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Indican as influenced by bacillus acidophilus therapy.

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Over 150 urinalyses were made on 40 psychotic patients. The number of daily bowel movements were recorded, and showed a range varying from normal to severe chronic constipation. Various experimental procedures with *B. acidophilus* were employed. Such an investigation must be continued for a considerable period of time before any conclusions can be drawn. However, in reporting progress, it is interesting to note that in only five instances did the indican present exceed 20 mg. which is generally regarded as the upper limit of normal excretion. Some of the patients with severest constipation had very small amounts of indican present in the urine. In general patients who received *B. acidophilus* milk had a smaller amount of urinary indican than patients receiving *B. acidophilus* milk in which the viable organism had been killed.

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Leucocytes in relation to the mechanism of thyroid-accelerated metamorphosis in the larval frog.

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In the larval frog the chief locus of blood-cell formation is the kidney. The intertubular regions of this organ are filled with many erythrocytes and leukocytes in various stages of development. The spleen and, to a less extent, the mesentery are also hemopoietically active, but are of minor importance. In the adult frog, however, conditions are different. The spleen is

here the principal hemopoietic center, the kidney playing little part. At some time in the developmental history of the frog, therefore, the chief locus of blood-cell formation is shifted from the kidney to the spleen. A study has been made to determine the effect upon the hemopoietic centers of accelerated metamorphosis induced by feeding tadpoles with thyroid extract.

A few days after the first administration of thyroid extract definite changes may be seen in the kidney and spleen. The intertubular stroma of the kidney is largely drained of its blood-cells. Some stimulation of the hemopoietic tissue that is left occurs. Erythrocytes, lymphocytes, special granulocytes (pseudo-eosinophils or neutrophils) and eosinophils are drawn from the kidney in great numbers. A marked shrinkage in size of this organ results which is evident microscopically. At the same time a myeloid metaplasia is effected in the spleen and mesentery. Erythrocytes are drained from the spleen and the splenic lymphocytes stimulated to differentiate into other erythrocytes. Lymphocytes from other parts of the body migrate to the spleen and are incorporated in it. The net result of this activity in animals in which metamorphosis is not too greatly accelerated is an increase in the proportion of lymphocytes to erythrocytes, and some increase in absolute size of the spleen. In these animals it may be said that the partial drainage of the intertubular regions of the kidney, and the stimulation of the spleen, apparently indicate the initiation of the shift of the main hemopoietic locus from the kidney to the spleen. Whether or not this shift can be carried to completion experimentally has not yet been determined.

Accelerated metamorphosis results in high mortality. All of our thyroid-treated tadpoles have died before complete resorption of the tail. Death usually occurs in this condition of metamorphic stasis. Examination of the hemopoietic organs of animals that have reached this stage suggests that death comes as a result of anemia. The spleen and kidney show that great numbers of their blood-cells have been drawn from them, the spleen being often totally exhausted. Accelerated metamorphosis sets up a demand for erythrocytes to furnish the basis for increased oxidation, and for leukocytes to aid in the processes of regressive and progressive change. The lymphocyte is the progenitor of the erythrocyte and of various types of leukocytes, and is itself derived from the mesenchymal cell. The successful prog-

ress of accelerated metamorphosis depends largely upon the ability of the lymphocyte to supply the erythrocytes and leukocytes needed. Metamorphic stasis and death we interpret to mean the failure of the lymphocyte to meet the extraordinarily great hemopoietic demands set up by the chain of reactions following repeated thyroid administration. This interpretation agrees with our observations on adult frogs following experimental hemorrhage and injection of a hemolytic toxin.

In a recent series of experiments on thyroid-treated tadpoles Swingle¹ has attempted to carry them over the stage of metamorphic stasis by means of hypophysis grafts. He finds the response variable. In some cases this treatment aids the progress of metamorphosis, in others it does not. We suggest that this variable response may be correlated with the hemopoietic reserve of the animals. In those in which the lymphocytes are still present in sufficient numbers the hypophysis graft may serve to aid metamorphosis. In those in which the lymphocytes have been practically exhausted the graft may perhaps have no effect.

Microscopic examination of several regions of a tadpole in process of metamorphosis reveals that there is a definite differential distribution of leukocytes. In the tail, a region of regressive change, the predominating types of leukocytes are lymphoid phagocytes (phagocytes derived from lymphocytes) and special granulocytes. Lymphocytes and eosinophils occur only in small numbers. In the intestine, also a region of regressive change, the predominating types are eosinophils and lymphoid phagocytes. The chief function of the eosinophils and special granulocytes in these regions appears to be to give off substances which help to break down adjacent tissues, thus rendering these more easy of ingestion and phagocytosis by the phagocytic leukocytes (lymphoid phagocytes chiefly). The eosinophils and special granulocytes themselves often go to pieces in the process and may then be ingested by the phagocytes.

In the rapidly growing limbs, regions of progressive change, the predominant type of leukocyte is the lymphocyte. Some lymphocytes are brought in by the blood-vessels, but the great majority are differentiated in situ from the mesenchyme. A conspicuous lymphocyte layer is present immediately beneath the basement membrane of the epidermis. Eosinophils, special

¹ *Journ. Exp. Zool.*, 1923, xxxvii, 219-257.

granulocytes and phagocytes are almost entirely absent. Carrel's recent experiments² dealing with the effect of leukocyte extract and leukocyte secretions upon tissue cultures show that leukocytes give off substances that stimulate growth of surrounding cells. Carrel used a mixture of all leukocytes in these experiments. In the rapidly growing tadpole limb, since the lymphocyte is the only type of leukocyte present in any numbers, it is obvious that any growth-promoting leukocytic secretion must come from it. Examination of the skin from the abdomen and back of the same tadpoles that have the conspicuous lymphocyte layer in the limbs shows that there is no similar collection of differentiating lymphocytes in these regions (regions in which little or no growth is taking place). From the negative standpoint, it would seem that eosinophils, special granulocytes and phagocytes could be ruled out from having a possible growth-promoting function since they predominate in the tadpole in regions of regressive change. We suggest, therefore, that the growth-promoting function of leukocytes, as demonstrated by Carrel, should probably be ascribed to the lymphocyte component of leukocytes.

In conclusion, it may be pointed out that the leukocytes are an important part of the mechanism by which the thyroid secretion brings about its characteristic results. Metamorphic differentiation is largely a sequence of progressive and regressive changes in various parts of the body. Lymphocytes are correlated with the former, granulocytes and phagocytes with the latter. The successful maintenance of the increased oxidation following thyroid administration depends upon the lymphocyte as progenitor of the erythrocyte.

² *Journ. Exp. Med.*, 1922, xxvi, 385-391.