teriorized kidneys, over a total period of several hours. Administration of carbon monoxide, in the dosage employed, produced equally marked diversion of blood from the cortex but the change was irreversible. Two final notes may be added to the above account. In the first place, partial denervation of one kidney, which was effected in a few cases, divided the single organ into a part which responded to anoxia and a part which did not; this was a convenience for some purposes. Secondly, if the stomach was over-full or the uterus seriously enlarged as a result of pregnancy, the kidneys tended to be found partially "shunted," if one may use the American expression for diversion of the cortical blood supply, from the outset.

Discussion. Toth's[1] anoxia experiments were carried out in dogs, and paling of the surface of the dog's kidney during diversion of the cortical blood flow is not readily detected because (1) the capsule is relatively thick, and (2) the cortical color changes are masked by superficial vessels which are unconcerned, or little concerned, in the diversion. Further, the findings of Trueta *et al.*, which showed the significance of such cortical diversion as opposed to an overall reduction in renal arterial inflow, were not begun until 1945. In a future paper two of the present writers (L.E.M, E.U.) will give quantitative details about the degrees of anoxia and of hypercapnia which are required for the production of the renal circulatory changes, and will describe the fluctuations of arterial blood pressure recorded during these changes, together with other features of interest. They may also give evidence about the urine flow as affected by anoxia, and offer a possible explanation for the time-lag between the return of color to the kidney surface and the disappearance of the wrinkling from that surface. In this preliminary account, however, the main object is to describe the more obvious features and to point out that the simultaneous use of innervated and denervated kidneys, with the completeness of the denervation shown by a tracheal occlusion test, allows one rapidly to determine if a poison, such as dioxan (see De Navasquez,[3]) or a bacterial toxin, affects the kidneys through nervous intermediation or otherwise. Publication of this present paper is, therefore, a necessary prelude not only to the communication of further finding about anoxia effects, etc., but also to the description of the results of experiments with a number of nephrotoxic substances.

Summary. 1. Acute anoxia, sufficient in degree, produces a marked diversion of the renal cortical blood flow in the innervated, but not in the denervated, kidney.

2. Simultaneous study of the reactions of the innervated and denervated kidneys is a simple way of distinguishing the mechanisms of action of different nephrotoxic substances.

[3] De Navasquez, S., *J. Hyg.*, 1936, **35**, 540; De Navasquez, S., *J. Path. Bact.*, 1938, **46**, 47.

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17185. Effect of Elevated Body Temperatures on Cryptococcosis in Mice.

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In a study[1] of the effects of temperature on the reproduction and viability of *Cryptococcus neoformans,* the number of viable cells decreased by 85% within 5 days at 103° F (39.4°C), but increased regularly at 99°F (37.3°C). The writer postulated that differences in body temperatures of laboratory mice and rabbits might account for differences in susceptibility to cryptococcosis. Mice, with rectal temperatures averaging 99.1°F, died

[1] Kuhn, L. R., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 573.

TABLE I.
Survival of Mice Injected with *C. neoformans* and Maintained Either at 35 to 36°C or 24 to 27°C.

Dosage of *C. neoformans*	Method of inj. and No. injected	Time after injection	No. surviving in mice maintained at temperatures indicated		
			24-27°C	35-36°C	35-36°C after being kept at 24-27°C for time indicated
					2 days
2 to 2.5 million in 0.5 ml of saline	Intravenous 15 in each temp. group	0 hr	15	15	15
		48 ''	15	11	15
		11 days	0	11	10
		20 ''	0	10	6
		30 ''	0	6	3
					8 days
Same	Intraperitoneal 18 in each temp. group	0 hr	18	18	18
		44 days	0	12	9
		60 ''	0	7	4
					2 days
120 to 150 thousand in 0.03 ml of saline	Intracerebral 25 in each temp. group	0 hr	25	25	25
		24 ''	25	21	25
		10 days	4	15	20
		20 ''	0	8	6
		30 ''	0	6	2

regularly and relatively rapidly of experimental infections, while rabbits, with a mean temperature of 103.15°F, were affected only rarely and slowly.

To determine if mice could be maintained with elevated body temperatures long enough to study their reaction to cryptococcosis, groups of Swiss mice were kept at various temperatures above 30°C. In still air at 35 to 37°C with 25 to 35% relative humidity, rectal temperatures rose rapidly and remained above 102°F.* Although a few mice died during an initial day or two of discomfort for all, the majority survived and were in apparent good health at the end of a month, although averaging only 1.3 g gain in weight compared with 7.1 g in room temperature controls. At this time, the rectal temperatures of 2 separate lots of heat-adapted mice averaged 102.8 and 103.4°F, ranging from 101 to 105°F.

