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Changes Occurring in the Blood Picture During Fetal Life.

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(Introduced by F. H. Swett.)

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While studying the blood of newly born infants, the characteristics of the blood picture at that period were observed to differ from those of the adult in a very interesting manner. In brief, the erythrocytes were present in greater numbers, were of greater mean volume, and the hemoglobin content was higher than normally seen in human adults. These observations raised the question concerning the nature of the factors which effect those alterations between the blood pictures of the 2 periods of life. The possibility was also suggested that a clear understanding of these factors might aid in the elucidation of the mechanisms of various blood dyscrasias of adult life. With these ideas in mind it seemed advisable to establish first the normal course of blood changes which occur in the fetus during intra-uterine life, and then later to investigate the mechanism of their production. The present work deals with a series of blood studies on embryos of the domestic pig, *Sus scrofa.*

This experimental animal was chosen because its blood is very similar to that of the human and because experimentation of recent years has demonstrated the presence of the so-called anti-anemic principle in the mucosa of the hog stomach. This latter fact suggested the possibility that this substance may exert a similar controlling effect on the hematopoietic function in the pig and in the human—as well as in various other animals less adaptable to laboratory experimentation. Support has been given to this idea by the work of Miller and Rhoads[1] who, working with the pig, produced a form of hyperchromic anemia with associated gastric anacidity by means of dietary restriction. Extract made from the livers of these anemic animals was not therapeutically effective when administered to patients suffering from pernicious anemia.

While work on the present series was in progress, Wintrobe and Shumacker[2] published a large series of blood studies on fetuses of various animal species, including the pig. Our findings corroborate their observations on the latter, and since a thorough review of the

[1] Miller, D. K., and Rhoads, C. P., *J. Clin. Invest.*, 1935, **14**, 153.

[2] Wintrobe, M. M., and Shumacker, H. B., Jr., *Am. J. Anat.*, 1936, **58**, 313.

pertinent literature was included in their paper it will be omitted here.

Pig embryos were obtained from the abbatoir immediately after they had been removed from the parent animal, and the hearts were still beating when blood specimens were drawn by cardiac puncture. The study included three embryos from each of eighteen litters which ranged in age from 42 to 106 days of gestation as estimated from the crown-rump length.[3] Variations in the size of litter mates were frequent and some variations in the blood picture were noted among animals of the same approximate age. Immediate studies by two observers included red blood counts, hemoglobin determinations and reticulocyte counts. The hemoglobin determinations were made by the acid-hematin method, using Hellige hemometers corrected by Van Slyke oxygen saturation so that 15.5 gm. of hemoglobin per 100 cc. blood were equivalent to 100%. The reticulocyte counts were made on fresh blood smears stained by brilliant cresyl blue. Fixed Wilson-stained smears were prepared for study

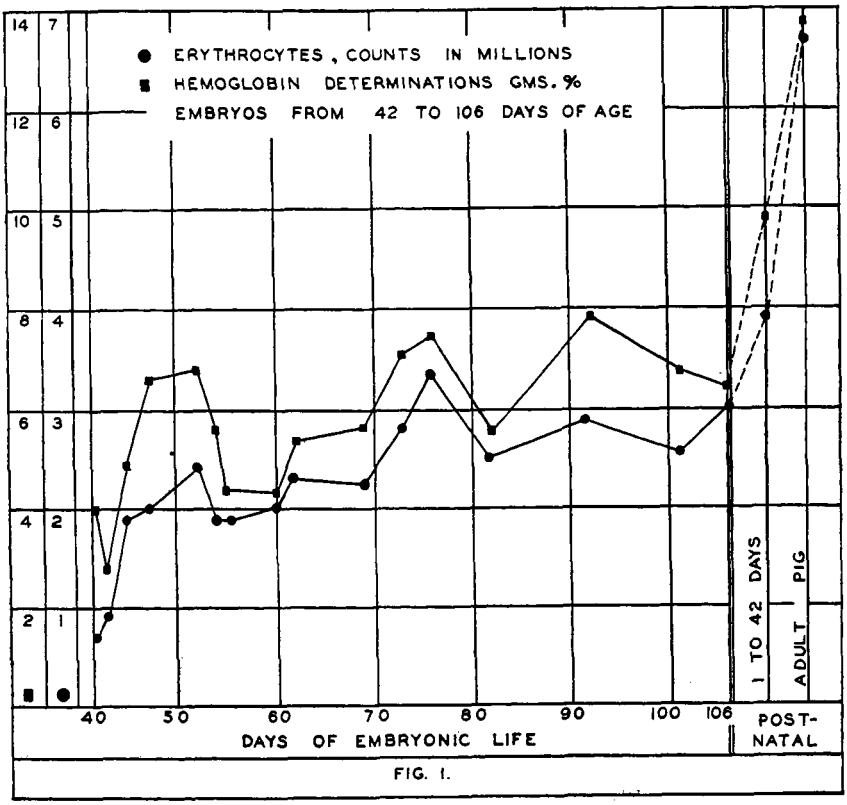

FIG. 1.

