In bovine articular cartilage which possesses an exceedingly low respiration and thereby a relatively higher aerobic glycolysis than the other tissues mentioned, the inhibition averaged 57 per cent.

Results of a representative experiment with calf cartilage are listed in Table 1. It is seen that glucose

TABLE I

THE ACTION OF GLUCOSE ON THE RESPIRATION OF CARTILAGE*
Mean rates over three-hour period

Substrates	None	Glucose	Pyruvate	Succinate	Glucose + Pyruvate	Glucose + Succinate
		(M/100)	(M/50)	(M/25)		
Q_{O_2}†	.079	.029	.079	.103	.062	.080
Inhibition by Glucose	...	−.050 (− 63%)	...	...	−.017 (− 22%)	−.023 (− 23%)
Acceleration by Pyruvate and Succinate	...	...	± 0	+.024	+.033	+.051

† Cmm. O_2/mg dry weight/hour.
* Articular cartilage from the metacarpal-phalangeal and metatarsal-phalangeal joints of a calf two months old. About 125 mg dry weight of cartilage slices per experimental vessel. $k_{O_2} = .98$
Gas: Air Medium: Phosphate-Ringer's

retards oxygen consumption by 63 per cent. Similar effects were obtained by the addition of mannose, but no effect was obtained with fructose which is not glycolyzed by cartilage. The inhibition observed in oxygen (53 per cent.) was of the same order as in parallel determinations in air (59 per cent.). The magnitude of the respiratory inhibition in cartilage is neither due to a drop in the pH of the medium incident to the high rate of acid formation after the addition of glycolyzable hexoses to the slices nor to an accumulation of glycolytic splitting products or their derivatives (lactate, pyruvate, succinate). Table 1 shows an example of the results obtained with pyruvate and succinate. Pyruvate does not alter the rate of the spontaneous O_2 consumption, but it induces an acceleration of the oxygen uptake if the respiration is inhibited by glucose. Succinate[8] accelerates respiration in the presence of glucose to a greater extent than in its absence. Apparently the addition of glucose suppresses cellular processes which result in the formation of pyruvic and succinic acids since the addition of these acids abolishes more than half of the respiratory inhibition by glucose (*cf.* Table 1).

Elliott and Baker[5] as well as Victor and Potter[6] observed that the retardation of respiration by the addition of glucose was paralleled by a rise of the R.Q., indicating a replacement of respiratory substrates of the tissue by the added glucose. The latter authors pointed out that the change of the R.Q. after the addition of glucose was compatible with a shift from protein oxidation to carbohydrate combustion. Warburg and colleagues[9] showed that the formation of ammonia in tissue slices deprived of glucose is especially high in glycolytically active tissues and that the addition of glucose inhibited the excretion of ammonia. This inhibition was considered an expression of the protein sparing action of glucose. The investigation of Dickens and Greville[10] indicate that the oxidation of glucose rather than its glycolysis is responsible for the retardation of the protein catabolism. It seems possible that the addition of glucose causes a decrease of oxygen consumption in such tissues in which the hexose is not oxidized with the same velocity as the cellular substrates, the oxidation of which it replaces. Such a mechanism would explain the frequent occurrence of the Crabtree effect in aerobically glycolyzing tissues where a relatively sluggish oxidation of glucose coincides with a high protein catabolism in the absence of sugar.

This tentative explanation does not intend to imply that glucose oxidation replaced only the combustion of protein nor that glucolysis does not prevent to a certain extent protein catabolism, as was suggested by Warburg.[9] The explanation supports the view, however, that the Crabtree effect is not a reversal of the checking action of respiration on glycolysis but a separate process which indicates the sparing of cellular substrates by the combustion of extracellular glucose. Thus, the Crabtree effect may belong to the reactions which underlie the stimulative action of respiration on cellular anabolism (Pasteur effect b).

The mechanism of the effect is being investigated further.

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APPEARANCE OF SKELETAL ABNORMALITIES IN THE OFFSPRING OF RATS REARED ON A DEFICIENT DIET

THE following observations were made when rats, which were reared on deficient diets, were bred. All rats used were of the Sprague-Dawley strain. One group of females was reared on a diet consisting of yellow cornmeal 76 per cent., wheat gluten 20 per cent., calcium carbonate 3 per cent., sodium chloride C.P. 1 per cent. (Steenbock and Black rachitogenic diet No. 2965),[1] which was supplemented with viosterol (each rat received 60 I.U. every tenth day). On this diet the animals were retarded in growth and

[8] Lactate behaves similarly.

[9] O. Warburg, K. Posener and E. Negelein, *Biochem. Zeit.*, 152: 309, 1924.

