Influence of Emotional Stress on the Renal Circulation

ROLF BLOMSTRAND and FOLKE LÖFGREN

THE very important question as to whether and in what way emotional stress interferes with the blood circulation in the kidney is as yet on the whole unanswered.

Some reports are found in the literature which state that the production of urine is quantitatively and qualitatively influenced by stimuli emanating from the psychical sphere. The results are based mainly on experiments in which various clearance techniques have been employed. Dogs, subjected to unpleasant stimuli, react with an inhibition of diuresis, according to an investigation of Dobreff (1926). Rydin and Verney (1938) obtained the same result. Antidiuresis in rabbits after emotional disturbance was observed by Brod and Sirota (1949). O'Connor and Verney (1941-42, 1945) produced an emotional reaction in dogs and thereby ascertained in addition to reduced diuresis an increase in the chloride excretion. Blake (1951) incited emotion in dogs by frightening them with automobile horns and established considerable diuretic changes, among others a reduction of the sodium excretion. Bing and Vinther-Paulsen (1952) observed a blanching of the kidney in mice in connection with fright reactions. Bykow and Alexejew-Berkmann (1930, 1931) let dogs drink water under certain constant circumstances whereby conditioned reflexes were established. Later these were capable of increasing the diuresis when they were evoked without simultaneous water supply. Similar investigations were carried out by Marx (1931) and by Eagle (1933). Hoff *et al.* (1949) demonstrated that an electrical stimulation of pressor areas in the cerebral cortex in cats produces a renocortical ischemia.

Psychogenetically produced changes in the renal function have also been observed in humans. As early as 1877 Charcot described the occurrence of anuria in connection with an hysteric attack. Marx (1926) gave an account in his work "Die psychische Beeinflussung des Wasserhaushaltes" of the influence of hypnotic suggestion on the diuresis in man. Similar observations were made earlier by Heilig and Hoff (1925). Smith (1939-40) described examples of altered diuretic conditions during alarm in man which he interpreted as being dependent on psychogenic renal vasoconstriction. Frey (1950) emphasized the clinically well-known fact that psychic influences strongly affect the urine production.

The aim of the present study is to ascertain whether and in what way the renal circulatory pattern is influenced in a state of emotional stress.

Material and Methods

This investigation was carried out on 22 adult cats weighing between 1.8 and 5.1 Kg. A urethral catheter (#4) was introduced into the aorta descendens via the right common carotid artery under etherization. The catheter was passed so far down that its tip was immediately above the kidney level which was x-ray controlled. In the catheter was injected a 5% solution of heparin, 0.15 cc./Kg. of body weight. This dose proved to be sufficient for preventing coagulation in the catheter canal

From the Institute of Anatomy, University of Lund, Lund, Sweden.

Received for publication June 20, 1955.

during the relatively long time the experiment lasted. The catheter canal was then closed. The incision in the neck was sutured and the free end of the catheter was fastened in the skin between the scapulae. A good while after the completion of ether administration but with the animal still anesthetized 1 cc. of India ink per Kg. of body weight was slowly injected in 3 of the experimental animals in order to obtain an idea of the circulatory pattern in the kidney.

The other experimental animals were treated as follows: A leather strap with an attached leash was loosely fastened around the thorax, and the animal was transferred to a "sleeping box," where it was allowed to sleep for a couple of hours or even more if it seemed to want to sleep longer. Before the animal became completely awake infiltration anesthesia was performed in the median line of the abdomen with 4% solution of adrenalin-free procaine, which was accomplished in the majority of cases without any noteworthy reaction. The animal was left thereafter in peace in the sleeping box for another 30 minutes. When the experimental animal left the sleeping box it appeared on the whole to be very little affected by the treatment which it had undergone. Thus a cat of a friendly nature which liked to be petted would begin to purr when patted, and in some cases the animal ate and drank.

