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# Experimental Induction of a Disorder Resembling Toxemia of Pregnancy in the Rabbit.

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A clinical and pathological investigation of a spontaneous and highly fatal intoxication in pregnant rabbits indicated that the disorder was of endogenous origin and that it was analogous to toxemia of pregnancy in women.[1, 2] The occurrence of the disease in typical form in pseudopregnant and in post-partum animals eliminated the possibility of a toxic factor arising from the products of conception. On the other hand, the presence of productive changes in the pituitary in contrast to the degenerative character of lesions in other organs suggested that an abnormal secretory activity might be a primary factor in the genesis of the intoxication. Accordingly, attempts were made to induce the disorder in experimental animals with various pituitary preparations.

Pituitary extracts were prepared by first grinding the anterior lobes of fresh beef glands with sterile sand to form a paste. After the addition of 3 cc of distilled water per gram of anterior lobe tissue, the mixture was agitated for 6 hours in a mechanical shaker. Following centrifugation, the supernatant fluid was withdrawn and used immediately or stored for a brief interval at freezing temperature.

Subcutaneous or intraperitoneal injections of 5 cc of this extract, 500 rat units of Antuitrin S* or 1 cc of Antuitrin* made on the 27th day of gestation and repeated on the 29th day induced a disorder which resembled the spontaneous disease in many particulars. On the other hand, control inoculations of sterile saline or fresh and autolyzed extracts of beef muscle and liver failed to reproduce any feature of the condition.

The clinical pictures and pathological changes induced by beef pituitary preparations, Antuitrin S and Antuitrin were similar but, in general, a less severe disorder followed the administration of Antuitrin S than occurred after injections of the other materials. The severity of the induced disease was directly proportional to the incidence of spontaneous toxemia of pregnancy in the family group used and the different clinical types of the spontaneous disorder were

1 Greene, H. S. N., *J. Exp. Med.*, 1937, **65**, 809.

2 Greene, H. S. N., *J. Exp. Med.*, 1938, **67**, 369.

* Parke, Davis & Company.

duplicated in almost every respect in experimental animals of different genetic constitution. In some instances, loss of appetite and slight indisposition were the only manifestations, while in others the picture was that of a profound intoxication with excessive salivation, thirst, acetone breath and prostration the cardinal signs. The blood pressure was always decreased and a drop to 30 mm of mercury from a preinoculation level of 80 mm commonly followed the administration of the beef pituitary preparation.

The chemical blood changes were less pronounced but were in general agreement with those observed in the spontaneous disease. The most marked alterations from normal were the presence of acetone, elevation of non-protein nitrogen, urea nitrogen and creatinine, decrease of calcium and increase of inorganic phosphate. The uric acid value was not consistently changed.

The disorder following a single injection on the 27th day of gestation occasionally terminated in death, while that induced by 2 injections given on alternate days resulted in death in approximately 40% of cases. At autopsy, animals that died or were killed 2 to 3 days after the last injection showed changes comparable with those observed in spontaneous toxemia of pregnancy and in addition, the ovaries contained large, hemorrhagic follicles. The predominating changes were found in the liver, kidneys, and adrenal glands. Microscopically, the liver showed widespread, intense, fatty degeneration and areas of necrosis which were sometimes peripheral in distribution but were usually scattered without constant relation to the zones of the lobule. The kidney showed pronounced fatty changes and, occasionally, bilateral cortical necrosis was found but acute inflammatory changes were never noted. Fatty degeneration occurred in all portions of the adrenal and frequently a homogeneous, fatty, necrotic zone entirely separated the cortex and the medulla. As a rule, the adrenal changes were most pronounced and the liver and kidney lesions least marked in animals that died after a short, clinical disorder, while the reverse held in animals that died or were killed after a longer illness.

At the present time, aqueous anterior lobe extracts in various concentrations and dosages have been administered in 45 pregnant rabbits and a disorder comparable to one of the clinical types of spontaneous toxemia of pregnancy resulted in 95.5% of cases. In like manner, the administration of Antuitrin S to 13 pregnant animals gave positive results in 84.6% of cases. Antuitrin has been used in 4 experiments and toxemia resulted in all instances.

The spontaneous intoxication is not identical with the toxemias of

pregnancy in man but the rôle of the 2 diseases in pregnancy is the same and such differences as exist may well be of a generic order. In like manner, there are some differences between the spontaneous and experimental intoxications in the rabbit which may be attributable to the fact that in one case the disease is of gradual evolution while in the other it is precipitated abruptly. The evidence so far obtained is sufficient to warrant further investigations of the possible rôle of the pituitary in the etiology of the human disorder.

## 10510

## Rate of Elimination of Divinyl Ether.

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We have found that the rate of elimination of divinyl ether from an anesthetized dog does not follow the formula first developed for acetone by Widmark[1,2] $C_t = C_o.e^{-V\lambda t/m}$ where $C_o$ is the original concentration of volatile substance in the blood; $C_t$ the concentration after time t; t, the time; V, the alveolar ventilation; $\lambda$, the partition coefficient between air and blood; and m, the "reduced volume". A mathematical treatment has also been applied to the elimination of ethyl ether by Henderson and Haggard.[3,4] Widmark's simplified formula is $C_t = C_o.e^{-\alpha t}$ where $\alpha$ is the "elimination constant" and which in the logarithmic form becomes $\log C_t = \log C_o - \alpha t$. If, therefore, the rate of elimination of a substance which follows this formula is plotted on semi-logarithmic paper with $\log C_t$ plotted against t a straight line should be obtained the slope of which is determined by the elimination constant.

Curve I in Fig. 1 is the typical straight line obtained for ethyl ether with dogs based on the data of Haggard.[4] Curve II, also from Haggard's data, shows the effect of administering carbon dioxide on the rate of elimination by increasing the alveolar ventilation. At point (A) on the curve the administration of carbon dioxide was stopped and the subsequent portion is essentially parallel to Curve I.

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1 Widmark, E. P., *Acta Med. Scandinavica*, 1919, **52**, 57.

2 Winterstein, H., *Die Narcose*, Berlin, 1926, p. 220.

3 Henderson, Y., and Haggard, H. W., *Noxious Gases*, New York, 1927

4 Haggard, H. W., *J. Biol. Chem.*, 1924, **59**, 753.