

The absence of additive phenomena in these experiments does not permit the assumption that these substances may be administered with impunity. The toxic effects of digitalis are well known, and those of calcium are also being recognized. In digitalis administration the presence of a damaged heart in which sudden circulatory accidents may occur, is usually a complicating factor. Likewise, calcium alone produces a wide range of cardiac arrhythmias, some of which might well prove fatal in the presence of preëxisting cardiac damage. It has been observed that atropinized hearts occasionally develop ventricular fibrillation with calcium, and it is possible that hearts which because of disease show a tendency to ectopic ventricular rhythms might be set into ventricular fibrillation by amounts of calcium which produce only transient disturbances in a normal heart. This may be the mechanism of sudden death reported by Wolffe and Bellet which occurred during administration of calcium to a patient suffering from paroxysmal tachycardia.<sup>5</sup>

*Conclusion.* In the normal unanesthetized rabbit heart the effects of calcium and digitalis are not additive.

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#### Total Coproporphyrin I Excretion in Pernicious Anemia.

KONRAD DOBRINER AND W. HALSEY BARKER. (Introduced by C. P. Rhoads.)

*From the Hospital of the Rockefeller Institute for Medical Research.*

The mechanism of the disturbed metabolism of the respiratory pigments in pernicious anemia has been a matter of controversy.<sup>1-4</sup> Theoretically, qualitative and quantitative disturbance may occur at any stage in the construction and destruction of the hemoglobin molecule, but it is not clear whether the increased bile-pigment production and excretion is consequent to a quantitatively increased destruction of hemoglobin similar to that of hemolytic jaundice, or whether it is due to a partial or total pathologic metabolism of the precursors of hemoglobin.

<sup>5</sup> Wolffe, J. B., and Bellet, S., *Ann. Int. Med.*, 1930-31, **4**, 794.

<sup>1</sup> Addis, T., *Arch. Int. Med.*, 1915, **15**, 413.

<sup>2</sup> Eppinger, H., *Die hepatolienalen Erkrankungen*, Berlin, 1920.

<sup>3</sup> Whipple, G. H., *Arch. Int. Med.*, 1922, **29**, 711.

<sup>4</sup> Rous, P., *Phys. Rev.*, 1923, **3**, 75.

Porphyrin and urobilin excretion in a case of pernicious anemia have been investigated quantitatively. It has been reported that an increased coproporphyrin I excretion in both the urine and feces is present during relapse, and that lower values are present during remissions.<sup>5, 6, 7</sup> However, because of the lack of adequate methods the reported data are inconclusive. Watson<sup>8</sup> reported adequate data on feces, but omitted determinations of the porphyrin in the urine.

*Case History.* A 61-year-old white male entered with anemia of 4 years' duration. Inadequate treatment with liver extract had been employed and the disease had progressed. Physical examination showed a subicteric tint of the skin, emaciation, and some atrophy of the papillae of the tongue. Examination of the blood on admission showed 900,000 R.B.C., hemoglobin 23%, mean corpuscular volume 1.13, color index 1.21, icterus index, 7, and W.B.C. 3,250. The blood smear and the histologic picture of the bone marrow were characteristic of pernicious anemia. Gastric analysis failed to reveal free hydrochloric acid, even after histamine. Details of treatment, and hematologic response are briefly summarized in Chart I. The patient received an injection of 5.0 cc. of liver extract (Lederle & Co. concentrate) and 10.0 cc. of liver extract (Eli Lilly & Co.) intramuscularly on the 16th and 17th days of observation respectively.

The methods used for porphyrin separation and quantitative measurement were similar to those previously described.<sup>9, 12</sup> The urobilin was determined as urobilinogen by the Watson modification of the Terwen method.<sup>10</sup> The coproporphyrin excreted was identified as coproporphyrin I by melting-point determination.

Quantitative coproporphyrin and urobilin determinations were made during the periods of relapse, treatment, and remission (Text Fig. 1). The total coproporphyrin output during the 15-day control period in relapse averaged 632 gamma per diem and the urobilinogen averaged 442 mg. Shortly after therapy was instituted the reticulocytes rose rapidly to 60%; during this period there was little change in the total coproporphyrin and urobilinogen output (611 micrograms coproporphyrin and 533 mg. urobilinogen daily average). The amount of coproporphyrin in the urine decreased from 158 to 100 micrograms. After the reticulocyte response was completed and 7 days after the onset of therapy the total amount of coproporphyrin

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<sup>5</sup> Duesberg, R., *Arch. exp. Path. u. Pharm.*, 1931, **162**, 268.

<sup>6</sup> Watson, C. J., *J. Clin. Inv.*, 1935, **14**, 116.

<sup>7</sup> Brugsch, J., *Th. Z. ges. exp. Med.*, 1935, **95**, 490.

<sup>8</sup> Watson, C. J., *J. Clin. Inv.*, 1937, **17**, 389.

