Summary and conclusions. In patients with mental or emotional disorders, increased activity of vasomotor mechanisms responsive to postural change may occur; this is observed irrespective of diagnosis. In some psychotic patients disturbances in mental content and mood, consisting of intensification of pre-existing psychotic manifestations, occurred at times when it may be assumed that cerebral blood flow was diminished. Observations suggest that lobotomy causes no distinctive change in postural vasomotor reactivity when time for complete healing is allowed.

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17060. Effect of Autolyzed Yeast, Yeast Nucleic Acid and Related Substances on Body-Temperatures of Rats.*

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It is common practice to produce fever experimentally in rats by means of the subcutaneous injection of a solution of autolyzed yeast. During the routine use of this procedure, we found that administration of the autolyzed yeast intraperitoneally produced a fall instead of a rise in body-temperature. In the present paper we are reporting this phenomenon and some efforts to determine what constituent or constituents of the yeast may be responsible for the temperature effects. The activities of autolyzed yeast, yeast nucleic acid, and the nucleic acid derivatives, guanine, uracil, xanthine, and allantoin were investigated.

Materials. The autolyzed yeast was prepared in the usual way by making a suspension of 15 g of commercial baker's yeast in 100 cc of water. This suspension was allowed to stand for several days at 37°C with occasional shaking. The solid material was then separated in the centrifuge and the clear, dark brown, supernatant "autolysate" was used as the experimental material. The magnesium salt of yeast nucleic acid was prepared according to the method of Baumann.[1] All nucleic acid derivatives used were Eastman products and when necessary were brought to essentially neutral condition before administration.

Experimental. The experimental animals were young adult white rats about equally divided between males and females in each experiment. The animals were fasted overnight before use. High colonic temperatures were taken with mercury thermometers by means of the technic previously described.[2] As soon as the initial temperature was obtained, the substance under investigation was injected either intraperitoneally in the lower left abdominal quadrant or subcutaneously craniolaterally to the base of the tail. After injection, the animals were kept at room temperature in individual wire cages without food or water. The room temperature varied between 25.5 and 28.5°C.

With the exception of the yeast, which was given as a "15%" autolysate, all test substances were administered in 0.1% solution.

Results. Fig. 1 shows the response in temperature following the intraperitoneal injection of 2 cc of a "15%" yeast autolysate contrasted with that after the subcutaneous injection of 2 cc of the same material. The average maximum rise in body-temperature after subcutaneous administration was 1.9°C and appeared at about the 5th hour. After

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1 Baumann, E. J., *J. Biol. Chem.*, 1918, **33**, XIV.

2 Hill, R. M., Ware, A. G., and Schultz, F. H., *Cancer Research*, 1943, **3**, 839.

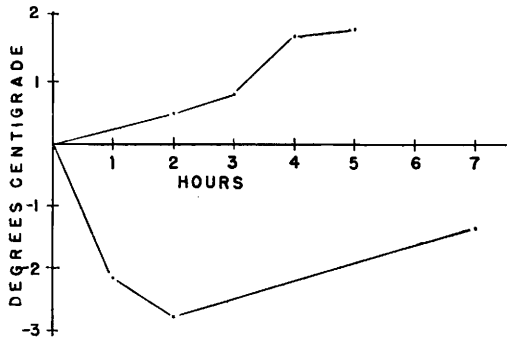

FIG. 1.
Average body-temperature change after administration of 2 cc of "15%" yeast autolysate. Upper curve, 150 rats, subcutaneous injection. Lower curve, 15 rats, intraperitoneal injection.

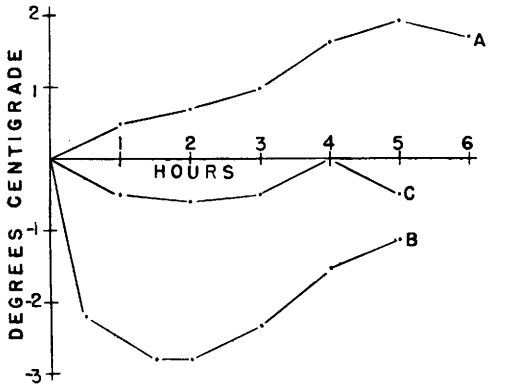

FIG. 2.
Average body-temperature change after administration of 2.5 cc of 0.1% magnesium nucleinate. A, 8 rats, subcutaneous injection. B, 8 rats, intraperitoneal injection. C, average body-temperature change after intraperitoneal injection of 2.0 cc of 0.1% guanine, 8 rats.

intraperitoneal administration, a rapid fall in body-temperature occurred, which reached an average minimum of 2.7°C below the initial value at about the 2nd hour after injection.

