THE EFFECT OF HEMATIN ON THE CIRCULATION AND RESPIRATION.*

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Plates 2 to 5.

In the course of investigations which one of us has been conducting upon the toxic manifestations of hematin when introduced into the animal circulation, the nature of the effects elicited with both sublethal and lethal doses of alkaline hematin was such as to indicate clearly that we were dealing with a substance that possessed a definite action upon the circulation and the respiration. Some phases of the toxic action of hematin in the rabbit have been described in detail in another paper,[1] and it is sufficient here to point out that the most characteristic clinical effect of the injection of small doses of hematin was found to be the production of a paroxysm similar to the malarial paroxysm in man. During the cold stage of this paroxysm, a marked constriction of the skin vessels occurs, seen especially in the ears, with a lowering of the surface temperature. This vasoconstriction gives place to an equally marked dilatation of the skin vessels and elevation of surface temperature with the onset of the hot stage of the paroxysm. It was further noted that, in those animals which succumbed to the toxic action of hematin within a short time after its administration, respiratory distress, marked prostration, extreme pallor, convulsions, and failure of the respiration were almost constant symptoms. In these animals there was usually found, post mortem, a pronounced splanchnic congestion with hemorrhage into the viscera and into the peritoneal cavity.

Accordingly, a study of the physiological action of hematin in

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[1] Brown, W. H., *Jour. Exper. Med.*, 1912, xv, 579.

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alkaline solution offered a hope for a tangible explanation of these and other phenomena, many of which are characteristic alike of both hematin intoxication and human malaria.

The hematin used in these experiments was prepared from ox blood; the mode of preparation of the hematin and the alkaline solution was the same as that employed in experiments previously reported.[2] The solution used in all cases was formed of an 0.85 per cent. sodium chloride solution containing 2 per cent. sodium bicarbonate and either four or five milligrams of hematin per cubic centimeter. The effects obtained by the injection of this solution were controlled by injections of the same preparation of alkaline salt solution as that used in the preparation of the hematin solution. The injections were all made into the femoral vein.

Action on the Circulation.—The effect of hematin upon the blood pressure and upon the distribution of the blood in the body is very pronounced. Following the injection of doses of less than six milligrams of hematin per kilo of body weight in the cat or in the dog, a slight rise of the carotid pressure may occur. The injection of six to eighteen milligrams per kilo, however, produces a great fall of blood pressure in the cat which reaches a maximum in from one to five minutes and remains below normal from twelve to thirty minutes, or even longer in exceptional cases. In the dog the fall in pressure is usually not so great, but the duration of the effect is usually more prolonged than in the cat. The extent to which hematin may lower the blood pressure is shown in figures 1 and 2. Both of these tracings are from the cat and represent respectively effects of doses of eighteen and twenty-two milligrams of hematin per kilo of body weight.

On plethysmographing a loop of intestine and one hind leg simultaneously, and recording alterations in volume with piston recorders, it was found that prior to the fall of blood pressure there occurs a dilatation of the intestinal vessels which begins before the blood pressure starts to fall and continues for a long time. In one experiment the blood pressure remained below normal for about twenty

[2] Brown, W. H., *loc. cit.*

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minutes, when other procedures interrupted the record. In several of the experiments the intestinal dilatation was of an extreme grade. During the fall of blood pressure the vessels of the leg constrict markedly. This compensatory action is not so perfect in the cat, in which the dilatation of the splanchnic vessels is less marked, and the fall of blood pressure is more marked than in the dog. In one experiment the cutaneous constriction started later than the intestinal dilatation, which would suggest that the constriction may be due, in part, at least, to the depletion of the cutaneous vessels to supply the engorged splanchnic vessels. We have concluded, however, that the cutaneous constriction is active for the reasons which follow.

In one experiment a slight rise of blood pressure followed the injection of hematin although the injection caused splanchnic dilatation. From our observations on the heart it is improbable that this rise of blood pressure was due to increased cardiac output, and in this case the constriction of the cutaneous vessels would seem to have more than compensated for the splanchnic dilatation. Unfortunately, there was no plethysmographic tracing from the leg in this experiment.

Figures 1 and 2 show typical tracings of the splanchnic dilatation and its relation to the blood pressure in the cat, while figure 3 shows plethysmographic tracings of the intestine and leg and the carotid pressure of the dog.

