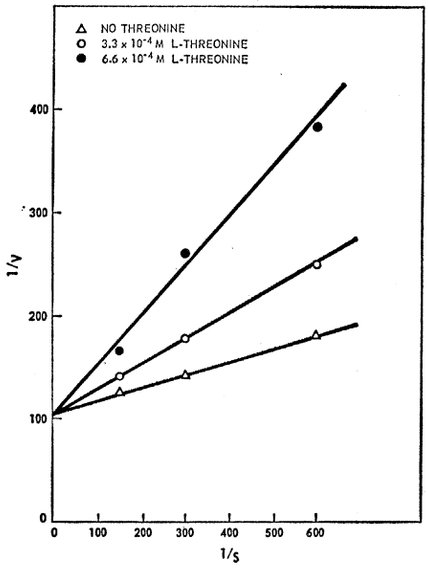

Fig. 2. Competitive inhibition of homoserine dehydrogenase activity by L-threonine; double reciprocal plot of substrate concentration and initial reaction velocity. The reaction mixtures contained, in a final volume of 3 ml: tris(hydroxymethyl)aminomethane, *p*H 8.4, 270 μmole; EDTA, sodium salt, 3 μmole; NADP, 0.4 μmole; L-threonine as indicated; centrifuged sonic extract, equivalent to 1.4 mg of protein. Reduction of NADP at 25°C was measured by following absorbancy at 340 mμ in a cuvette with 1-cm light path. $1/V$, reciprocal of initial reaction velocity, measured as increase in absorbancy per minute (from data obtained during the first 5 minutes after substrate addition). $1/S$, reciprocal of homoserine concentration, in moles per liter.

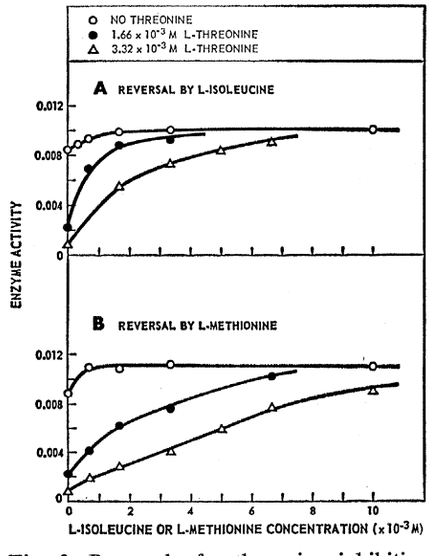

Fig. 3. Reversal of L-threonine inhibition of homoserine dehydrogenase activity by L-isoleucine (*A*) and L-methionine (*B*). The mixtures contained 20 μmole of L-homoserine and the other amino acids as indicated. Other experimental conditions as in Fig. 2. Enzyme activity is expressed as increase in absorbancy (340 mμ) per minute per 2 mg of protein.

it may be noted that the D-isomers of isoleucine and methionine as well as the L-isomers of lysine, leucine, and valine are ineffective in reversing the inhibition caused by L-threonine.

Although the biosynthetic pathways shown in Fig. 1 are based on studies with other organisms, there is no evidence as yet that they differ in *R. rubrum*. In certain bacteria, such as *E. coli*, an important control in isoleucine synthesis is end-product inhibition of threonine deaminase (*8*). In *R. rubrum*, however, we have been unable to demonstrate inhibition of threonine deaminase activity by isoleucine (*9*). Our studies indicate that, in *R. rubrum*, isoleucine exerts control by influencing other reactions in the biosynthetic chain. Preliminary experiments have disclosed that, in addition to its effects on homoserine dehydrogenase, isoleucine also can affect the activity of aspartokinase, the enzyme which phosphorylates aspartic acid (see Fig. 1). L-Threonine strongly inhibits aspartokinase activity and the inhibition is prevented by L-isoleucine, but not by L-methionine.

Evidence indicating a physiological role of these effects was obtained from relevant growth experiments. Growth of *R. rubrum* in the medium mentioned previously is completely inhibited by addition of $3.3 \times 10^{-4}M$ threonine, presumably because of interference with methionine synthesis. Further supplementation with either methionine or homoserine in low concentration ($1.6 \times 10^{-5}M$) does, in fact, abolish the threonine inhibition; similar results have been reported (*10*) with the photosynthetic bacterium *Rhodopseudomonas spheroides*. In the case of *R. rubrum*, reversal of inhibition of growth by threonine is also effected by isoleucine, but considerably higher concentrations are required ($3.3 \times 10^{-4}M$). The foregoing results are evidently consistent with the conclusion that in the intact cell isoleucine can exert regulatory control on methionine synthesis by the mechanism observed in the experiments in vitro, namely, by reversing feedback inhibitions caused by threonine.

The results of this investigation suggest that, in general, metabolic products may exert rapid control of synthesis both by end-product inhibition and by reversal of feedback inhibition established by certain intermediates. Presumably, enzymes subject to controls of the latter kind must be sensitive to critical differences in the relative concentrations of substrate, ultimate end products, and the inhibitory intermediates. A more detailed study of the homoserine dehydrogenase of *R. rubrum* may shed light on the mechanism of such effects, which appear to be examples of "allosteric" interactions (*11; 12*).