Infections with a pathogenic strain† of *C. neoformans* were compared in Swiss mice weighing 17 to 19 g and kept either at 24 to 27°C or at 35 to 36°C. Groups maintained at each temperature level were injected intravenously, intraperitoneally or intracerebrally with 60-hour Sabouraud agar cultures of *C. neoformans* suspended in 0.85% sodium chloride. Doses for each group as well as the effect of environmental temperatures on survival are shown in Table I. Mice in all groups kept at 35 to 36°C outlived all those maintained at 24 to 27°C. Thus, although all of 15 intravenously injected mice kept at room temperature died of cryptococcosis within 11 days after being infected, only 4 of 15 died during the same period in the higher temperature group. Since these 4 died within 48 hours after injecting and incubating, their deaths cannot be attributed to the slowly developing cryptococcus infection. No other heat-adapted mice died until 19 days after injection. Six survived 30 days without apparent effects.

Although intraperitoneal infections developed more slowly, only 6 of 18 mice kept at 35 to 36°C died during the 44 days following injection. All of the control mice died during the period. In 3 of the 6 heat-adapted mice which died, no cryptococci were found by smear or culture. Seven were still living in apparent health 60 days after being injected.

Intracerebrally injected mice showed less

* Rectal temperatures were taken with narrow bulb thermometers made by Rascher and Betzold, Inc., Chicago, Ill.

† Army Medical School strain D-2, isolated from a human case at autopsy.

striking differences between the temperature groups. Some kept at 35 to 36°C outlived all the room temperature controls, however.

With each of the series described above, an equal number of mice was similarly injected but kept at 24 to 27°C for 2 or 8 days prior to being moved to the higher temperature. Mice in each of these sets lived longer than those kept only at room temperature, but fewer survived than in the groups placed at 35 to 36°C immediately after injecting (Table I).

Fatal infections in many of the heat-adapted mice may have accompanied body temperatures under the average of 103°F, where cryptococci remain viable or even increase *in vitro*. Also, the temperature of the incubator fell to 33 and 32°C during two overnight periods, and all rectal temperatures taken in the morning were at or below 100.5°F. Rectal temperatures of incubated mice showing signs of infection usually were below 100.5°F and decreased as the animals became moribund.

In the light of the previous *in vitro* studies,[1] the results given above suggest that a direct effect of temperature on the growth and viability of *C. neoformans* should be considered in explaining the degree of natural resistance shown by rabbits.

Inhibition of virus infections in small animals kept at high environmental temperatures has been observed, according to Francis.[2] Coplin and Mills[3] found that white mice which had been adapted to moist heat were *more* susceptible to *Streptococcus hemolyticus* than were mice kept at lower temperatures.

Temperatures of 103°F and above may be inimical to the growth and viability of other fungi causing systemic mycoses. Textbooks of medical mycology direct that cultures be incubated at both room temperature and at 37° for Monilia, Coccidioides, Histoplasma, Sporotrichum, and Blastomyces as well as for *C. neoformans*. The writer found[1] that the optimum for rapid growth of *C. neoformans* was approximately 29°C and some workers in this field now consider 28 to 30°C to be optimal for all the pathogenic fungi listed above. It would not be surprising, therefore, if more of these organisms fail to maintain themselves at elevated body temperatures.

It is interesting to consider the possible use of fever therapy, alone or combined with chemotherapy, in treating human cryptococcosis (torulosis). Specific therapy appears to be questionable or even lacking entirely,[4,5] and human cases usually show little or no elevation of body temperature. Cox and Tolhurst[6] discuss the possibilities of hyperthermia in the light of the earlier *in vitro* studies of the writer.

Summary. 1. Many mice infected with a pathogenic strain of *Cryptococcus neoformans* and maintained, with elevated body temperatures, at 35 to 36°C, lived longer than all infected mice kept at 24 to 27°C.

2. These and previous *in vitro* studies suggest that a direct effect of temperature should be considered in explaining the degree of natural resistance of rabbits to cryptococcosis.

3. Elevated body temperatures might be useful in assisting treatment of human cryptococcosis.

[2] Francis, Thomas, Jr., In Bacterial and Mycotic Infections of Man. Edited by Dubos, R. J., 1948, p. 98, J. B. Lippincott Co.

[3] Coplin, J. W., and Mills, C. A., *Science*, 1939, **90**. 275.

[4] Cox, Leonard B., and Tolhurst, Jean C., Human Torulosis, 1946, pp. 79, 129, Melbourne University Press.

[5] Conant, Norman F., In Bacterial and Mycotic Infections of Man. Edited by Dubos, R. J., 1948, p. 600, J. B. Lippincott Co.

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