$$r = 0.03 \cdot \left(\frac{e^{\lambda_u \cdot \Delta t}}{e^{\lambda_{ac\,u} \cdot \Delta t}} \right) \quad \ldots . (B)$$

in which Δt = age of mineral considered minus 8×10^8 years.

The essential data for these minerals are:

Keystone, S. D., uraninite:
$U = 66.90$, $L' = 0.67$, $t = 1465 \times 10^6$ yr.
Sinyaya Pala, Carelia:
$U = 61.41$, $L' = 0.91$, $t = 1852 \times 10^6$ yr.

The results of such calculations are:

Mineral	r from (A)	r from (B)
Uran. Keystone, S. D.	0.0053	0.0061
Uran. Sinyaya Pala	0.0027	0.0024

We see that the two calculated values in the case of each mineral check reasonably well. It is also evident that r for the Keystone mineral is a little more than ½ per cent. and for the Sinyaya Pala about ¼ per cent. It is to be noted also that the difference of age of these two minerals is roughly 4×10^8 years. Considering these results it would be desirable to have the experimental values of r from these minerals.

The following general conclusions about actino-uranium seem plausible:

(1) Actino-uranium seems to be an independent isotope of uranium.

(2) Its disintegration constant is about $\lambda_{ac\,u} = 2.5 \times 10^{-9}$ yr^{-1} or $T = 2.7 \times 10^8$ years.

(3) Its amount in minerals appears to conform to the idea that it is initially of a definite amount in proportion to the uranium and that this relative proportion decreases with the age of the mineral.

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ON THE MECHANISM OF BIOLOGICAL OXIDATION AND THE FUNCTION OF THE SUPRARENAL GLAND

CLINICAL and experimental observations on the symptoms of suprarenal deficiency have indicated that the suprarenal gland is in some way involved in the mechanism of oxidation. For this reason I have studied for many years processes of oxidation, with the hope of finding the clue to the function of the cortical part of the gland. Vegetable tissues were used in these studies to a great extent.

Most of the common plants and fruits can be divided into two main groups: those which show discoloration on injury (apple, banana, potato), and those which do not (lemon, orange, cabbage).

Extending earlier observations of Palladin and M. W. Onslow, it was found[1] that the most prominent oxidation system of tissues which discolor on injury is the so-called phenoloxidase system. This system consists of a phenoloxidase and a phenol, which latter is a derivative of catechol and is chemically closely related to epinephrin. In the presence of molecular oxygen, this phenol is oxidized by the phenoloxidase to an ortho-quinone. In the intact tissue, this quinone is rapidly reduced by hydrogen, which is derived from the foodstuffs. If the tissue is injured, this reduction does not take place; the quinone remains in the oxidized state and undergoes secondary changes, or combines with other cellular constituents. The quinones and their secondary products are highly colored and thus cause discoloration of the tissue.

It is known that quinones have a very high bactericidal power. It has been shown in the latest experiments on potatoes that injury to the tissue leads to increased oxidation of the phenol and therefore to increased production of quinones, so it seems probable that the phenoloxidase systems also play a part in the natural immunity of plants which contain this oxidation system.

Most vegetable tissues which do not have the phenoloxidase system and which do not discolor on injury contain a highly active peroxidase and very little catalase. Further investigation has shown that these tissues also contain, in relatively high concentration, a substance which is characterized by its strong reducing properties. This substance has been isolated in crystalline form and has been found to be a hitherto unknown compound related to the carbohydrates. This acid is an isomer of glucuronic acid and has been named "hexuronic acid." This acid shows quite unexpected activity. It reduces salts of silver even in the cold and in an acid solution. It is the most reactive derivative of the carbohydrates hitherto discovered and prepared in free condition.

The most striking property of this substance is its reversible oxidizability, by which two of its hydrogen atoms can be split off in a reversible way. The substance owes its high reactivity to these two labile hydrogen atoms, and not to the carbonyl group.

