to evaluate the relation of vasoconstriction to camphor action by anatomical study of the cerebral circulation before, during, and following camphor convulsions as compared to that in

normal animals. Two animals were killed by decapitation at each of these stages, and two control animals were sacrificed by decapitation. The benzidine method of Doherty, Suh, and Alexander[51] was used to demonstrate the state of the cortical blood supply. Our results gave no evidence of vasospasm, there being no demonstrable cerebral capillary anemia at any stage of camphor intoxication. When muscle spasm is eliminated by the use of curare or erythroidine, a severe depression of oxygen consumption by the brain still occurs,[52-54] thus indicating a probable mechanism of camphor action other than vasoconstriction. We conclude that vasospasm has little to do with the production of neuronal necrosis by camphor.

Biochemical Mechanisms of Action of Camphor

The biochemical mechanism by which camphor effects convulsions is unknown. Certain phenomena are known to be associated with convulsions, but as yet complete cycles of action of but few convulsants have been determined. With convulsions, there is an immediate increase in oxygen consumption.[49,52,55,56] Venous oxygen levels of the brain fall markedly during convulsions, independent of oxygen levels of arterial blood.[57] The lowering of arterial oxygen levels due to tonic spasm of respiratory muscles is of less importance than the local oxygen deficit due to excessive oxygen consumption.[52,55,58] Glucose consumption is increased and there are lower levels of phosphocreatine and of adenosine triphosphate during and following convulsions.[59-61] Inhibition of cholinesterase and consequent accumulation of acetylcholine are factors in the action of some convulsants,[52] and excessive formation of citrate,[62] disturbance of glutamic acid-glutamine equilibrium,[63] and effects due to liberation of ammonium ions are other alterations which have been related to convulsions.[63] Since oxygen and glucose are prime suppliers of expended energy, they are involved in the cycle of action of any convulsant. The biochemical agents utilized especially in this expenditure may be the high energy phosphate compounds such as phosphocreatine. Complete depletion of the intra-neuronal supply of these phosphate compounds may be the cause of neuronal death. These known alterations during convulsions do not explain how a convulsant initiates the chain of events that lead to excessive energy demands. Studies of the relation of camphor to oxygen or glucose consumption, or to the destruction of phosphate compounds, have not been performed *in vivo* or *in vitro,* but it may be assumed that camphor acts in a manner similar to that of most other convulsants.

Narcotics prevent the depletion of neuronal energy stores by the convulsant drugs. A knowledge of how this depletion is prevented

gives some idea of the biochemical cycles through which energy is transferred in convulsions, as well as some idea of how the depletion is prevented.[64,65] For instance, barbiturates inhibit oxidation,[66] probably in the cytochrome oxidase system at the cytochrome b–flavoprotein electron transfer level.[67-69] This oxidative interference is more pronounced in the gray matter than in the white matter, indicating a direct relation to the neuronal body rather than its axon. However, a similar action upon ganglionic oxidation affects transmission of the nerve impulse at the synapse.[70] The action of barbiturates cannot be localized completely to one process or to one oxidation level, since these drugs affect pyruvate, lactate, and glutamate oxidation as well as that of glucose.[66] Potassium ion concentration is known to affect the action of narcotics.[71] These many mechanisms and sites of action involved by narcotics and convulsants illustrate the difficulty of analyzing the mode of action of camphor on the basis of data now available.

Effect of Pentobarbital upon Animals Given Camphor

The following experiments on the action of barbiturates upon animals given camphor were undertaken to demonstrate the abolition of convulsions by barbiturates and to demonstrate the therapeutic value of barbiturates.

Ten mice were given camphor and pentobarbital intraperitoneally and a control series of 10 mice were given camphor only (Table II). The animals in the test series (mice nos. 35 to 44) became stuporous and then somnolent within 10 minutes, but again exhibited motor activity and complete recovery from the narcosis about 1½ hours after first administration of the drug. No animal had convulsions and, aside from the 1½ hour period of narcosis, they exhibited no abnormal behavior. In the control series, convulsions occurred in all mice.