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20 May 1963

Aberrant Thyroid Tissue in the Mouse

Abstract. *Aberrant thyroid tissue was observed at the base of the heart in seven of 2634 mice of the BALB/c strain. Such tissue was not seen in any of 1033 mice of the Strong A strain. The normal thyroid gland of the BALB/c mouse was observed to be more loose than that of the Strong A mouse and isolated follicles were frequently observed in tissue sections at either pole of the gland which were not attached to the body of the thyroid.*

Aberrant thyroid tissue is known to occur in man and a variety of lower animals. Most aberrant thyroids result from the failure of all or part of the thyroid anlage to descend from the

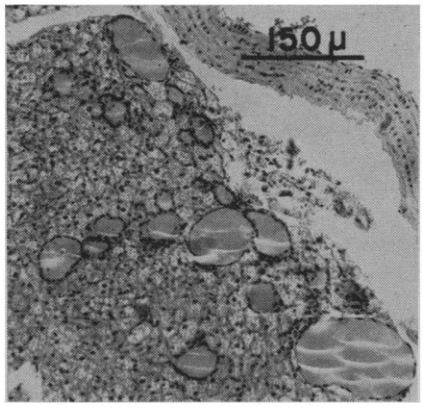

Fig. 1. A group of thyroid follicles within multilocular fat near, but not immediately adjacent to, the aorta. Hematoxylin and eosin stain (× 90).

floor of the pharynx to its normal cervical position, or from its descending beyond its normal adult location (*1*, *2*). In the first case aberrant thyroid tissue may occur at any median point from the tongue to its normal position and in the second case it occurs caudal to the normal position to include its location within the thoracic cavity. In man the thoracic thyroid has been described in the mediastinum behind the sternum, adjacent to the aorta, within the upper part of the pericardium, and in the interventricular septum of the heart (*2*). Another form of aberrant thyroid is the result of an anomaly of development of the fetal tissues as a whole. In man this is most common in the ovary and is considered a teratoma (*3*). Aberrant thyroid has been described in the rat (*4*), guinea pig (*5*, *6*), dog (*7*), rabbit (*6*), and baboon (*8*). I am not familiar with any reports of its occurrence in the mouse.

It is of importance to recognize the occurrence of aberrant thyroid tissue in experimental animals, for, as in man, unusual clinical pictures and thyroid function tests can result from the presence of aberrant tissue. In laboratory animals aberrant thyroid must be considered when unusual results are obtained from extirpation or other experimental procedures. Complete removal of the thyroid gland does not insure removal of all functional thyroid tissue.

Microscopic examination of tissues representative of all organ systems was conducted on 2634 mice of the BALB/c strain (without the milk factor) and 1033 mice of the Strong A strain. The heart of each mouse was serially sectioned from the apex to the base including the great vessels entering and leaving the heart. In seven BALB/c mice (five female, two male) aberrant thyroid tissue was observed at the base of the heart (Fig. 1). In six of these, the tissue occurred within the multilocular fat at the base of the heart near but not immediately adjacent to the aorta. In the other animal the tissue was within the pericardium at the base of the heart. In each of these mice a thyroid gland was present in the normal adult position. The aberrant tissue was identical in microscopic structure to normal thyroid tissue and in all probability was functional.

It is of interest that aberrant thyroid tissue was observed only in the BALB/c strain. In a comparison study on the normal thyroid gland of the two strains of mice, it was observed that in both strains the capsule is extremely thin or inapparent. In the Strong A mouse the thyroid gland is well confined and ends abruptly on all surfaces whereas in the BALB/c the thyroid is more loose and frequently strings out at the anterior and posterior poles of the gland. Small groups of follicles and occasional single follicles are frequently seen at either pole away from the body of the gland separated by multilocular fat and occasionally by striated muscle. This may indicate that portions of the thyroid anlage of the BALB/c mouse frequently do not descend with the entire structure or descend beyond the normal adult position.

Unfortunately, tissues were not removed from the pharynx or the base of the tongue, hence it could not be determined if lingual thyroid masses were present.

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27 June 1963

Elasticity of Articular Cartilage: Effect of Ions and Viscous Solutions

Abstract. *The deformability of articular cartilage is increased by cations, more so by polyvalent than monovalent ones. Trivalent cations also depress elastic recovery. Failure of viscous solutions to alter the elastic behavior suggests ultrafiltration by cartilage as a possible mechanism in synovial lubrication.*

Deformability and resilience are major properties of articular cartilage that provide shock absorption and reduce friction in the functioning of joints. The elastic behavior of cartilage is, to a large extent, dependent upon mechanical extrusion and repenetration of tissue fluid, and is influenced by the concentration of salts in the milieu (*1*, *2*). In this study, the disarticulated heads of the tibias from 38 freshly killed dogs were used to test the effects of various ions and the viscosity of the immersion medium on the elasticity of the cartilage.

The cartilage was first equilibrated in physiological saline solution at 37 ± 1°C for 75 to 90 minutes. A compressometer (*1*, *3*) was then used to apply a static load of 83 g/mm² to the surface of the cartilage for 12 minutes. Linear deformation was recorded as a function of time, as was recovery when the load was removed. The measurements were repeated thereafter at the same site after the cartilage had again been equilibrated in the different solutions. The solutions, except where noted, were isotonic, calculated (*4*) as NaCl equivalents without correction for activity coefficients. The divalent cation solutions were 0.11*M* $CaCl_2$, $BaCl_2$, and $MgCl_2$; the trivalent solutions were 0.085*M* $AlCl_3$, $LaCl_3$, $FeCl_3$, and $[Co(NH_3)_6]$ Cl_3 (*5*). Monovalent cationic substitutes for Na^+ were 0.15*M* KCl, LiCl, and NH_4Cl. Tetramethyl ammonium chloride was used to provide a large cation that would be less firmly bound to the polyanions (*6*) of