Two especially quiet and placid animals were injected when awake with India ink in the same manner as described in the foregoing to ascertain to what extent the actual surgical technique and the previously mentioned treatment had a disturbing effect on the hemodynamic state of the kidney. After having completed the injection an incision was rapidly made in the procainized abdomen and the kidney was removed. The animal was killed by a rapid cut up through the diaphragm and the heart. The remaining 17 experimental animals were confronted with a barking dog. A rage reaction was thereby evoked in which the cat's pupils became maximally enlarged, the ears were pressed backward on the head, and the tail became bushy in the characteristic manner of a furious cat. It snarled, spit, showed its teeth, bared its claws, and struck with its paws toward the dog. Feces and urine were often passed. India ink was injected under as constant conditions as possible and the animals were treated as described in the foregoing. The exterior of the excised kidney was examined, whereafter it was bisected and the cut surface was studied under a binocular lens. The India ink-filled glomeruli stood out very clearly and it was easy to record whether or not these had been accessible to the India ink injection in the different levels of the cortex. The kidney was fixed in a 10% solution of formaldehyde, whereafter 100-200 μ thick frozen sections were prepared. In some cases the sections were stained with benzidine.

Results

Absence of Emotional Stress

The kidneys from the 3 animals injected with India ink under anesthesia were all uniformly darkly tinged by India ink on the surface. On examination of the cut surface the cortex appeared as a dark border around the lighter and more reddish medulla (Fig. 1). Except for a certain variation in the amount of India ink in the individual glomeruli the cortex presented a uniform picture, with a homogenous India ink-filling of all parts and levels of the vascular bed. On inspection with a lens it was seen that the vessels of the medulla also contained a moderate amount of India ink.

The distribution of India ink in the kidneys from the 2 especially quiet and placid animals, which had been injected while awake without previous confrontation with a dog, agreed essentially with that obtained from animals injected under anesthesia. There was perhaps an exceedingly slight unevenness in the distribution of India ink in cortex but no definite difference could be noted.

Induced Emotional Stress

Kidneys from the cats that had been confronted with a dog were generally more or less strongly blanched on the surface, which could be practically free from India ink. The

characteristic of this group, however, was a mottled renal surface. In certain cases large strongly blanched areas alternated with smaller ink-filled spots. Sometimes the upper or lower pole of the kidney was observed to be completely ink free, separated from the other ink-filled surface by a distinct line of demarcation. Often it was a question of an entirely irregular spottiness, where the ink-filled areas varied filled (Fig. 2). In all cases there was a constriction of different parts and components of the cortical vascular bed, whereby the passage of India ink into a certain region was completely or partly prevented. Distended glomeruli were not observed and, therefore, the contraction probably did not lie behind the glomerulus in the vas efferens but always in front of it. Sometimes all the glomeruli which

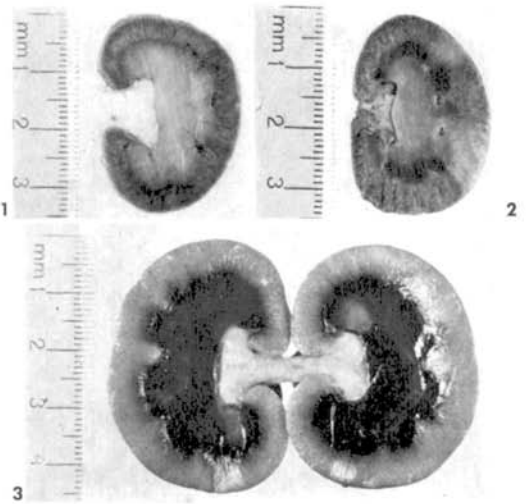

Fig. 1. Kidney section from a cat at rest (intravital India ink injection). **Fig. 2.** Kidney section from a cat in a state of emotional stress. Alternating blanched and ink-filled areas in cortex (intravital injection). **Fig. 3.** Kidney section from a cat in a state of emotional stress. Medulla saturated with India ink but cortex uniformly ink free (intravital injection).

greatly in size. Over the India ink-pigmented fields the renal capsule appeared very often to be elevated and fluctuating. Incision revealed at times concentration of an ink- and blood-tinged serous fluid under the renal capsule, corresponding to these areas. On the whole it was typical that on bisection of the kidney abundant thin fluid flowed from the cut surfaces. In other words, the kidney was edematous and swollen with distended capsule.