[3] Warlick, B. L., *J. Morph. and Physiol.*, 1928, **46**, 59.

and for cell measurements. Hematocrit determinations[4] were made on oxalated blood and mean corpuscular volumes and mean corpuscular hemoglobins were calculated from the results.

In the earliest embryos studied (42 days gestation) the erythrocyte counts and hemoglobin determinations were low (Fig. 1). At this time the mean corpuscular volume and mean corpuscular hemoglobin were high (Fig. 2). Characteristic erythrocytes of this period were large (Fig. 3) and showed striking variations in size

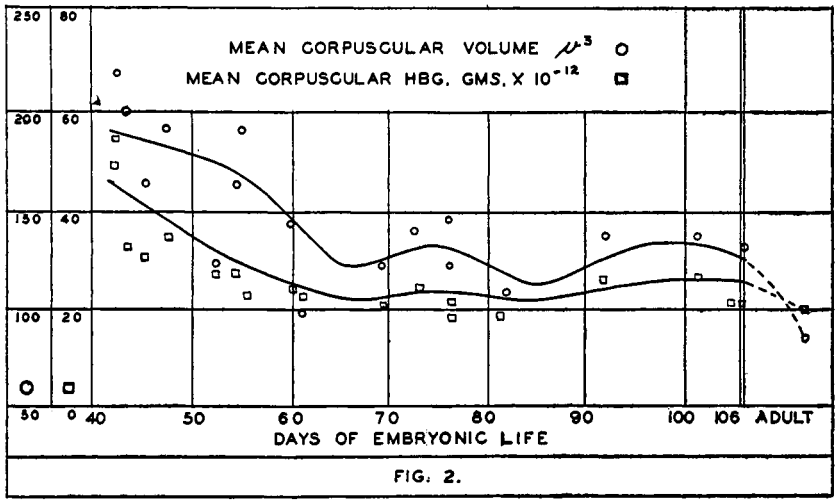

FIG. 2.

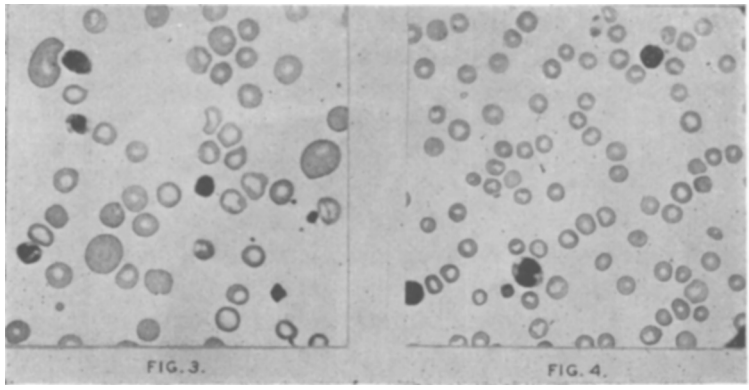

FIG. 3.
Macrocytosis with marked variations in size and shape of erythrocytes at 42 days. Wilson Stain (Photomicrograph x 375).

FIG. 4.
Blood at 106 days showing relative and actual decrease in size of erythrocytes with greater uniformity of contour. Wilson Stain (Photomicrograph x 375).

[4] Wintrobe, M. M., *Am. J. Med. Sci.*, 1929, **177**, 513.

