THE RENAL COMPLICATIONS OF HEMATIN INTOXICATION AND THEIR RELATION TO MALARIA *

WADE H. BROWN, M.D.
CHAPEL HILL, N. C.

Descriptions of the paroxysm[1] and of the changes in the blood[2] produced by the intravenous injection of alkaline hematin and their relation to human malaria have been presented in previous articles, and it is the object of this paper to add a third group of conditions which may properly be described as the renal complications of hematin intoxication.

The description of these renal complications is based on a study of two classes of material: First, the urine and kidneys of a large series of rabbits, in which the production of renal lesions and disturbances of function were not the objects of the experiments, but were merely incidental; and second, twenty rabbits, in which the production of renal complications was made the prime object of the experiments.

The hematin and hematin solutions used in these experiments were the same as in former experiments. The animals were fed, for the most part, on a variety of green foods, with hay and ground grains, and allowed to take water at liberty. The food in a given experiment was kept constant as to quality throughout the experiment, and the amount of water consumed during twenty-four hours was determined by supplying measured amounts in vessels so arranged that none could be wasted. The water remaining in the vessel at the end of twenty-four hours was measured and corrections for evaporation were made from control vessels. In only a few experiments were definite amounts of water given by stomach tube. The urine collected from metabolism cages was used for routine study, but the qualitative findings were confirmed by bladder urine in many instances. Observations were made on the normal urine for one or two days before the injection of hematin. In this connection it should be noted that the daily amount and character of rabbit's urine is so variable that but little importance can be attached to slight variations in the amount of urine, the urine-water ratio or the character of the urine. The results of the hematin experiments were controlled by a

* Submitted for publication April 21, 1913.
* Aided by a grant from the Rockefeller Institute for Medical Research.
* From the Pathological Laboratory of the University of North Carolina.

1. Brown, Wade H.: Jour. Exper. Med., 1912, xv, 579.
2. Brown, Wade H.: Jour. Exper. Med., 1913, xviii.

series of animals that received an equivalent volume of alkaline salt solution under the same conditions as those receiving hematin.

The extreme irregularity in the results of these experiments has shown conclusively that no given dose or combination of doses of hematin can be expected to produce a given effect on the kidneys of the rabbit, and the results reported are to be interpreted as the most probable effect from a given degree of hematin intoxication.

THE URINE

Amount.—A single dose of 10 mg. of hematin per kilo of body weight, or less, will produce no alteration in the daily amount of urine. If such doses are repeated from day to day, however, slight increases in the output of urine and in the ratio of the urine to the water consumed are gradually developed. The increased volume of urine is also present where slightly larger doses of hematin are administered, but as the dose approaches 20 mg. per kilo, there is a distinct decrease in both the daily amount of urine and the ratio of the urine to the water consumed. In exceptional instances there may be a complete suppression of urine for twenty-four hours or longer. On discontinuing the hematin, this phase of decreased output of urine gives place to increased urinary secretion and to an increase in the urine-water ratio, both of which exceed the normal within two to three days. This change is more enduring — in one animal it persisted for twenty-one days, when observations were discontinued.

Color.—The urine in hematin intoxication is highly colored, varying from a brownish-yellow to a dark reddish-brown and occasionally shows a greenish fluorescence. A smoky-red urine is seen in some instances.

Acidity and Specific Gravity.—The reaction and the specific gravity of the urine show no constant alterations. Both of these features vary widely in the rabbit under normal circumstances, and the variations after injections of hematin are therefore difficult to relate to any action of hematin.

Albumin and Casts. — A trace of albumin and a few hyalin or granular casts may appear in the urine after even a single injection of 10 mg. of hematin per kilo of body weight. The daily repetition of this dose of hematin seldom fails to produce an albuminuria with casts. As much as 20 mg. of hematin per kilo of body weight will produce a marked albuminuria with an abundance of hyalin, granular and epithelial casts, or even blood casts. Neither the amount of albumin nor the number or variety of casts, however, can be predicted from the amount of hematin injected.

Blood and Hemoglobin.—The most interesting phase of disturbed renal function, referable to hematin poisoning, is the occurrence of

hematuria and hemoglobinuria. Severe intoxication with hematin frequently results in hematuria of a variable degree. The amount of blood may be so slight as not to be suspected from the appearance of the urine, or so great as to give the urine a distinct red or smoky color. The condition is occasionally produced by a single large dose of hematin (20 to 25 mg. per kilo.); it occurs with greater frequency from the maintenance of a given concentration of hematin in the circulation for twelve to twenty-four hours. This can be done best by injecting three or four doses of 10 to 15 mg. of hematin per kilo within such a period of time. The test on the vitality of the animal is a severe one, and the size of the dose and frequency of repetition must be judged by the condition of the animal; even then many fatalities will result before the desired effect is produced.

