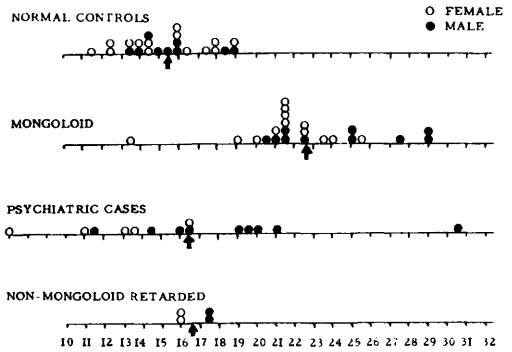

FIG. 1. Triiodothyronine uptake values of erythrocytes, expressed in percentages.

overlapping of values was encountered. Though no correlation with age has been noted by other workers or by us, we found a single remarkably high value in a senile psychotic patient 90 years old.

Summary. The chromosomal anomaly of mongolism suggests the likelihood of enzymatic anomalies. In a series of enzymatic studies in mongolism a tendency to high oxygen uptake and low phosphorylation rate in the red blood cells was encountered. In the present study a high triiodothyronine uptake of rbc was found, which throws light on both the high respiratory rate and the uncoupling of phosphorylation. The range of high thyroid hormone uptake values was almost completely outside the range of normal controls, though a few adult psychiatric cases were found with slightly elevated values.

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Tolerance to Bacterial Endotoxin Produced by Proliferation of Gram Negative Bacteria in the Kidney. (26639)

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Tolerance to the toxic effects of endotoxins of Gram negative bacteria has been demonstrated only after repeated injections of dead Gram negative bacteria or their products, but not during the course of clinical or experimental infections(1,2,3). Previous clinical observations by the author suggested that tolerance to bacterial endotoxin did occur during the course of human pyelonephritis and prompted investigation of the effect of experimental pyelonephritis on the pyrogenic response to endotoxins. This preliminary report is based upon the initial observations made during this study.

Material and methods. Unilateral pyelonephritis was produced in six 2.0-3.0 kg male New Zealand rabbits by intravenous injection of 1×10^9 *E. coli* (0-111:B-4), followed immediately by occlusion of the right ureter for 36 hours. A loose ligature had been placed about the ureter previously through a right flank surgical approach and fixed externally for subsequent tightening. Six weight matched control rabbits underwent a similar operative procedure without ureteral occlusion and received an equivalent endotoxin challenge of 1×10^9 formalin killed *E. coli* (0-111:B-4) on the same day. The pyrogenic response of the control and pyelonephritic rabbits to 0.5 μg of purified *S. enteriditis* lipopolysaccharide (Difco) was determined 10 to 21 days later.

The rabbits were maintained in wire cages in an air conditioned room without restraint during the experimental period. Two hours were allowed for acclimatization and determination of base line temperatures. *S. enteriditis* endotoxin was injected in the marginal ear vein and temperatures were deter-

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TABLE I. Fever Indices in Rabbits Given 0.5 γ *S. enteriditis* Endotoxin.

Rabbits with pyelonephritis	Control rabbits
7	46
16	34
19	52
4	42
17	51
15	46
Mean 13 ± 5.5	45 ± 6.01
$T_{10} = 8.78, P < .001$	

mined every 30 minutes for an additional 6½ hours. Temperatures were recorded on a Yellow Springs Telethermometer using thermocouples implanted deeply in the paraspinous muscles. Temperature curves were plotted on 1.0 cm graph paper with each centimeter representing 30 minutes and 0.5° (F.) temperature. The area above the base line was measured by an Ott Universal Planimeter and this reading was recorded as the fever index.

All glassware was heated at 180°C for 3 hours prior to use. The endotoxin was suspended in pyrogen free saline (Abbott) for injection.

Results. The rabbits in whom pyelonephritis was produced were lethargic and febrile for 3 to 4 days after injection of viable *E. coli.* The control rabbits exhibited similar symptoms for 18 to 24 hours after injection of dead bacteria. Both groups of animals had normal temperatures (<103°F.), were active, and appeared healthy at time of challenge with purified endotoxin.

The challenge dose of 0.5 μg of *S. enteriditis* lipopolysaccharide routinely produced a striking temperature elevation with a maximum rise of 3°F or more and the fever persisted for 6 hours or longer in all control animals. Fever indices of 34 units or more were observed in control animals. The mean fever index for this group was 45 ± 6.0 units.

In contrast (Table I), rabbits with pyelonephritis had maximum temperature elevations of less than 3°F and the temperature always returned to the preinjection level within 4½ hours. The mean fever index (13 ± 5.5 units) in the 6 rabbits with pyelonephritis was significantly lower than that observed in the controls ($T_{10} = 8.78$, $P < .001$).