The splanchnic dilatation seems to be due almost entirely to the depression of the vasomotor center, since section of both the splanchnic nerves usually prevents entirely the dilatation and greatly reduces or entirely removes the blood pressure-lowering action of hematin. In fact, after cutting the splanchnics, we have noted a rise of blood pressure which further indicates that the cutaneous constriction is active rather than passive to the splanchnic engorgement. In one experiment a distinct but rather small splanchnic dilatation together with a very slight fall of blood pressure followed the injection of hematin after the splanchnics were cut. This single experiment indicates that a small fraction of the dilating effect of the drug is peripheral.

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Action on the Heart.—The only definite effect of hematin upon the rate of heart-beat that we have noted is a slowing. In a few instances where doses of less than six milligrams of hematin per kilo of body weight were injected a transient acceleration of a few beats per minute occurred. Although the degree of retardation of the heart action is extremely variable, within certain limits it is proportional to the size of the dose of hematin. This is especially noticeable in the cat in which a dose of twelve to eighteen milligrams per kilo almost invariably produces a typical vagal pulse (figures 1 and 2). The same effect is less easily produced in the dog. As no slowing of the pulse rate occurs after the administration of atropin or section of the vagi, we may conclude that the slowing is due to stimulation of the cardio-inhibitory center.

An extreme irregularity in the amplitude and rhythm of the heart-beat occurred in many of our experiments on the cat but rarely in experiments on the dog (figure 2).

One experiment was performed with the heart in a plethysmograph and the changes in the heart volume were recorded by means of a piston recorder. The injection of hematin was followed by a marked loss of tone in both systole and diastole and a great decrease in the cardiac output. This reaches a maximum within about one minute and then the tone of the heart gradually returns until it becomes greater than the normal although the output remains diminished (figure 4). The heart, therefore, plays a part in the blood pressure-lowering action of hematin. The relative parts played by the splanchnic dilatation and the decreased cardiac output probably vary greatly in different experiments.

Action on the Respiration.—The primary effect of the large doses in which we employed hematin resulted frequently in an increased rate, but rarely in an increased amplitude of the respirations, a decreased amplitude being much more frequent. It seems probable from our records, however, that had we used smaller doses a stimulation of the respiration would have resulted. The larger doses of hematin produce marked depression of the respiration. In several of our experiments, especially on the cat, the respirations rapidly diminished in size until there occurred a complete cessation of the

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respiration. This period of complete stoppage lasts thirty seconds or longer and is terminated spontaneously by very small respirations which gradually increase in size until the normal is reached. The rate is also slow, following the paralysis of the respiration, and this likewise increases gradually to the normal (figures 1 and 2). Death under hematin is due to paralysis of the respiration, the heart continuing to beat for some time after the respiration ceases.

CONCLUSIONS.

1. Doses of less than six milligrams of hematin and, under certain conditions, larger doses may cause a slight rise of blood pressure.

2. Large doses of hematin cause a profound and prolonged fall of blood pressure. The principal factor in this fall of blood pressure is the marked dilatation of the splanchnic vessels. The splanchnic dilatation either does not occur at all or but very slightly if the splanchnic nerves are cut. The splanchnic dilatation is partly compensated for by a marked constriction of cutaneous vessels and it seems probable that the cutaneous constriction is active and not simply passive to the splanchnic engorgement.

3. Hematin acts upon the cardio-inhibitory center causing a marked slowing of the rate of heart-beat, and in large doses produces a typical vagal pulse or even marked irregularities in the amplitude and rhythm of the pulse. Under hematin the heart at first shows great loss of tone but later the tone increases beyond the normal. The cardiac output for a time is greatly diminished.

4. In the large doses employed by us, hematin depresses the respiratory center and death under hematin is due to paralysis of this center.

EXPLANATION OF PLATES.

PLATE 2.

FIG. 1. Cat; weight, 2.8 kilos. Two injections of 5 c.c. of hematin (9 mg. of hematin per kilo) were given one and one half minutes apart. The second injection was given at 7. Read from left to right.

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PLATE 3.

FIG. 2. Cat; weight, 3.4 kilos. Three injections of 5 c.c. of hematin (7.3 mg. of hematin per kilo) were given two and one half minutes apart, the third injection being given at 5. Read from left to right.

PLATE 4.

FIG. 3. Dog; weight, 11.5 kilos. Four injections of 3.5 mg. of hematin per kilo were given in rapid succession. Read from left to right.

PLATE 5.

FIG. 4. Cat; weight, 2.3 kilos. 5 c.c., or 8.5 mg. of hematin per kilo, were given at 2 and repeated at 3. Read from left to right.