In correspondence to this spottiness of the renal surface the cortex was incompletely ink belong to one and the same interlobular artery were disconnected from the circulation, sometimes only a few of them. In this way an ink-filled region could sometimes comprise the entire breadth of the cortex, sometimes only its outer or inner level or also a field in its intermediate part. It should be strongly emphasized that the basal part of the cortex which contains the so-called juxtamedullary glomeruli did not differ in any way in its reaction from the other levels of the cortex. The juxtamedullary glomeruli are just as often

and accidentally shunted off from the circulation as the other glomeruli. At times the ink-free region is as wide as only a couple of interlobular arteries but most often considerably more.

In some cases the cortex and practically all the glomeruli were inaccessible to the injection of India ink. In these cases the medulla was strongly saturated with ink and the cortex lay as a light border around the black medulla, a picture in direct contrast to that we obtained from animals at rest (Fig. 3). Careful inspection revealed in these cases that no glomeruli were ink-filled in the real sense but only very blackly ink-tinged. Certain glomeruli, however, appeared more distinctly than others and these were usually located more often peripherally than basally.

Occasionally the ink-free region extended like a sector straight through the cortex and medulla right down to the papillary tip, but it is characteristic that the medulla as a whole was more or less saturated with ink, most strongly in the subcortical layer. The degree of the ink injection of the medulla appears to be inversely proportional to that of the cortex, so that the more intensive and comprehensive the capillary constriction in the cortex the greater the ink concentration in the medulla. The fine ink streaks which run from the medulla a little way into the cortex are veins which empty into the proximal part of the interlobular veins.

Discussion

In the first place we have to thank Walter B. Cannon for our knowledge about the physiological basis of emotions. He demonstrated that the visceral and somatic reactions that attend every emotion are released by way of the sympathetico-adrenal system and that they can be regarded as an adaptation of the organism in response to the demands of the actual situation. That emotional stress in rats produces a lymphopenia in intact animals but not in those whose adrenal cortex has been removed provides more recent evidence that a discharge of adrenalin takes place.[15] The explanation proposed is often referred to as Cannon's "emergency theory," even if we know today that Cannon's "downward discharge" does not go only over the adrenal medulla but also over the adrenal cortex and hypophysis. Verney (1947) thus showed that emotional stress caused a discharge of antidiuretic hormone, therefore an effect of the neurohypophysis.

Different investigators, among them Bard (1928), have demonstrated that emotional reactions such as rage presuppose an engagement of the posterior part of the hypothalamus, just that area which is currently regarded to be sympathetic in nature.[20, 32]

Renal Circulatory Patterns

The circulatory pattern which appears in the kidney during a state of rage—a more or less anemic cortex but a considerably well-filled medulla—resembles the picture of renal circulation which Trueta *et al.* describe. Trueta believes that under certain conditions because of greater sensitivity to stimuli and constrictor substances in the corticular glomeruli, the blood is diverted from the cortex through the juxtamedullary glomeruli and medulla. Thus this circulatory pattern is obtained if adrenalin is administered or if the sympathetic nerves around the renal pedicle are electrically stimulated. In spite of intensive research throughout the world no one, however, has succeeded in confirming unreservedly the findings of Trueta. The present study, to be sure, has found in a state of rage a displacement of the blood in the kidney in favor of the medulla, but the juxtamedullary glomeruli did not deviate in any way from the others in the mode of reaction or degree of ink penetration. On the contrary, many cases were observed where the juxtamedullary glomeruli were empty when the more perpiheral ones were filled.