In addition to the significant difference in magnitude and duration of fever of the 2 groups the pattern of the fever curves was strikingly different. Fig. 1 illustrates the fever curves of a control rabbit and a rabbit with pyelonephritis. The control animals had an initial febrile peak followed by another temperature rise exceeding the initial fever peak 2½ to 3½ hours after administration of endotoxin. This is typical of the pyrogenic response to endotoxin in rabbits. The fever curve of the pyelonephritic rabbit exemplifies the response in endotoxin tolerant rabbits. The initial febrile reaction is essentially unaltered but is followed by a prompt return to base line levels. In all rabbits with pyelonephritis the maximum temperature elevation was observed within 1½ hours after endotoxin administration while maximum temperature always occurred more than 2½ hours after endotoxin challenge in the controls.

Catheterized or post mortem bladder urine from the pyelonephritic rabbits contained *E. coli.* Necropsy revealed moderate unilateral hydronephrosis and histologic pyelonephritis in 2 rabbits and unilateral pyonephrosis in 2 others. *E. coli* was cultured from the right kidney of these 4 animals. Two

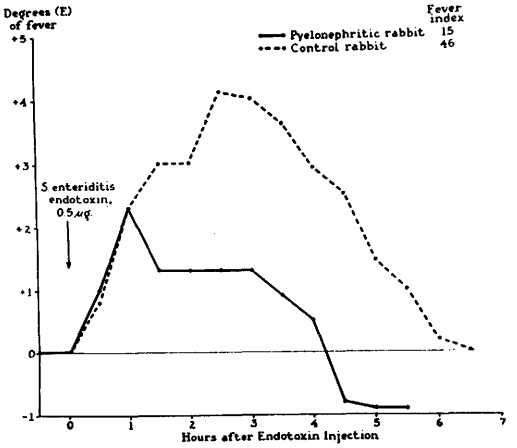

FIG. 1. Fever curves observed in a control rabbit and a rabbit with pyelonephritis after administration of 0.5 μg of *S. enteriditis* endotoxin. Similar curves were observed in the other control and pyelonephritic rabbits.

pyelonephritic rabbits were saved for further investigation. Cultures of the urine and kidneys were sterile and no gross or microscopic renal abnormalities were observed in the control rabbits.

Discussion. Although it has been well recognized that tolerance to endotoxin may be readily induced it had not previously been observed to result from actual bacterial infection(2,3). The present study indicates that infection of the kidney by Gram negative bacteria is capable of inducing tolerance to heterologous endotoxin. A previous study failed to demonstrate pyrogen tolerance following experimental *E. coli* peritonitis in rabbits(2), but these apparently conflicting observations may reflect only a difference in the 2 types of infection. The experimental peritoneal infection was acute and the animals either succumbed rapidly or recovered without evidence of persistent chronic infection. Pyelonephritis, on the other hand, was associated with bacterial proliferation which continued to the time of endotoxin challenge. The latter infection allowed more prolonged exposure of the reticuloendothelial system to endotoxin. This agrees with previous observations that repeated prolonged endotoxin challenge produces tolerance more effectively than a brief exposure.

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Abnormal Palate Morphogenesis in Mouse Embryos Induced by Riboflavin Deficiency.* (26640)

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Kalter and Warkany(1) produced a variety of anomalies in the offspring of pregnant mice by feeding a riboflavin-deficient diet containing galactoflavin (a riboflavin antagonist). The frequency of the various anomalies differed among the several inbred strains used. Cleft palates occurred in 76% of the offspring from treated mice of the DBA strain. Embryonic development was not investigated by these authors, so the following study was undertaken to search for a critical deviation in palate morphogenesis during induction of riboflavin deficiency.

Materials and methods. Pregnant mice of the DBA and C57BL strains were fed a riboflavin-deficient diet containing 12 mg galactoflavin† per g of diet, starting at 10⅓ days postconception and transferring to regular diet at 14⅓ days. Uteri were collected at 14 to 16 days postconception or at 18⅓ days, fixed in Bouin's fluid, and the embryos dissected out for palate examination and for estimates of "developmental age" according to their stage of morphological development (2).

Results. Treated litters of the DBA strain at 14 to 16 days postconception differed grossly from untreated litters in 2 respects. First, the treated embryos were quite edematous; second, the long axis of the snout was usually at right angles to the body axis instead of being pressed down on the chest as in the control embryos.

Table I shows the condition of palate morphology(3) relative to the embryo's morphological rating, the latter calculation being based on the developmental state of several external features(2). The palates of all control embryos had moved to the horizontal plane and started to fuse by morphological rating 11 in this experiment and by 12 in a previous experiment(3). Some of the

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