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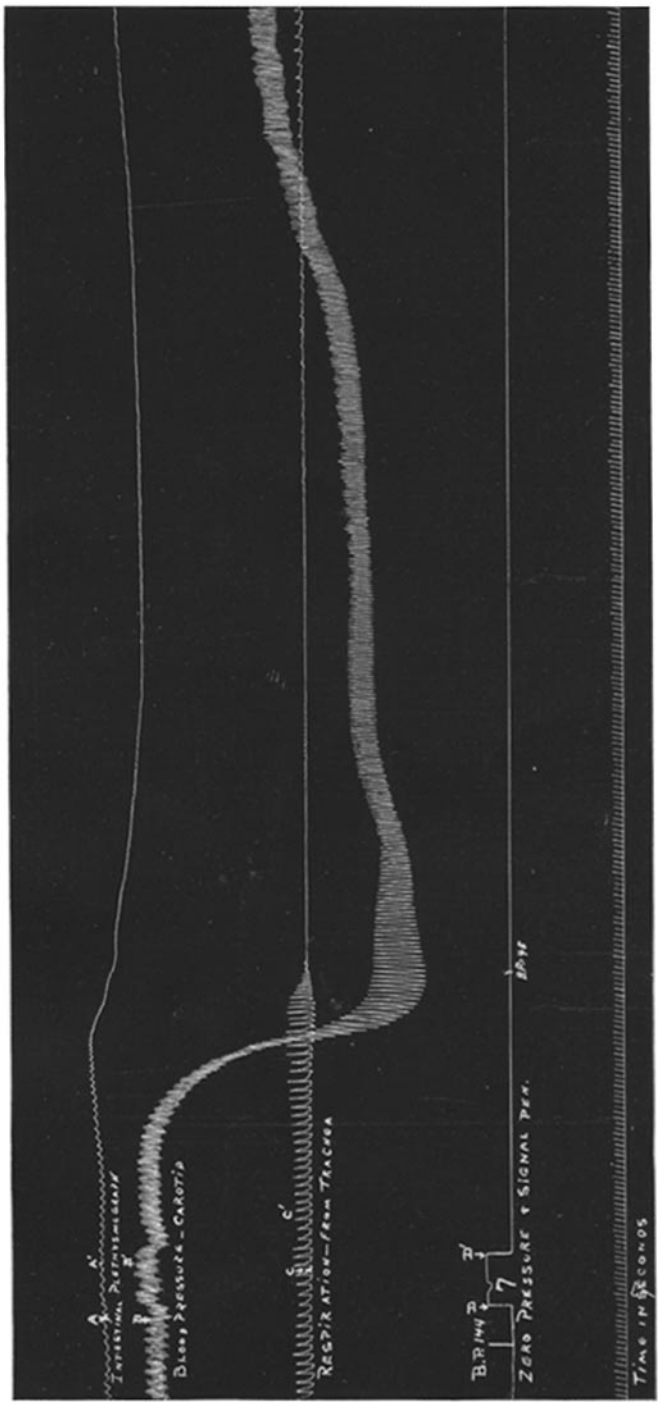

FIG. 1.

(Brown and Loevenhart: Effect of Hematin.)

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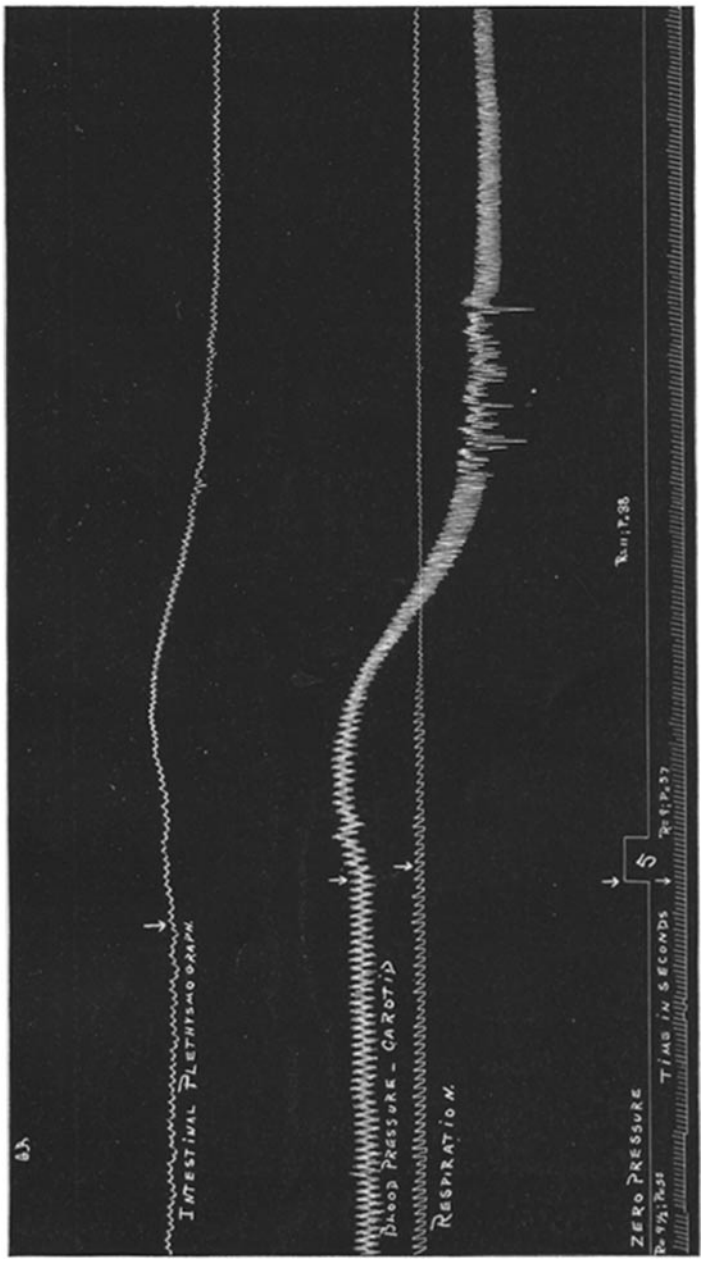