Vasa Rectae Verae

Thus, if in our opinion it is hardly plausible that a shunting of the blood takes place via the juxtamedullary glomeruli, according to Trueta's view, it is, nevertheless, conceivable that the circulatory pattern which we have recorded can arise if the medulla received blood from another source than the vasa rectae

spuriae. Smith (1951) believes with the support of clearance techniques that the nonglomerular circulation of the medulla is insignificant from a physiological point of view. But even if these vessels are few and insignificant, they are, of course, if they remain patent during a simultaneous constriction of the cortical vessels, sufficient for permitting the passage of the small amount of India ink required for staining the medulla on injection in sharp contrast to the otherwise blanched kidney. The nonglomerular blood vessels to the medulla have been called the vasa rectae verae and they emanate from the thick-calibered arcuate and interlobar arteries. The current opinion as to this nonglomerular blood supply of the medulla dates from observatsions made by Virchow (1857), Retzius (1858), Schweigger-Seidel (1865) and others. Landois (1891) even believed that the blood could be shunted through the vasa rectae verae without having to pass the cortex. Palmlöv (1949) writes . . . "whole series of medullary vessels can often be seen emerging directly from an arcuate vessel." The present authors have also frequently had occasion to ascertain how the vessels emerge from the part of the circumference of the arcuate arteries that is opposite to the medulla. Sooner or later these vessels, like the vasa rectae spuriae, are subdivided into a great many finer arterioles, thereby making horsetail-like formations situated intertubularly in the medulla. In our opinion the so-called Ludwig's vessels appear to be morphologically related to these vasa rectae verae. The former emanate especially from the vasa afferentes, which belong to the juxtamedullary glomeruli.

Glomerular Degeneration

MacCallum (1926, 1939) maintains that the entire blood supply of the medulla is originally provided by the cortical vasa efferentia but that later in life or under pathological renal conditions some glomeruli degenerate so that finally only one glomerular vessel remains to form the connecting link between the original vas afferens and the vas efferens. Thus in this manner a nonglomerular blood supply to the medulla should be established. Trueta has studied these degenerated glomeruli in corrosion preparations and has pointed out that they lie basally in the cortex, thus belonging to the juxtamedullary type of glomeruli. According to Trueta, all the vasa rectae verae which possibly exist in a kidney arise secondarily through such a degenerative process. Smith (1951) regards their functional significance as problematic.

Arteriovenous Anastomoses

Notwithstanding a possible shunting of the cortical vessels it is conceivable that the circulation in a restricted sense may proceed through true arteriovenous anastomoses, which have been found in the kidney by physiologists as well as anatomists. Steinach (1885) injected into the carotid artery *Lycopodium* spores too large to pass through the glomeruli. Some of the sphores were refound in the renal vein. Steinach's findings were verified by Golubew (1893). Spanner (1937, 1938) found in the human kidney numerous arteriovenous anastomoses in the sinus, the cortex, and the fibrous capsule. Simkin *et al.* (1948) injected into the renal artery of human subjects glass spheres with a diameter of as much as 400 μ, and into living rabbits spheres with a diameter of up to 180 μ. In both instances the glass spheres were observed to pass out into the renal vein. Shonyo and Mann (1944) have made injections of neoprene into the vascular trunk and confirmed the occurrence of arteriovenous anastomoses. They write: "Such shunts probably occur regularly in the normal renal circulation of several species of animals." They locate these anastomoses among other places in the subcortical zone. Barrie *et al.* (1950) have likewise described connections between arterioles and veins in the region between the cortex and medulla. In our investigation we have ascertained that the subcortical zone is always the most strongly ink-saturated part of the medulla.

Effect of Venous Stasis

The venous network of the medulla is much richer than that of the cortex. If there is an accumulation of India ink on the venous side, the medulla will therefore appear strongly

injected in comparison to the cortex and the condition can easily be misinterpreted as a shunting of the injection fluid through the medulla. Rothlin and Cerletti (1952) have warned against this insidious trap: "Only moderate increases in venous pressure are required to present pictures of a highly filled medullary vascular bed, even if at the same time the arterial inflow is reduced." Of course there is also an increase in pressure in the venous vascular bed on adrenalization of the animal and we could also prove that a rage-reaction kidney exhibited indications of congestion. Lindegård and Löfgren (1953) have demonstrated that kidneys from rabbits poisoned with corrosive sublimate reveal a general venous stasis and postmortem they show a blood distribution very similar to that described by Trueta. Insull *et al.* (1950) have demonstrated that the filling of the cortex and medulla varies greatly with the pressure of the injection. Thus a uniform filling of all glomeruli is obtained with an injection pressure of 50 cm. H_2O, whereas a perfusion pressure of 25 cm. H_2O gives a filling of only the juxtamedullary glomeruli and vasa rectae. Nevertheless we could observe a spotted renal surface as a characteristic picture which indicates that the injection pressure was sufficient for forcing the India ink entirely through the cortex.

