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.

ance of hair. The dietary essential which prevented or cured the pathological manifestations was termed the mouse anti-alopecia factor. In its absence from the diet, growth ceased and extensive alopecia developed, followed by severe dermatitis. Liver was found to be a good source of the protective factor, and concentrates were prepared from this organ.

Many of the properties of the active substance suggested that a phosphoric ester of inositol was involved. For example, our best concentrates contained organically-combined phosphorus. The active substance was precipitated by barium hydroxide and was insoluble in alcohol. Furthermore, it was found that cereal grains, known to be good sources of the phosphoric ester of inositol, were also good sources of the anti-alopecia factor. All these facts seemed to justify a test of the potency of phytin, the salt of inositol phosphoric acid. While the assays were in progress, a crystalline substance was isolated from active liver concentrates which proved to be inositol. Phytin caused restoration of hair and resumption of growth in the depleted animals. Activity was not limited to the phosphoric ester, for inositol itself was subsequently found to be potent.

Assays were performed as described previously, and were always based on curative rather than preventative technique. For both phytin and inositol the level fed was 100 mg per 100 gm of ration. Cures have also been obtained with 10 mg of inositol per 100 gm of ration. Gain in weight, as well as restoration of hair, followed administration of these substances.

Inositol was isolated from the non-dialyzable, alcohol-insoluble portion of aqueous liver extract. This fraction had been autoclaved with alkali in order to render the active substance dialyzable. The crystals which were obtained melted at 214–216° and had a carbon content of 39.8 per cent. Inositol in the same bath melted at 215–216°.

The above facts indicate that the mouse anti-alopecia factor is inositol or its derivatives. They suggest that inositol exists in liver in alkali-labile combination with a large molecule which renders the former non-dialyzable. While it has been reported[2] that inositol stimulates the growth of certain strains of yeast, its place in the nutrition of higher animals has not previously been observed. Details of the work will be published elsewhere.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A NEW TYPE OF SHIELDED GLASS ELECTRODE[1]

THE high resistance of glass electrodes and their consequent sensitivity to stray currents require careful shielding in addition to an adequate insulation. The shielding is important when the electrode is to be employed at distances from the measuring apparatus that require long leads. This shielding is ordinarily accomplished by the use of a more or less flexible metal sleeve, thus providing an equipotential layer around the lead. The sleeve is conveniently connected to the equipotential shield about the measuring apparatus. Commercially manufactured shielded wires are frequently employed.

The special feature of the shielded glass electrode now to be described is an arrangement by means of which the KCl-solution which ends in a fluid junction surrounds completely the stem of the electrode and the entire lead up to the terminal of the measuring apparatus. In this manner the KCl-solution that is a part of the low resistant half of the circuit acts as a shield against external stray currents. With our equipment best results were obtained when the terminal of the reference half cell was connected to the equipotential shield around the potentiometer or directly to the ground.

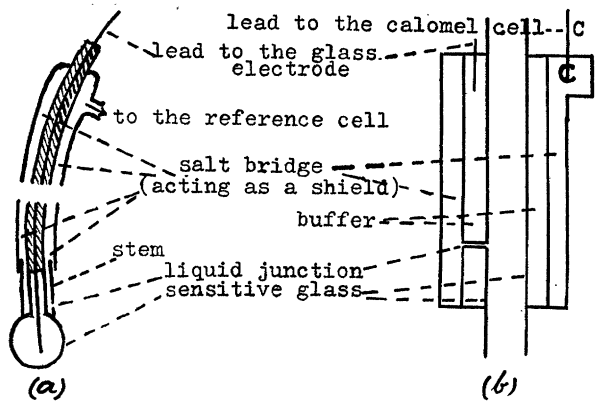

FIG. 1. Diagrams of glass electrodes (a) bulb type, (b) condenser type with the use of the salt bridge as a shield.

Fig. 1 shows two types of glass electrodes, the bulb type (a), and the condenser type (b), also used as a continuous flow electrode with the use of the KCl-solution as a shield.

The arrangement calls for a very careful insulation

[1] From the Laboratory for the Study of Peripheral Vascular Diseases, Department of Surgery, New York Hospital and Cornell University Medical College.

[2] E. V. Eastcott, *Jour. Phys. Chem.*, 32: 1094, 1928.