Free hemoglobin in the urine, not associated with hematuria, has been observed in a very few instances. Hemoglobin was demonstrated by the guaiacum test in voided urine and bladder urine in five animals out of fifty examined. In two of these cases the guaiacum test was confirmed by the spectroscope. Three other animals gave a positive guaiacum test from voided urine which was not confirmed by bladder urine. Of these eight animals, all except three showed, post mortem, either hemorrhagic lesions of the kidneys, extensive hemorrhage into the peritoneal cavity, or both, which might have accounted for the presence of hemoglobin in the urine. Of the three undoubted instances of pure hemoglobinuria, one occurred in the course of a chronic intoxication, and the other two from the repeated injection of 20 to 25 mg. of hematin twice daily; one animal developed hemoglobinuria after the fourth injection, and the other after the seventh. All efforts to devise a method of administering the hematin that would produce this condition in a greater percentage of cases proved futile. Most of the attempts resulted in the production of hematuria. It is evident, therefore, that there are other factors than the hemoglobinuria that are essential to the production of a high concentration of hematin in the circulation.

THE KIDNEYS

Mild hematin intoxication, whether acute or chronic, produces no characteristic lesions in the kidneys. There is a slight increase in the size of the organs and a slight brown pigmentation. The epithelium of the convoluted tubules and of the ascending loops of Henle usually shows parenchymatous degeneration. In the chronic cases a few hyalin casts in the tubules and foci of round-cell infiltration in the boundary zone and in the cortex also furnish evidence of injury.

The injection of large doses of hematin, however, may produce very profound and characteristic lesions. In the acute stages the kidneys

are much enlarged and are uniformly dark-brown or purplish-red in color, or are diffusely mottled with small opaque yellow areas of necrosis and areas of hemorrhage. The kidneys are moist, the cortex is thickened and the straight vessels and glomeruli are intensely congested. The boundary zone usually shows the most pronounced congestion and irregular streaks of hemorrhage may extend from this zone into both the cortex and medulla. In rare instances, small infarcts are present. The most characteristic alterations are found in the glomeruli. The glomeruli are enlarged and their vessels are enormously dilated and congested. In some instances, many of the glomerular capillaries are occluded by hyalin masses that stain a brassy-red with eosin; such glomeruli are apt to show hemorrhage into the capsular space. On the other hand, the glomerular tuft may completely obliterate the capsular space. The glomerular epithelium is very slightly swollen and a few desquamated cells are present. To a less degree, other vessels of the kidney are dilated and congested, while many of the smaller vessels show hyalin thrombi or emboli. Greenish-brown pigment is found, especially in the glomerular capillaries, both as free granules and masses and within phagocytic cells.

The uriniferous tubules, more particularly the convoluted tubules and the ascending loops of Henle, show marked parenchymatous degeneration with desquamation of the epithelial cells, or even foci of necrosis. In extreme instances almost the entire cortical system may be necrotic. Occasionally, the tubular epithelium will show granules of greenish-brown pigment, much of which, as it reacts for iron only after oxidation with hydrogen peroxid[3] and is soluble in dilute alkalies, must be regarded as hematin. This pigmentation is more common in living than in necrotic cells. An abundant albuminous precipitate and many varieties of casts are found in the tubules throughout the kidney. Hemorrhage into the tubules is found in many cases of extreme intoxication. The hemorrhage is usually patchy in its distribution — seldom diffuse — and occurs in the region of those glomeruli that show hemorrhage or occlusion of their vessels. In some of these cases, there is also a diffuse staining of the epithelium with hemoglobin and granules or droplets of hemoglobin are found in the cells, in the lumen of the tubules and in the capsular space. The presence of hemoglobin was observed in three instances in which there was no hemorrhage. The presence of hemoglobin was verified by oxidation with hydrogen peroxid and obtaining an iron reaction, and by the presence of brownish, granular and crystalline deposits in the cells and lumen of the tubules in specimens fixed in a solution of formaldehyd immediately after the death of the animal.[4]

3. Brown, Wade H.: Jour. Exper. Med., 1911, xiii, 477.
4. Browicz: Virchows Arch. f. path. Anat., 1900, clxii, 373.

The interstitial tissues are usually edematous and there may be foci of hemorrhage. Foci of necrosis are usually surrounded and invaded by polymorphonuclear leukocytes.