FIG. 2.

Brown and Loevenhart Effect of Hematin.

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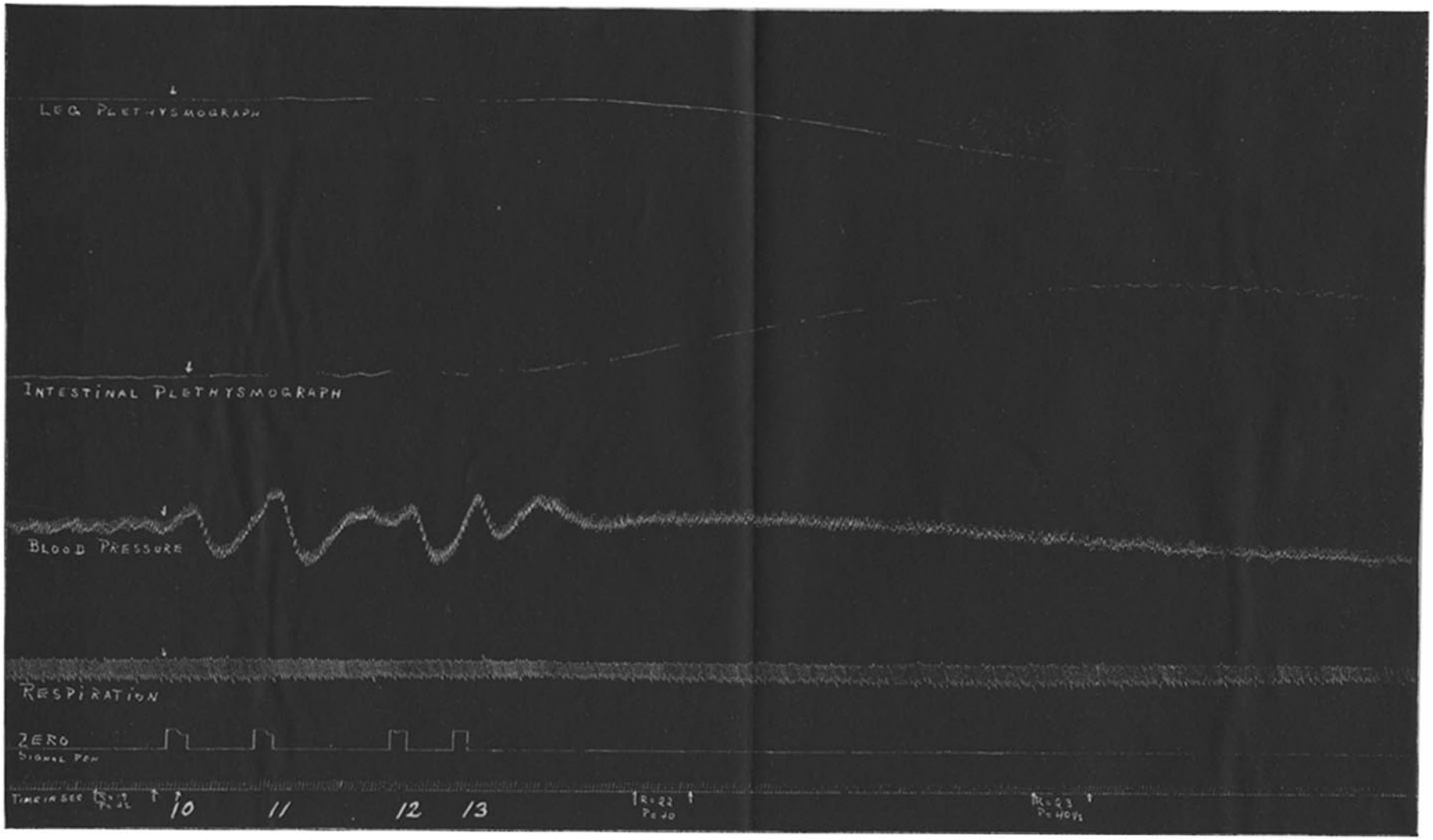