Renal Anemization and Essential Hypertension

Tigerstedt and Bergman (1898) found that certain hypertensive substances are of renal origin. We know, primarily from Goldblatt's (1938, 1947) classical experiments, that an anemization of the kidney is required in order to release the mechanism which leads to a transient elevation of the blood pressure. In the discussion little attention has been paid, however, as to whether an anemization of the kidney under physiological conditions actually takes place. The deep influence on the renal circulation which is exerted by emotional stress has been found in the present investigation to be evidenced by an anemization of the kidney. It might be said that we have found a reproduction of Goldblatt's experiments in nature. Emotional stress seems to act quite simply as a considerable number of Goldblatt's clamps placed on the peripheral branches of the renal vascular trunk.

On this account these findings can perhaps be included in the discussion on the pathogenesis of essential hypertension, naturally with the knowledge of its exceedingly complex and polyphyletic nature. It should be reasonable to assume that the anemization of the kidney which follows emotional stress leads on the one hand to a hypoxemia, which can conceivably become directly deleterious to the renal vasculature if it is established frequently and for a long period of time; on the other hand, indirectly through release of pressor agents it causes a transient hypertension, which in turn, repeated sufficiently often, results in time in a renal arteriolar sclerosis (along with sclerosis of the arteriolar vasculature in many of the other organs and tissues of the body), followed by manifest hypertonia.

It has frequently been brought out in discussion that the essential hypertension is often established in people with a certain psychic constitution and against a background of a certain emotional pattern. The interested reader is referred to the reports of Binger *et al.* (1945) and Wolff *et al.* (1948).

A closer investigation of the question as to whether stresses of modern life and a certain psychic mode of reaction can be manifested somatically as an essential hypertension is one of the most urgent problems of the present day. Neurogenic as well as humoral factors must be considered. In regard to the latter attention must be paid to the vasolability of the kidney cortex under psychogenetic influence.

The reason that certain animals reacted with a spottiness in the cortex and others with a shunting of larger vascular regions could not be elucidated. One should perhaps be inclined to believe that the phenomena were related to the duration or intensity of the rage reaction, but this does not seem to be the case. Probably individual variations, such as a varied sensitivity in the renal vasomotor apparatus, should be considered, perhaps in the same way as the cutaneous vasomotility in the face of humans varies considerably from person to

person during emotional stress. Several investigators have postulated that it is just such a constitutional instability of the vasomotor system as a whole which is the real cause of the development of hypertension in certain individuals under the stresses of modern life.

Summary

Cats reduced to a state of emotional stress after confrontation with a barking dog exhibit a profound alteration of the renal circulation. The cortex is more or less strongly anemized. This is evidenced on intravital injection of India ink either as an irregular mottling or as a uniform absence of ink in the cortex, whereas the medulla is hyperemic or strongly ink injected. No diversion of the blood or India ink through the juxtamedullary glomeruli is noted. The tendency of the renal cortex to become anemized under psychogenic influence with the subsequent release of pressor agents ought to be regarded in a consideration of the pathogenesis of essential hypertension.