In two instances anemic infarcts were observed from occlusion of relatively large vessels by masses of hyalin material.

In the early stages of recovery from hematin intoxication and at the time the kidneys are showing an increased urinary secretion, several important changes from the above description are to be noted. The glomerular tufts now decrease to normal size or are shrunken, while the capsular spaces and tubules are dilated and contain desquamated epithelial cells and an abundant albuminous precipitate.

In chronic intoxications, and as recovery from acute intoxications progresses, the kidneys are but slightly enlarged, but still show a brown pigmentation. The surface may present a few scattered areas of hemorrhage and necrosis, as in the acute stage, interspersed with small depressed scars. The glomeruli are irregular, some being enlarged while others are much contracted. The tubular epithelium shows various degrees of degeneration, with a slight desquamation, or even patches of necrosis. Many tubules show regenerating epithelium with numerous mitotic figures. In these areas of regenerating tubular epithelium there is usually a pronounced interstitial infiltration of plasma cells and an increase in the connective tissue.

DISCUSSION

Clinically and pathologically, slight degrees of hematin intoxication cause only such alterations in urine and kidneys as are commonly observed in many febrile conditions. In more severe intoxications the irregularity and uncertainty of the effect on the kidneys is quite striking; some of these cases again show only the disturbances of a febrile state, while others present the clinical picture of an acute nephritis and a very few a definite hemoglobinuria. Throughout, the one constant feature is the albuminuria with casts and degenerative lesions in the kidneys — all probably the result of a slight toxic injury. The wide range of variety in urine and kidney lesions that may be superimposed on this common basis under constant experimental conditions suggests strongly the element of chance in the effect of hematin on the kidneys. This chance factor is operative through the blood-vessels. It has been demonstrated by physiological methods that hematin produces a marked dilatation of the splanchnic vessels[5] and causes injury to the vessel wall. Microscopically, the glomerular vessels in particular show these changes and, in addition, obstruction to circulation in many areas by hyalin thrombi or

5. Brown, Wade H., and Lovenhart, A. S.: Jour. Exper. Med., 1913, xviii. (In press.)

emboli. This occlusion of vessels seems to be the chance occurrence that determines the major part of the renal complications of hematin intoxication. The foci of tubular necrosis are but minute infarcts; the hemorrhage also is largely determined by vascular occlusion, although the injured and weakened vessel wall predisposes to hemorrhage.

A few kidneys have shown such a uniformity in the character and distribution of the lesions that one might be tempted to regard them as instances of acute nephritis, but in view of the great preponderance of lesions that are undoubtedly due to vascular occlusion and injury I am inclined to regard them all as of like nature.

No light has been thrown on the important subject of hemoglobinuria except that it is possible of production by intravenous injections of hematin in a very small percentage of cases. The hemoglobinemia resulting from hematin intoxication undoubtedly reaches the threshold value of a kidney showing vascular and tubular injury at a point below that of the normal kidney.

It is not possible to correlate closely the renal complications of hematin intoxication with those of human malaria. The disturbances of function and the lesions of the kidneys have been found much more pronounced in hematin intoxications than in comparable grades of malarial infection in man, while the predominance of the glomerular lesions observed in these experiments is not found in malaria. These differences are partly due to the difference in the concentration of hematin in the blood. It is believed, however, that the analogy is sufficiently close to render the facts disclosed by these experiments of value as a basis for a clearer comprehension of the mode of production of the renal complications of human malaria.

SUMMARY

1. Mild grades of hematin intoxication produce degenerative lesions in the kidneys and the urine shows a trace of albumin and casts.

2. Severe grades of hematin intoxication result in extensive dilatation, injury and occlusion of the renal vessels by hyalin thrombi or emboli, all of which are most pronounced in the glomerular vessels. Extensive degeneration and necrosis of tubular epithelium, hemorrhages and even anemic infarcts result from these vascular lesions. In such cases, the urine presents the characteristics of an acute nephritis.

3. In rare instances of severe hematin intoxication, hemoglobinuria may occur.

4. During the period of recovery from acute hematin poisoning and in chronic poisoning, the kidneys show both degenerative and proliferative processes. The glomerular tufts shrink and the capsular space and tubules are more widely dilated. The tubular epithelium shows degen-

eration and active regeneration with abundant mitotic figures. There are foci of round-cell infiltration and of connective tissue increase. There is also a slight diffuse increase in connective tissue. The urine is increased in amount and contains albumin with hyaline and granular casts.

5. The renal complications of hematin intoxication are believed to be due primarily to dilatation, injury and occlusion of renal vessels under the action of hematin.