The latest studies performed on cabbage leaves have brought out the fact that in this plant hexuronic acid plays a central rôle in normal respiration. It has been shown that the cabbage leaf contains a very active enzyme which oxidizes hexuronic acid at a high rate, oxidizing off its two labile hydrogen atoms. The oxidized hexuronic acid is then again reduced. In this way, the hexuronic acid connects as a hydrogen car-

[1] A. Szënt-Györgyi, "Über den Oxydationsmechanismus der Kartoffeln," *Biochem. Ztschr.*, 162: 399–412, 1925.

rier, on the one hand the oxidation systems which utilize oxygen, and on the other the foodstuffs which are the source of hydrogen.

The enzyme responsible for the rapid and reversible oxidation of hexuronic acid has been called "hexoxidase." Its properties are different from the properties of other known oxidizing enzymes. Study of the kinetics of this enzyme has clearly shown that this enzymic function is a complicated one and that the hexuronic acid is not immediately oxidized by the enzyme. The enzyme contains a special substance or grouping, "x," which is first oxidized by the oxygen. This oxidized "x" then in turn oxidizes the hexuronic acid and is itself reduced again. No cyan-sensible oxygen activation is involved in the oxidation of "x," so that this oxidation probably goes hand in hand with the formation of hydrogen peroxide. This would explain the presence of the highly active peroxidase which would complete the system, utilizing the peroxide thus formed.

Extending these studies to the suprarenal gland, it was found that the suprarenal cortex contains a strong reducing agent, the high concentration of which is sharply characteristic for this organ. This substance has been isolated in crystalline form and has been found to be identical with the hexuronic acid from plants.

Hexuronic acid completely inhibits formation of pigment in all systems in which a "melanoid" pigment is formed through the oxidation of a phenol. In biologic systems a minimal concentration of hexuronic acid is sufficient to give complete inhibition. The absence of hexuronic acid in Addison's disease could give thus a clear explanation of the mechanism of formation of pigment.

Experiments, however, performed on animals after extirpation of the suprarenal glands, have shown that hexuronic acid is unable to prolong life. Hexuronic acid given in two cases of Addison's disease seemed to have some beneficial effect but did not restore the patients to full activity. It seems to be certain, therefore, that besides hexuronic acid some other substance is elaborated by the suprarenal cortex to which this organ owes its vital importance. The formation of pigment, however, which in Addison's disease is not dependent on the gravity of the case, seems to be connected with hexuronic acid. It seems to be highly probable that the other hitherto unknown product of the cortex plays in the animal tissue a part analogous to that of the "x" substance of the oxidation system of the cabbage leaf, which has been mentioned.

The careful survey from a chemical standpoint of reducing substances of the suprarenal gland also has brought out the fact that the medulla contains, besides epinephrin, a strong reducing agent which is specific for the medullary tissue. The substance has not yet been isolated. In many ways its behavior is analogous to that of hexuronic acid, but it seems not to be identical with it. This substance also inhibits formation of pigment, and it is possible that its absence also is a factor in the production of pigmentation in Addison's disease. It is possible that both reducing substances, hexuronic acid and the reducing substance of the medulla, play an important part in the stabilization of the other active principles present (epinephrin and the unknown hormone of the cortex). It can easily be shown *in vitro* that epinephrin is highly autooxidizable at the hydrogen-ion concentration of the tissue. The oxidized molecule rapidly undergoes irreversible secondary changes. In the presence of hexuronic acid or in the presence of the reducing substance of the medulla the oxidized molecule of epinephrin is at once reduced again and is protected in this way from secondary irreversible changes.

There are thus four specific substances elaborated by the whole suprarenal gland. In the medulla are found epinephrin and a strongly reducing substance. In the cortex are found hexuronic acid and the probable presence of another active principle, the existence of which seems to be established by the recent work of Hartman and his collaborators, of Stewart and Rogoff and by the most recent investigation of Swingle.

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