[10] F. Dickens and A. Greville, *Biochem. Jour.*, 27: 1123, 1933.

[1] H. Steenbock and A. Black, *Jour. Biol. Chem.*, 64: 263, 1925.

development. The vagina opened at the age of three to four months, the regular cycles started at between four and five months, the first matings took place at between five and six months, at which age the rats weighed only about 150 grams. In this group of 18 animals, 32 pregnancies were observed. A total of 164 young was born either spontaneously or by cesarean section; of these, 107 were apparently normal, while 57 presented multiple congenital abnormalities.

An abnormally short mandible was found in 39 animals. This defect was so marked that the tongue was exposed to a large extent. Many animals also had deformed extremities. Syndactylism of different grades was observed in 32 young. A short tail was seen in 12 animals. One hundred and four of the young were cleared by the Spalteholz method to facilitate the study of the skeleton. In 42 of these specimens the lower legs showed reduction in size or absence of the tibia; in 20 the fibula was shortened or absent; in 22 there was fusion of the ribs; and in 14 there was fusion of the centers of ossification of the sternum.

Another group of females of the same strain was reared on a more adequate diet consisting of yellow cornmeal 78 per cent., wheat gluten 18 per cent., calcium carbonate 1 per cent., sodium chloride C.P. 1 per cent., and dried pig liver 2 per cent.[2] This diet resulted in much better growth and development of the animals. This group consisted of 24 females which had 39 pregnancies resulting in 294 young. None of the latter showed deformities of the mandible or extremities like those described in the previous group. The only external abnormality observed in the offspring of the animals on this diet was absence of the tail in one animal. Eighty of the 294 young were cleared, but they showed none of the skeletal deformities found in the previous group.

A third group of 12 female rats of the Sprague-Dawley strain was raised on an adequate diet (Bill's modification of Steenbock's stock diet).[3] Thirty litters born to these animals consisted of 216 young. One abnormal animal was noted in this group. It weighed only 2½ grams and when cleared showed short femurs and an abnormal sternum. One hundred and nineteen young in this group were cleared, but they showed no abnormalities.

At the present time we are extending these experiments along both genetic and nutritional lines.

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[2] R. E. Remington, *Jour. Nutrition*, 13: 223, 1937.
[3] C. E. Bills, E. M. Honeywell and W. A. MacNair, *Jour. Biol. Chem.*, 76: 251, 1928.

MODIFICATION OF THE CHEMISTRY AND PHARMACOLOGICAL ACTION OF THE CARDIAC GLYCOSIDES[1]

ALTERATION of the molecular structure of a drug frequently results in modification of its pharmacologic action. The digitalis bodies exist in nature as chemical combinations of one or more sugars with hydroxylactones of sterol hydrocarbons. This suggests the possibility of modifying the digitalis bodies by replacing the sugar with a vasodilator, thus obtaining a cardiac glycoside molecule which might embody the desirable therapeutic actions of both drugs.

Two molecules of theophylline can be combined chemically with one molecule of a genin obtained by removing the sugar radical from a squills glycoside.[2] This dimethylxanthine genate can be prepared as short needle-like yellow crystals having a molecular weight of 758.2 and an empirical formula of C38 H46 O9 N8 (presumably C24 H28 O3 (C7 H7 O2 N4) 2 .2H2O). When injected intravenously in cats the lethal dose of this theophyllinated genin is much greater than that which might be expected on the basis of the amount of genin used in its preparation. The lethal dose of a mechanical mixture of theophyllin and the genin, on the other hand, is in proportion to its genin content. The theophyllinated genin, the squills glycoside, the mechanical mixture, and also digitalis show the same progression of electrocardiographic changes; T wave inversion and ventricular premature beats occur with the same degree of frequency, while nodal rhythm and ventricular tachycardia appear after approximately the same percentage of the lethal dose. Changes in the S-T segment, however, appeared in a far lower percentage of the animals given the theophyllinated genin than in those given digitalis, squills glycoside or a mechanical mixture of theophyllin and the squills genin.

These preliminary studies suggest that dimethylxanthine and the squills genin have been combined in a single molecule retaining some of the digitalis-like properties and modifying others. Further studies of the chemical and pharmacological properties of this preparation are necessary as well as clinical studies to ascertain the therapeutic value of the drug.

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THE NATURE OF THE ANTI-ALOPECIA FACTOR

IT has recently been shown[1] that the mouse requires a new vitamin for normal growth and for mainten-

[1] From the Medical Research Department of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.
[2] This preparation was supplied by Parker Dorn, Inc., Worcester, Mass.
[1] D. W. Woolley, *Jour. Biol. Chem.*, 136: 113, 1940.