The protective action of pentobarbital is demonstrated by the absence of fatality in mice given camphor and pentobarbital, as compared to seven deaths in 10 mice

TABLE II

Protective Action of Pentobarbital Against Camphor in Mice

Mice nos.	Camphor in oil	Pentobarbital	Narcosis	Convulsions*	Death*
	mg./100 gm.	*mg./100 gm.*			
35–44	30	7.2	1½ hours	0/10	0/10
45–54	30	0	0	10/10	7/10

* Number of mice having convulsions or dying over number of mice tested.

given camphor and saline solution. The 10 mice in the first series (nos. 35 to 44) were given similar doses of pentobarbital and camphor 24 hours after the first injection, and again 48 hours after the first injection. All 10 animals were killed 96 hours after the first injection, and were necropsied and their brains examined. No neuronal damage or other lesions were found. Similar anatomical studies were made on a control group of mice given only three successive daily doses of 1.8 mg. of nembutal. Again no lesions were found. It will be recalled from experiments reported in Table I

that repeated convulsions produced by multiple doses of camphor alone will produce neuronal necrosis in about 30 per cent of mice given two or more doses of camphor.

Mice nos. 1 to 10 demonstrated the lethal effect when 95 per cent alcohol was used as a solvent for camphor.

These experiments indicate that pentobarbital not only prevents convulsions but also protects the mouse from detectable tissue damage. The possibility that barbiturates at a therapeutic concentration might add by an anoxemic effect to the damage produced by camphor is considered unlikely in view of the protective action repeatedly demonstrated.

Summary and Conclusions

Knowledge of the pathologic anatomy of camphor poisoning is augmented by the report with necropsy findings of an additional human case. Of special significance is the observation of neuronal necrosis, a heretofore unreported finding in human camphor poisoning. Similar neuronal destruction was produced experimentally by multiple dose administration of camphor to mice.

The pharmacologic and biochemical actions of camphor are reviewed. The action of camphor was studied in relation to barbiturate antagonism of camphor. A possible conclusion which may be drawn from this study is that the site of action of camphor is intraneuronal and upon the oxidation cycle at a phase above the flavoprotein-cytochrome b level of the cytochrome oxidase system. Camphor probably acts in a manner similar to other convulsants, causing rapid oxidation and depletion of high energy phosphorus compounds, but the exact manner in which this high energy chain reaction is initiated is unknown.

Experiments were performed which demonstrate clearly the inhibition of camphor convulsions in mice by barbiturates. This is the *in vivo* counterpart to *in vitro* studies that demonstrate barbiturate inhibition of oxidation on brain substrates. Anatomical studies of mice given camphor and barbiturates demonstrate that with prevention of convulsions by barbiturates there is also protection against neuronal damage. Since barbiturates similarly suppressed convulsions in the fatal human case we report, we conclude that use of barbiturates in patients with camphor poisoning is therapeutically sound.

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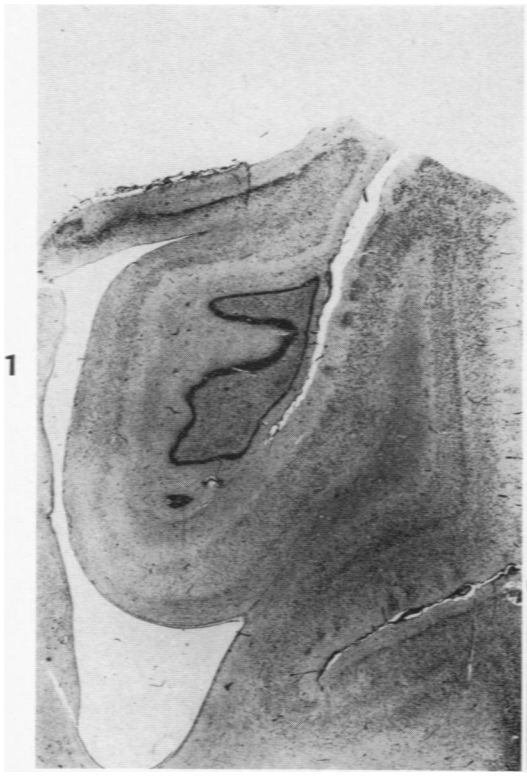
LEGENDS FOR FIGURES

FIG. 1. Hippocampus, human case. Rarefaction and pallor of Sommer's sector of hippocampus resulting from neuronal necrosis. Nissl stain. × 11.

FIG. 2. Hippocampus, human case, showing selective neuronal necrosis of pyramidal layer. Arrow indicates two pale, ghost-like bodies of necrotic neurons, several of which are included in this field. Nissl stain. × 380.