FIG. 3.

(Brown and Loevenhart: Effect of Hematin.)

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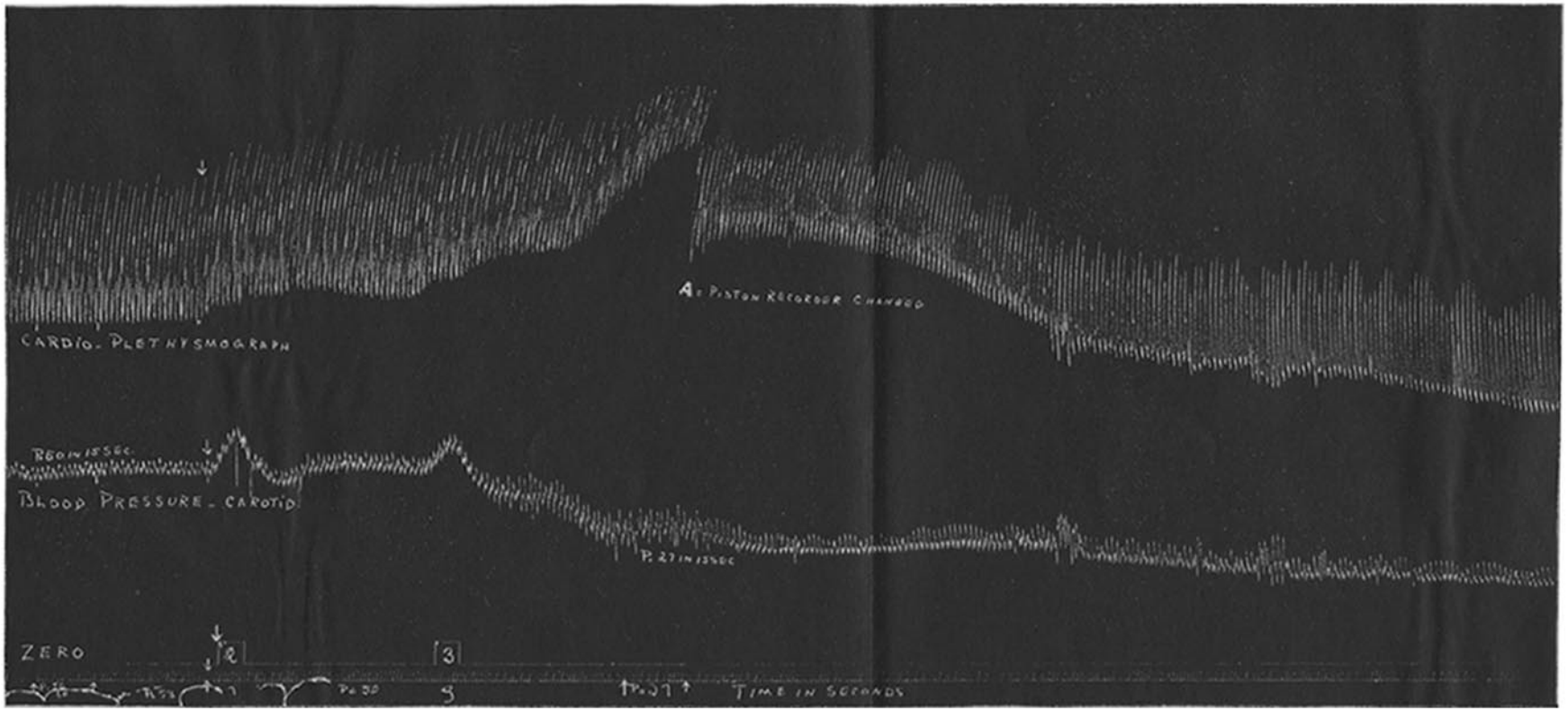

FIG. 4.

(Brown and Loevenhart: Effect of Hematin.)