In Fig. 2 are shown the results of similar experiments in which 2.5 cc of a 0.1% solution of the magnesium salt of yeast nucleic acid was used. The average maximum rise in body-temperature after subcutaneous administration was 1.8°C, which occurred at about the 5th hour. The average minimum body-temperature after intraperitoneal injection was 2.9°C below the initial value and appeared after about 1.5 hours. The similarity between the results with yeast autolysate and with yeast nucleic acid is striking. Although 2.0 cc of a "15%" yeast autolysate was used on the one hand and 2.5 cc of a 0.1% nucleic acid solution was used on the other, the amount of nucleic acid injected into each animal was about the same, according to the analyses of yeast reported by Von Euler, Ahlstrom and Högberg.[3]

The effect of guanine injected intraperitoneally was slight (see the average curve in Fig. 2) and was not evident in all the animals. Guanine showed no effect when administered subcutaneously. Adenine, uracil, xanthine, and allantoin had no effect on the body-temperature by either route of administration.

During hypothermia, the rats were quiet, perhaps somewhat depressed, and showed a tendency to lie on the side. However, when they were disturbed, they reacted as quickly as untreated animals, and seemed normal in every way.

The rise in body-temperature after subcutaneous injection of autolyzed yeast or the magnesium salt of nucleic acid was slow and the peak was prolonged. The fall after intraperitoneal injection of these substances was rapid, the degree of body-temperature change was greater, and in most instances the return to the initial value occurred in a shorter time. These facts suggest that the difference in response to the two routes of administration may be due to different rates of absorption. However, very small doses given intraperitoneally do not produce hyperthermia, and large subcutaneous injections do not produce hypothermia. Another possibility is that the hypothermia following intraperitoneal injections is a manifestation of shock. Against this is the normal appearance of the peritoneal and other serosal surfaces, and the absence of visceral hyperemia, petechiae, and edema in the animals sacrificed at the time of maximum hypothermia.

Discussion. The fact that very small amounts of yeast autolysate or yeast nucleic acid given intraperitoneally did not produce hyperthermia and very large amounts given subcutaneously did not produce hypothermia would seem to rule out differences in the rate

[3] Von Euler, H., Ahlstrom, L., and Högberg, B., *Z. f. physiol. chem.*, 1942, **277**, 1.

and amount of absorption as the cause of the contradictory effects on body-temperature. Our experiments imply that the property of producing hyperthermia after subcutaneous injection and hypothermia after intraperitoneal injection is inherent in the nucleic acid molecule. The fact that the large nucleic acid molecule was active though the smaller hydrolysis products of nucleic acid were not suggests that molecular or particle size may be important in causing body-temperature changes. This raises the questions of phagocytosis of the material in the peritoneal cavity and its absorption by way of the lymph channels, and the possibility that hypothermia is associated with activity of the reticulo-endothelial system. Investigations of these questions are in progress and will be reported later.

Summary. Subcutaneous injection of 2 cc of a "15%" yeast autolysate in rats produced a significant rise in body-temperature. Intraperitoneal injection of the same material produced a significant fall in body-temperature. Both qualitatively and quantitatively similar results were produced by the injection of 2.5 cc of a 0.1% solution of the magnesium salt of yeast nucleic acid. Slight lowering of the body-temperature occurred in some animals after intraperitoneal injection of guanine. Subcutaneous injection of guanine had no effect on body-temperature. Adenine, uracil, xanthine, and allantoin had no effect on the body-temperature of rats by either route of administration.

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17061. Development of Macrocytic Erythrocytes in Leukemic Subjects Receiving Folic Acid Antagonist, 4-Aminopteroylglutamic Acid (Aminopterin).

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Temporary remissions in acute leukemia have been produced by the therapeutic administration of the folic acid antagonist 4-aminopteroylglutamic acid (aminopterin). Farber[1,2] has reported remissions in children. Dameshek[3,4] has produced equally good results in adults. The exact mechanism of the action of aminopterin is not known. It is a folic acid antagonist in that it possesses the property of inhibiting the growth of *Streptococcus faecalis R.* or *L. casei* in the presence of marginal levels of folic acid. Farber[2] noticed hypersegmentation of neutrophilic granulocytes in the peripheral blood and megaloblasts in the marrow in leukemic patients receiving folic acid antagonists. If aminopterin is a true folic acid antagonist one can theorize that morphologic changes might be produced in the erythrocytes. In a series of 25 patients (children and adults) with acute leukemia of all types treated with aminopterin, results were obtained in 7 of these individuals which support this theory.

Experimental. Daily doses of ½ to 1.0 mg of aminopterin were given intramuscularly. One cc of crude liver containing 2 U.S.P. units was given with each dose of aminopterin.

Frequent complete blood counts were done on all patients receiving therapy. Occasional bone marrow biopsies were also obtained. More complete studies were obtained when macrocytosis and anisocytosis was observed in the circulating red blood cells. These studies included red cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, morphologic observations on the erythrocytes and measurement of the mean erythrocytic diameter by the

1 Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., and Wolff, J. A., *New England J. Med.*, 1948, **238**, 787.

2 Farber, S., *Blood, J. Hemat.*, 1949, **4**, 160.

3 Dameshek, W., *Blood, J. Hemat.*, 1948, **3**, 1057.

4 Dameshek, W., *Blood, J. Hemat.*, 1949, **4**, 168.