FIG. 3. Central gray matter of hippocampus, human case, showing selective neuronal necrosis. Nuclear pyknosis and eosinophilic homogenization of the cell body are exhibited by all neurons but one in this field. Hematoxylin and eosin stain. × 700.

FIG. 4. Hippocampus, mouse 9, showing selective neuronal necrosis in dentate gyrus. The zone of homogeneous paleness of necrotic neurons contrasts sharply with the basophilia of the sector in which interstitial edema is the only alteration. Nissl stain. × 210.



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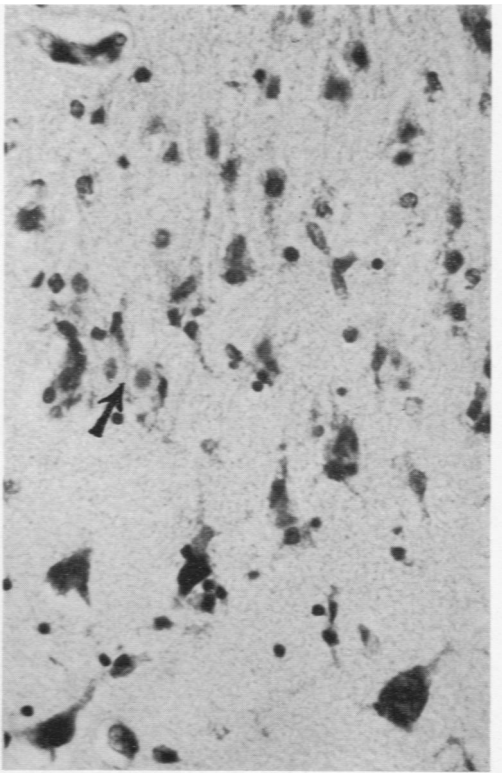

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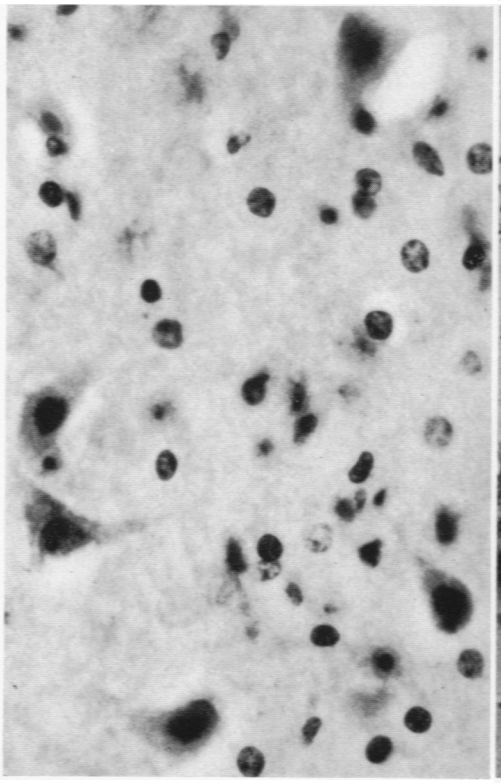

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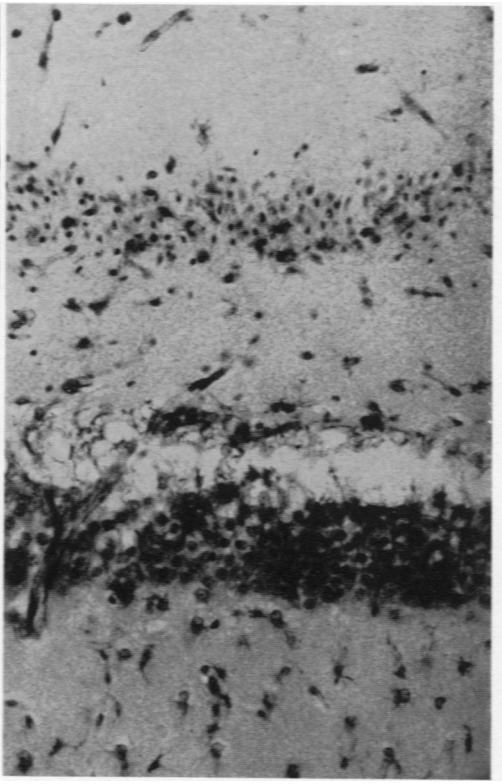

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