<sup>10</sup> Watson, C. J., *Arch. Int. Med.*, 1931, **47**, 698.

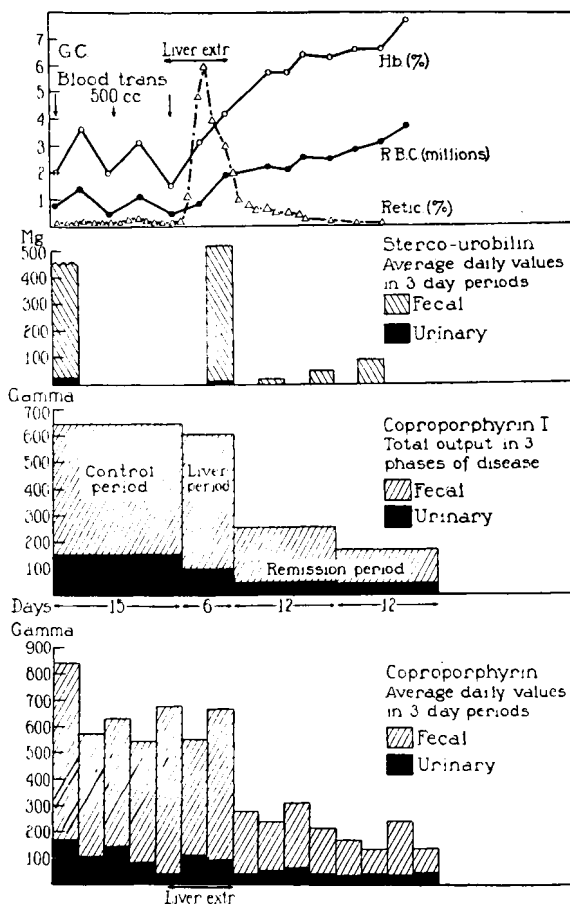


FIG. 1.

excreted decreased rapidly to 261 and 172 micrograms daily average and for the urobilinogen to 40 mg. and 93 mg. respectively in the next two 12-day periods. Increased protoporphyrin was excreted in the feces.

Previously published work has demonstrated the close relationship between coproporphyrin I excretion and construction of the respiratory pigment, and has shown evidence of a proportional as well as a disproportional construction of Type I and Type III porphyrins in various pathological conditions.<sup>9, 11, 12, 13</sup> Whereas a definite dis-

<sup>9</sup> Dobriner, K., *J. Biol. Chem.*, 1936, **113**, 1, and in press.

<sup>11</sup> Dobriner K., Localio, S. A., Strain, W. H., *J. Biol. Chem.*, 1936, **114**, XXVI.

<sup>12</sup> Dobriner, K., Strain, W. H., Localio, S. A., *PROC. SOC. EXP. BIOL. AND MED.*, 1937, **36**, 752, 755.

<sup>13</sup> Dobriner, K., *PROC. SOC. EXP. BIOL. AND MED.*, 1937, **36**, 757.

turbance of pigment construction in pernicious anemia is indicated by this study, it is not possible to state whether the observed increased coproporphyrin I excretion is a simple increase of a normal process or is an abnormal or disproportional type of construction such as is present in porphyria.<sup>11</sup>

The levels of coproporphyrin I and urobilin excretions in pernicious anemia are similar to those reported for hemolytic jaundice.<sup>12</sup> Moreover, the changes in the rate of output after specific therapy in the two conditions are alike. These facts suggest that the increased coproporphyrin I excretion in pernicious anemia during relapse reflects a normally increased production proportional to an increased Type III porphyrin formation rather than a pathological production resulting in a disturbed ratio between the formation of Type I and Type III compounds.

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### **Intravenous Injection of Aminoacids in Regeneration of Serum Protein Following Severe Experimental Hemorrhage.**

ROBERT ELMAN. (Introduced by E. A. Graham.)

*From Department of Surgery, Washington University School of Medicine, and Barnes Hospital, St. Louis.*

Nine pairs of experiments were performed, dogs of the same size, sex and condition being used as far as possible for each experiment. Under local anesthesia 3.5% of the body weight was bled from the femoral artery and immediately the same volume of Ringer's solution replaced into the femoral vein. One half hour later the first specimen of blood was taken from the jugular vein. Each dog was then given intravenously over the course of 3 hours a volume of fluid equal to 3.5% of the body weight. To one, 10% glucose in Ringer's was given; to the other 5% glucose plus 5% aminoacid mixture in Ringer's. Six hours after the beginning of the injection a second sample of jugular blood was taken; a third specimen was obtained 24 hours later when the experiment was finished. Additional samples of blood were taken in all animals to determine the level of its aminoacid content. No symptoms were produced by the injections and the dogs remained in good condition throughout the period of observation. Though allowed water, all food was withheld, not only during the experiments but for a period of 48 to 72 hours previous-