On the other hand, it will be clear to everyone who is familiar with this subject that the above results, and particularly \((E)\), open the way to a theory of the so-called Picard varieties of arbitrary varieties.\(^5\)


\(^4\) I am, however, informed by P. Samuel that he has been able to avoid all such difficulties by the use of a suitable birational transformation.

\(^5\) Weil, A., *Colloque d’Algèbre et Théorie des Nombres*, Centre Nat. de la Rech. Scient., Paris, 1950, pp. 125–127. I have been informed by T. Matsusaka, and also by A. Néron and P. Samuel, that they have independently developed theories of the Picard varieties. By means of the device referred to in footnote 4, Néron and Samuel have been able to derive the basic results on the existence of the Picard variety from the most elementary form of the criterion of the first kind.

**RAPID EFFECTS UPON THE RENAL CIRCULATION PRODUCED BY NEPHROTOXIC GLOBULIN ADMINISTRATION IN THE RAT**

**BY RICHARD W. LIPPMAN, HELEN U. MARTI AND E. ELMO JACOBS**

**INSTITUTE FOR MEDICAL RESEARCH, CEDARS OF LEBANON HOSPITAL, LOS ANGELES, CALIFORNIA**

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Although rabbit anti-rat-kidney serum has been shown to contain antibodies that localize in the glomeruli,\(^1\) renal tubule cells also are damaged by the administration of this serum or of rabbit anti-rat-kidney gamma globulin (nephrotoxic globulin, NTG). Indeed, the damaging effect of NTG on renal tubule cells has been shown in tissue culture explants, where indirect circulatory effects are excluded.\(^2\) It has been suggested that the tubular damage produced \textit{in vivo} by administration of NTG might result from either a direct effect upon the tubule cells or circulatory disturbances subsequent to NTG administration, or from a combination of these two factors.\(^3\)

Various methods have been used to study circulatory changes in the kidney. The injection of foreign materials, such as neoprene or India ink, may produce distortions of the vascular pattern, as a result of mechanical or pharmacologic effects. Such a quasi-physiologic method as the measurement of renal blood flow by means of para-aminohippurate or diodrast clearances cannot be used after NTG administration, since the
animals are anuric for at least 2 hours, a period of critical importance. The fluorescent dye vasoflavine presents technical difficulties which we have not mastered with entire satisfaction.

For these reasons, we have now devised a very simple method of examining the renal circulation. The rat was placed under light ether anesthesia, the abdomen was opened widely, the abdominal viscera were retracted gently with pads of cotton dipped in warm 0.85% sodium chloride solution, and a kidney was exposed to direct observation. The solution under investigation was then administered by intravenous injection, in a foot vein, and the kidney was observed for changes in the surface appearance. At any desired time the renal pedicle was rapidly and tightly occluded by application of a clamp, thus trapping blood in the renal vascular bed, since the artery and vein were simultaneously occluded. The kidney, with clamp on pedicle, was rapidly removed en bloc and a ligature was placed around the pedicle before removing the clamp. The entire kidney was then dropped into 10% neutral formalin in 0.85% sodium chloride solution. After 24 hours the kidney was sliced in half, and fixation was continued for another 24-hour period. Paraffin sections were made at a thickness of 15 μ, and were stained by the benzidine method of Ralph.4

Control globulin (GC) and NTG were prepared by the methods previously described in detail.5,6 In the control animals 1.0 ml. of GC (17.0 mg. total protein) was administered by intravenous injection. In the other animals 1.0 ml. of NTG (23.0 mg. total protein) was administered. For this experiment 39 rats of the Slonaker-Addis strain6 were used.

In the 8 male, 150-g. animals given GC no observable change in the surface appearance of the kidney could be seen during 2 minutes after the globulin injection. The kidney was clamped and excised, after the 2-minute period of observation, and sections were made for histologic examination. It was noted that the glomeruli contained erythrocytes in the capillary channels and, except for occasional rouleaux, their number was such that they could be identified as discrete bodies. Small numbers of erythrocytes could be seen in the peritubular capillaries and venules. Occasional dilated venous channels could be seen in the cortical area, and, adjacent to these, the peritubular capillaries appeared to contain more blood than vessels in other areas. Blood could also be seen in the major vessels and in the vasa recta, extending toward the pelvic papillae.

