mg histamine base per kilo of tissue. It is, therefore, somewhat doubtful whether any histamine was present. The liver assayed 5.0 mg of histamine base per kilo of tissue.

Three 400 g fetuses, obtained at term, were anesthetized with ether and arranged for the recording of the carotid blood-pressure. Two cc per kilo of peptone solution were injected intravenously in each case, and the resulting reactions recorded. The peptone solution used was a 10% solution of Bacto-Protone-Difco, which had previously been acidified, shaken with permutit, filtered, and then neutralized. Such solutions contain negligible quantities of histamine, are rich in proteose and have been found very satisfactory.[2] A severe reaction occurred in each instance. The reaction was fatal in one, and probably would have been fatal in the others, although in these any possible recovery was prevented by bleeding them to death so that histamine determinations of the blood could be made. The blood was incoagulable in each instance. The plasma in each instance had a histamine activity equivalent to 0.6 gamma histamine base per cc when tested on the etherized and atropinized cat.

Discussion. Histamine occurs in the liver, if not in the skeletal muscle of the dog fetus. The quantity appears to be less than that occurring in adult dogs, although more information is necessary to establish the average relationship. Peptone shock can occur in the dog fetus and, as is the case in the adult dog, it is associated with the liberation of histamine. These findings would seem to have a bearing on the question of the metabolism of histamine, indicating that an appreciable part, at least, of the histamine store in the tissues owes its existence to other than bacterial production.

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Toxic and Therapeutic Response of Blood and Bone Marrow to Sulfanilamide.

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Sulfanilamide may produce an acute hemolytic anemia, which comes on rapidly after therapy and may terminate fatally. More commonly, however, the drug causes a mild type of anemia which is

familiar to all physicians. The acute anemia is characterized by a marked reduction in the erythrocyte count and hemoglobin, a macrocytosis, reticulocytosis, leucocytosis, and increased icterus index. Wood[1] has reported an incidence of 21 cases of acute hemolytic anemia among 522 patients treated with sulfanilamide.

Therapeutic doses of sulfanilamide were administered to 9 patients. This group consisted of 4 cases of subacute bacterial endocarditis, 2 normal patients, and one case each of streptococcus sore throat, chronic pyelitis and Hodgkin's disease. The dosage varied from 24 g to 72.3 g given over a period of 8 to 17 days. Complete haematological studies including sternal bone-marrow aspirations were made before, during and after therapy. A modification of Pontoni's[2] technic was utilized in doing the differential cell counts of the bone marrow. The mean cell diameters of the erythrocytes were computed in 4 cases. Blood sulfanilamide levels were determined according to the method modified by Marshall.[3]

It was observed that there was a definite increase in the mean corpuscular volume of the erythrocytes after the administration of sulfanilamide. The average mean corpuscular volume (Table I) of the 9 cases before therapy was 86.0 cubic microns and after, 100.2 cubic microns respectively. The increase in volume was not dependent on the dosage of sulfanilamide. The effect of sulfanilamide upon the total erythrocyte count was variable. The depression in the erythrocyte count ranged from 190,000 to 1,280,000 with an average drop of 660,000. The hemoglobin, leucocytes, reticulocytes and icterus index were not markedly altered.

With the exception of some increase in the number of stab forms, the differential white cell count remained practically unchanged. Normoblasts were not found in smears of the peripheral blood. The mean cell diameter of the erythrocyte was slightly increased. The

TABLE I.
Average Value of Nine Cases Before and After Sulfanilamide.

	Hemoglobin	Erythrocytes	Leucocytes	Hematocrit	Mean corpuscular vol.	Reticulocytes %	Icterus index	g sulfanilamide
Before sulfanilamide	11.5	3,96	8,883	34.2	86.0	0.85	5.2	41
After sulfanilamide	10.3	3,30	7,816	33.1	100.2	1.14	6.1	

[1] Wood, W. B., *J. A. M. A.*, 1938, **111**, 1916.

[2] Pontoni, L., *Hæmatologica*, 1936, **17**, 833.

