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A quantitative study of the physiologic action of thyroxin.

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The isolation of thyroxin in pure crystalline form permitted the fact to be shown that thyroxin alone increases the rate of combustion in the animal organism. Furthermore, this increase is related quantitatively to the amount injected. One milligram given to an adult produces an increase of approximately 2.5 per cent. The substance acts in minute amounts for long periods, and produces such enormous increase in the output of carbon dioxid above the former level, that there is no escape from the conclusion that thyroxin acts as a catalyst.

Through a study of closely related compounds, which were synthetically prepared, the fact was demonstrated that thyroxin can exist in two forms: reduced and oxidized. Thyroxin, as isolated from the gland, is the reduced form.

Alpha oxy indol propionic acid, the precursor of thyroxin, acts as a reducing agent. It loses two atoms of hydrogen, with molecular oxygen, when the pyrrol ring in the molecule is open, and forms a bond from the nitrogen, to the number seven carbon in the benzene ring. This compound has feeble oxidizing power. When, however, the pyrrol ring is closed and the bond is present from the nitrogen to number seven carbon, the oxidizing power of the compound is very much increased. The oxidizing potentials of the open and the closed ring compounds, when both exist in their oxidizing form, have been measured, and a difference of at least 0.3 volt was found.

When they are injected into a normal dog, the reduced form, and the oxidized but open ring form, produce no visible response; the oxidized closed ring form causes a marked physiologic effect. There is a drop in blood pressure, an increase in pulse rate, a marked increase in respiration, and an increase in the rate of metabolism.

It is significant that oxidation in the animal organism is accelerated by the presence of an agent which is an active hydrogen acceptor, and the degree of stimulation is dependent on the oxidizing potential of this hydrogen acceptor.

The function of thyroxin is to furnish a compound that can be acted on by mild oxidizing agents, among which is molecular oxygen, and which can then by an intramolecular re-arrangement produce an intensely oxidizing substance.

This same mechanism of increasing the intensity of oxidation is evidently a reaction which is used by other catalytic agents in the body, bringing about an increased rate of combustion.

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The mechanism and significance of the fragility test.

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If erythrocytes are treated with a solution of castor oil soap of such concentration that the liberation of hemoglobin is complete in about ten hours, there is a period of several hours before any hemolysis takes place. Fragility tests during this period show that there is a decreased fragility of these cells to hypotonic salt solution.[1] As these cells differ from normal cells in that they are being subjected to an accelerated hemolysis, the decreased fragility indicates an injury to the cell.

It has been well established that upon injury or death, there is an exosmosis of salts from cells. The work of G. N. Stewart[2] has shown that blood cells may lose salts by exosmosis without the liberation of hemoglobin. It would appear then that when blood cells are immersed in a hypotonic salt solution, not only does water pass into the cells, but salts also pass out. The most dilute salt solution in which blood cells will not hemolyze, represents a situation in which enough salts can pass out of the cell,

[1] Green and Evans, PROC. SOC. EXP. BIOL. AND MED., 1923, xv, 290-291.

[2] Stewart, G. N., *J. Pharmacol. and Exp. Therap.*, 1910, i, 49.