References

1. Bard, P. *Am. J. Physiol.* 84:490, 1928.
2. Barrie, H. J., *et al.* *Lancet* 258:23, 1950.
3. Bing, J., and Vinther-Paulsen, N. *Acta physiol. scand.* 27:337, 1952.
4. Binger, C., *et al.* *Psychosom. Med.* 7:378, 1945.
5. Blake, W. *Am. J. Physiol.* 165:1, 1951.
6. Brod, J., and Sirota, H. *Am. J. Physiol.* 157:31, 1949.
7. Bykow, K. M., and Alexejew-Berkmann, J. A. *Arch. ges. Physiol.* 224:710, 1930.
8. Bykow, K. M., and Alexejew-Berkmann, J. A. *Arch. ges. Physiol.* 227:301, 1931.
9. Cannon, W. B. *Am. J. Psychol.* 39:106, 1927.
10. Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear and Rage.* New York, Appleton, 1929.
11. Charcot, J. M. *Lectures on the Diseases of the Nervous System.* London, 1877.
12. Dobreff, M. *Arch. ges. Physiol.* 213:511, 1926.
13. Eagle, E. *Am. J. Physiol.* 103:362, 1933.
14. Frey, E. *Die Funktionen der gesunden und kranken Niere.* Berlin, Germany, Springer, 1950.
15. Gellhorn, E., and Frank, S. *Proc. Soc. Exper. Biol. & Med.* 71:112, 1949.
16. Goldblatt, H. *Harvey Lect.* 33:237, 1937-38.
17. Goldblatt, H. *Physiol. Rev.* 27:120, 1947.
18. Golubew, W. Z. *Internat. Mschr. f. Anat. u. Physiol.* 10:541, 1893.
19. Heilig, R., and Hoff, H. *Deutsche med. Wchnschr.* 51:1615, 1925.
20. Hess, W. R. *Vegetative Funktionen und Zwischenhirn.* Basel, Switzerland, Schwabe, 1947.
21. Hoff, E. C., *et al.* *Fed. Proc.* 8:76, 1949.
22. Insull, W., *et al.* *Am. J. Physiol.* 163:676, 1950.
23. Landois, L. *A Text-Book of Human Physiology.* London, Griffin, 1891.
24. Lindegård, B., and Löfgren, F. *Kungl. Fysiogr. Sällsk. i Lund Förhandl.* 23: No. 6, 1953.
25. MacCallum, D. B. *Am. J. Anat.* 38:153, 1926.
26. MacCallum, D. B. *Am. J. Anat.* 65:69, 1939.
27. Marx, H. *Klin. Wchnschr.* 5:92, 1926.
28. Marx, H. *Am. J. Physiol.* 96:356, 1931.
29. O'Connor, W. J., and Verney, E. B. *Quart. J. Exper. Physiol.* 31:393, 1941-42.
30. O'Connor, W. J., and Verney, E. B. *Quart. J. Exper. Physiol.* 33:77, 1945.
31. Palmlöv, A. *Scand. J. Clin. Lab. Invest.* 1: 308, 1949.
32. Ranson, S. W. *Tr. Coll. Physicians Philadelphia* 2:222, 1934.
33. Retzius, A. *Virchows Arch. Path. Anat.* 15: 392, 1858.
34. Rothlin, E., and Cerletti, A. *J. Mt. Sinai Hosp.* 19:138, 1952.
35. Rydin, H., and Verney, E. B. *Quart. J. Exper. Physiol.* 27:343, 1938.
36. Schweigger-Seidel, F. *Die Nieren der Säugetiere und der Menschen.* Halle, 1865.
37. Shonyo, E. S., and Mann, F. C. *A.M.A. Arch. Path.* 38:287, 1944.
38. Simkin, B., *et al.* *A.M.A. Arch. Int. Med.* 81:115, 1948.
39. Smith, H. W. *Harvey Lect.*, 166, 1939-40.
40. Smith, H. W. *The Kidney.* New York, Oxford, 1951.
41. Spanner, R. *Klin. Wchnschr.* 16:1421, 1937.
42. Spanner, R. *Verhandl. Anat. Ges.* 45:81, 1938.
43. Steinach, E. *Sitzgsber. Wien. Akad. Wiss., math.-naturwiss. Kl.* 90:171, 1885.
44. Tigerstedt, R., and Bergman, P. G. *Am. J. Physiol.* 8:223, 1898.
45. Trueta, J., *et al.* *Studies of the Renal Circulation.* London, Blackwell, 1947.
46. Verney, E. B. *Proc. Roy. Soc. London, s. B.* 135:25, 1947.
47. Virchow, R. *Virchows Arch. Path. Anat.* 12: 310, 1857.
48. Wolff, S., *et al.* *Ann. Int. Med.* 29:1056, 1948.