After the administration of NTG a dramatic succession of events was observed on the surface of the kidney, in situ. Within 15 to 45 seconds after the injection was given, small livid areas, similar to petechiae, were seen on the exposed renal surface. These were so deeply red in color that, at times, the intervening renal tissue appeared to be blanched. This appearance was only by comparison with the deeply colored areas, and no true blanching occurred. The "petechiae" rapidly increased in number
until there was a gradual fusion of these livid areas, and the entire kidney became a deep, meaty red, but this color was not cyanotic. The complete change occurred within 2 minutes in most instances, with only an occasional animal that required 3 minutes. This experiment was performed on 19 male, 150-g. animals and, of these, in 7 the kidney was clamped and excised at intermediate stages, while in 12 the kidney was removed after 2 minutes or slightly more, when the gross surface change had become maximal. When sections were examined, it was found that the glomeruli contained many more erythrocytes than were contained in the glomeruli of animals which had received GC. Many more rouleaux were present, and the erythrocytes were at times so closely packed that it was impossible to identify them discretely. The number of dilated venous channels in the cortical area was increased, and there was an increase in the amount of blood contained in the peritubular capillaries and venules. In addition the vasa recta contained more blood than in the control specimens.

For comparison, 6 specimens were obtained in which the renal vein was isolated and ligated for 2 minutes prior to application of the pedicle clamp and removal of the kidney. In addition, in 6 other animals the renal artery was ligated for 2 minutes prior to application of the clamp and removal of the kidney. In specimens in which the renal artery had been ligated the entire kidney appeared to be almost devoid of blood, with a few isolated erythrocytes in each glomerulus and with very little blood in the peritubular capillaries and other vessels. In specimens obtained from animals in which the renal vein had been ligated there was massive congestion of the venous channels, including the peritubular vessels, but there was no significant change in the glomerular blood content.

While the technique described here does not exclude the possibility of intrarenal shifts in blood distribution during the period between application of the clamp and penetration of the fixative, the likelihood of a distorted picture is very much less than in most other methods that have been used to study the renal circulation. It is of interest to note that, in any given kidney section, there was some variation in the blood content between different radial segments. The experimental differences, however, far exceeded the variability observed in individual sections.

The most remarkable observation in this experiment was the speed with which NTG administration affects the renal circulation. Since the mixing time in the rat is approximately 2 minutes,7 and the vascular changes observed in the kidney begin after only 15 seconds, it would seem probable that such changes occur almost instantaneously when NTG arrives at the kidney. In previous work the speed with which such major changes occur has not been appreciated, and observations have usually been made at much longer intervals, ranging from 30 minutes to 1 week after the administration of NTG.
Obstruction to the venous outflow from the kidney, as demonstrated here, fills the peritubular vessels but does not appreciably alter the glomerular blood content. After NTG administration, the glomeruli, as well as the peritubular and venous channels, contain an increased amount of blood. Since efferent arteriolar constriction would increase the glomerular blood content but probably would diminish the amount of blood in venous channels, it would seem reasonable to suppose that the events observed are explained by an increased amount of blood reaching the kidney from the arterial side, rather than by obstruction to the venous outflow at any point. This idea is confirmed by the color change which, when grossly observed, does not have the appearance of cyanosis, which one would expect with venous congestion alone.

Exploratory experiments performed with India ink injection and vaso-flavine, in spite of the technical difficulties, have given results that confirm the information obtained by the much simpler method described here.

In the light of these experiments, it seems clear that the administration of NTG does not result in tubular ischemia. Additional preliminary experiments have shown that the renal hyperemia observed here lasts for some time, certainly more than 15 minutes, although possibly less than 1 hour. It would seem more reasonable to believe that the tubular damage after NTG administration is the consequence of a direct, non-circulatory effect upon the tubular cells.

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4 Ralph, P. H., Stain Technol., 16, 105 (1941).
5 We are deeply grateful to Prof. Dan H. Campbell and Jay Banovitz, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, for preparation of the NTG and GC used in these experiments.
6 Addis, T., and Gray, H., Growth, 14, 49 (1950).