

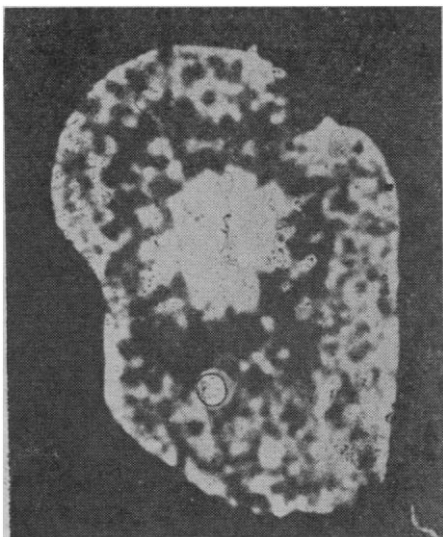


Fig. 1. Hemolysis in human blood agar covering a section of rabbit kidney, 6 hours after inoculation (rabbit No. 117) ($\times 6$). Clear zones of hemolysis are seen against a dark background of unhemolyzed erythrocytes. The peripheral band of spotty hemolysis is over the renal cortex; the central solid zone of hemolysis is over the outer medulla.

staphylococcal lesions were produced either by infection with *Escherichia coli* or by making multiple punctures of the kidney with a red-hot needle. No hemolytic activity could be detected in any of these lesions.

Although it appeared that staphylococci could produce hemolysin when growing within the renal parenchyma of a living animal, it was necessary to exclude the possibility that the conditions for producing hemolysin were present only in the necrotic tissue and exudate of the lesions. If the hemolysin is considered to have an important pathogenic role it should be produced in the tissue before necrosis or exudation. To investigate the temporal relations among hemolysin production, bacterial growth, and tissue injury, 20 rabbits were inoculated intravenously with 10^8 cells of *Staphylococcus aureus* (Wood 46 strain) per kilogram of body weight. Two or three animals were killed at each hour from 6 to 12 hours after inoculation; five were killed 18 hours after inoculation. Half of one kidney was homogenized for quantitative culture. At least five tissue blocks from each animal were studied for the presence of hemolysin by the method already described, rabbit and human erythrocytes being used in each test. Histologic sections prepared from the same tissue blocks used for the hemolysin studies were stained con-

ventionally and studied microscopically (Table 1).

Hemolytic activity was detected in three of the six rabbits killed 6 to 8 hours after inoculation (Fig. 1). At this time the kidneys contained an average of 3.9×10^2 bacteria per gram of tissue, but no bacteria could be found in the microscopic sections. There were no distinct histologic changes, but very subtle degeneration was present in some groups of renal tubules. By 9 to 12 hours after inoculation, hemolytic activity was present in the kidneys of seven of nine rabbits studied. The mean bacterial count was 4.3×10^5 per gram of tissue, and small colonies of bacteria were seen in the interstitial tissue of some of the specimens. Large zones of slight tubular degeneration were seen in several specimens. In one animal with microscopically visible bacterial colonies, small foci of early necrosis were seen adjacent to some of the colonies. No leukocytic infiltrates were present. Eighteen hours after inoculation, hemolytic activity was present in the kidneys of all five animals. The mean number of bacteria per gram of tissue had risen to 6.8×10^6 ; bacterial colonies were seen frequently in the sections and were larger than at 10 to 12 hours. Foci of renal necrosis were found in all animals. Occasionally it was possible to see necrosis in a concentric zone around a bacterial colony. Slight polymorphonuclear leukocytic infiltration was present at the periphery of some of the foci of necrosis. Six of the 15 rabbits in whose kidneys hemolysin was detected had activity against rabbit cells only; all of these were in the 6-to-12-hour group. There were no kidneys that showed hemolysis of human erythrocytes but no hemolysis of rabbit cells. In the kidneys in which both rabbit and human hemolysis was detected, the activity against rabbit cells was always somewhat greater than against human cells.

Evidence of hemolysin production during the genesis of staphylococcal lesions has been obtained in these experiments. The characterization of the hemolysin, however, was not certain. Its activity against various species of erythrocytes indicated that it could not consist entirely of α -hemolysin and suggested the presence of δ -hemolysin. Because of conflicting opinions about the heat stability of δ -hemolysin it is difficult to fully interpret the results. The appearance of detectable hemolysin be-

fore the occurrence of necrosis was consistent with the hypothesis that the hemolysin contributed to the subsequent tissue damage. The evidence at hand, however, did not exclude the possibility that other substances were responsible for at least part of the injury.

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References and Notes

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Melphalan Therapy and Exercise

In his refutation of the report of Bergsagel *et al.* that myeloma patients excreting type II (λ) Bence Jones protein fail to respond to melphalan therapy, Osserman [*Science* **149**, 564 (1965)] cites two such patients who did very well on this drug—a golfer ("in the 90's") and a pool swimmer ("100 to 150 yards daily"). As the pool swimmer cited, I find the underestimation of my athletic prowess annoying. The actual distance covered by my daily swim is 500 to 550 yards. This performance has been maintained regularly over almost 4 years of melphalan treatment. . . .

NAME WITHHELD

5 August 1965

Assessment of Drugs

Schneiderman, Myers, Sathe, and Koffsky [*Science* **144**, 1212 (1964)] have introduced "a substitute ranking measure for the therapeutic index . . . that would be based on minimizing the losses from the failure to cure plus the losses due to toxicity." The authors say that this new measure would allow better ranking of the net effectiveness of drugs than the therapeutic index. We do not agree. We object particularly on the following grounds:

1) Any drug-ranking measure should yield better results for drugs that provide good therapeutic properties over a wide range of dosage than for those