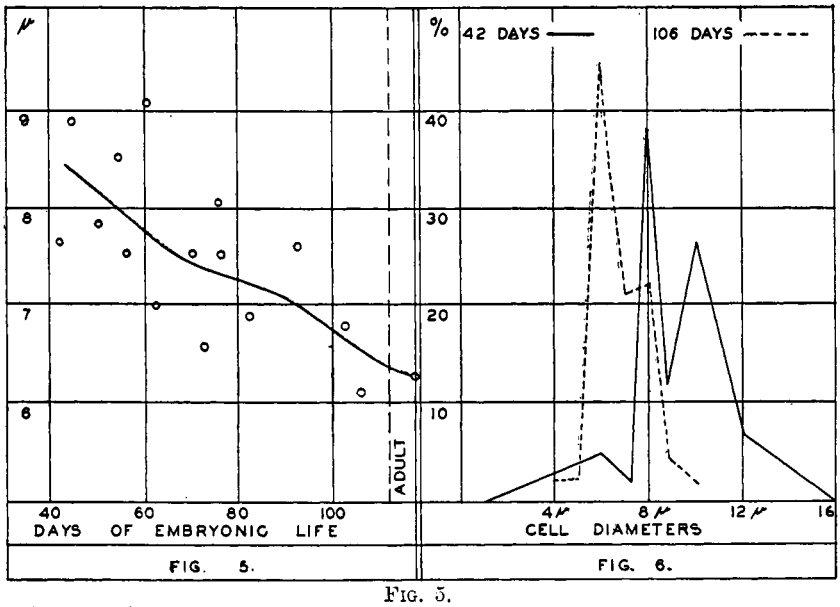

FIG. 5.
Average diameter, in micra, of erythrocytes at various stages of embryonic life.
FIG. 6.
Distribution of erythrocyte diameters at 42 and 106 days of embryonic life.

and form. Many bizarre immature forms were seen and many of these were deeply basophilic. Reticulocytes were numerous in the blood of the very young embryos.

As the period of gestation lengthened, interesting changes were noted. There was a steady increase in the total number of erythrocytes and in the amount of hemoglobin. At the same time there was a fall in mean corpuscular volume; and the mean corpuscular hemoglobin, which had been high in the youngest embryos, fell rapidly so that after the 60th day it never rose above 25×10^{-12} gm. The erythrocytes became progressively more regular in size and shape (Fig. 4), while fewer and fewer reticulocytes, nucleated cells and basophilic cells were seen in the circulating blood. In addition to a decrease in the average cell diameter (Fig. 5) as the period of gestation increased, the erythrocytes became more uniform in size (Fig. 6). Table I further demonstrates the changes seen between the bloods of the youngest and oldest embryos of the series. For sake of contrast, similar figures obtained by other workers for newly born and adult pigs have been included.

These findings are essentially in agreement with those of Wintrobe and Shumacker.[2] In another study Wintrobe and Shumacker[6] pointed out that the changes which occur in the blood dur-

6 Wintrobe, M. M., and Shumacker, H. B., Jr., *J. Clin. Invest.*, 1935, **14**, 837.

TABLE I.

Age	42 days	106 days	2-42 days post-natal	adult*
Total erythrocyte count in millions	0.74	3.0	3.9	6.8
Hemoglobin in grams %	3.6	6.76	9.7	14.0
Mean corpuscular vol. in cubic micra	216.0	128.0	—	72.0
Mean corpuscular hemoglobin in gm. x 10^{-12}	56.2	21.0	—	20.0
Average cell diam. in micra	8.9	6.01	—	6.3
Range of cell diam. in micra	2.0-16.0	4.0-8.5	—	—
Reticulocytes % (1000 cells counted)	28.8	8.0	—	—

*These figures have been compiled and calculated from several sources.[5, 1]

ing fetal life suggest very strikingly the changes which result in the blood of pernicious anemia patients when they are subjected to liver therapy. Certainly the blood picture of the early pig embryos included in the present series is so similar to that seen in such patients as to make a distinction difficult if a comparative study were undertaken. The presence of hyperchromic, macrocytic anemia; with high mean corpuscular volume and hemoglobin, associated with the appearance of immature erythrocytes in the circulating blood stream; would seem to satisfy the hematological criteria for making a diagnosis of pernicious anemia. The changes which follow in the blood of the fetus are indeed very similar to those which result from liver therapy in pernicious anemia. The exact relationship of the two states is only a matter of conjecture at present, but there seems to be justification for suggesting that the hematopoietic tissues of the fetus are influenced by the same anti-anemic factor which, when administered therapeutically to the patient, results in the familiar alterations in the blood picture of pernicious anemia. Perhaps the factor is absorbed from the mother or it may be elaborated by the fetus. Additional information is necessary before any conclusions on this point can be reached. Perhaps some evidence might be obtained by a study of fetal blood formation in the absence of an adequate maternal supply of the anti-anemic factor.

We wish to express our appreciation to Dr. Lewis H. Weed of the Department of Anatomy at the Johns Hopkins Medical School for making possible the collection of the material upon which this work is based.

[5] Palmer, C. C., *J. Agr. Res.*, 1917-1918, **9**, 131.