[3] Marshall, E. K., *J. Biol. Chem.*, 1937, **122**, 263.

free sulfanilamide level of the blood varied from 2.1 mg to 12.5 mg per 100 cc of blood with an average value of 6.2 mg per 100 cc of blood.

Therapeutic doses of sulfanilamide produce a moderate normoblastic bone marrow hyperplasia with most of these cells at the orthochromatic stage. The myeloid elements and megakaryocytes showed no conspicuous change. The differential cell count of the bone marrow showed an average myeloid-erythroid percentage of 69.5% to 30.5% before therapy, and a value of 46.2% to 53.8% after therapy. There is no relationship between the dosage of the drug and the normoblastic reaction of the bone marrow.

The toxic effect of sulfanilamide was observed in one case (Table II). It will be noted that an acute hemolytic anemia developed after the administration of 15 g over a period of 8 days. This was manifested by a marked depression of the hemoglobin and erythrocyte count, pronounced leucocytosis, macrocytosis, reticulocytosis, and elevated icterus index.

TABLE II.
Case of Acute Hemolytic Anemia.

	Hemoglobin	Erythrocytes	Leucocytes	Hematocrit	Mean corpuscular vol.	Reticulocytes %	Icterus index	g sulfanilamide
Before	9.1	3,50	14,500	32.0	91.4	0.9	5.0	15 in 8 days
After	5.25	1,66	57,800	18.0	108.4	58.0	15.0	

A moderate shift to the left of the Schilling Index was found in the differential cell count of the peripheral blood. The bone marrow showed a marked normoblastic and pronormoblastic reaction with most of the normoblasts of the basophilic type. The differential cell count showed a myeloid-erythroid percentage of 71% to 29% before therapy, and a value of 26.5% to 73.5% after therapy. The megakaryocytes were not affected.

Machella and Higgins[4] have recently demonstrated a marked anemia with increase in the volume of the red cells in white rats following the administration of 1 g of sulfanilamide per kilo of body weight. Using therapeutic doses of the drug in man, our results were quite similar. Continuation of sulfanilamide therapy after the development of macrocytosis did not induce an acute hemolytic process. An increase in the volume of the red cells was usually found to occur about the seventh day. The acute hemolytic anemia pro-

[4] Machella, T. E., and Higgins, G. M., *Am. J. Med. Sci.*, 1939, **198**, 804.

duced by sulfanilamide differs from the macrocytic anemia just mentioned in that it develops between the third and sixth days of therapy and is rapidly progressive in degree. By virtue of its rapid onset after the use of therapeutic doses, it is reasonable to believe that this form of anemia is due to an idiosyncrasy or susceptibility to the drug, rather than to the administration of toxic doses.

The macrocytic anemia which commonly follows treatment with sulfanilamide can be ascribed either to the development of an acute hepatitis or the direct effect of the drug upon the bone marrow. Due to the relatively short interval between the onset of therapy and the macrocytosis, it is not likely that the anemia is induced by liver changes. On the contrary, evidence of the action of sulfanilamide on bone marrow is demonstrated by its normoblastic response.

Conclusion. Therapeutic doses of sulfanilamide commonly produce macrocytic anemia and a normoblastic bone-marrow reaction. In the acute hemolytic anemia the bone marrow shows a more marked normoblastic reaction with predominance of young forms.

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Estrogen-Induced Hypospadias in the Female Rat.*

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Normal development of the external genitalia of the female rat can be grossly modified by treatment with estrogens, either antepartum or immediately postpartum.[1-4]

The normal female rat has a clitorine urethra with the urinary meatus located at the tip of the clitoris (the word "clitoris" is used to indicate the female phallus and not just the glans clitoridis). The proximal portion of the clitorine urethra is anatomically a true

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1 Hain, A. M., *Edinburgh Med. J.*, 1935, **42**, 101.

2 Greene, R. R., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 503.

3 Greene, R. R., and Ivy, A. C., *Science*, 1937, **86**, 200.

4 Turner, C. D., and Burkhardt, W. L., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 267.