amount to give a local reaction with inclusions was that equivalent to 0.01 mg. of Al_2O_3. Alundum is also a form of Al_2O_3 and is commonly used as an abrasive in the preparation of tissues for animal inoculation. In the usual procedure, however, it is completely removed from the tissue-suspensions by centrifugation.

Summary. The following non-virus materials were used in guinea pigs in addition to those already reported: suspensions of normal brain tissue; normal rabbit tissues (liver, spleen, kidney, testicle); commercial lecithin; alcoholic extract (lipins) of monkey brain; phosphatide of tubercle bacilli; and 1:2:5:6 dibenzanthracene. Of these only brain induced characteristic intranuclear inclusions. Aluminum hydroxide injected into other sites than the subcutaneous tissues of guinea pigs produced similar reactions with inclusions. The mouse responded only feebly with inclusions on injection of aluminum hydroxide while the rabbit again failed.[1] The approximate minimal effective dose of Al_2O_3 needed for production of the intranuclear bodies was found to be 0.01 mg. per cc. The various aspects of these findings are discussed.

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Relief of Myxedema and Cretinism by Iodinated Blood Serum.*

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Since Baumann's finding that thyroglobulin contains iodine, many investigators[1] have sought for the chemical mechanism by which hormonal activity is produced when the native protein is iodinated in the body. The isolations of (inert) diiodotyrosine and (active) thyroxine by hydrolysis of thyroglobulin, together with the formation of artificial thyroid protein from diiodotyrosine peptone[2] have suggested that under certain conditions the phenolic groups of diiodotyrosine may undergo conjugation to form an iodized thyronine nucleus. The rapid formation of active thyroid protein which occurs in glands of patients with exophthalmic goiter when iodine is

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1 Hutchison, R., *J. Physiol.*, 1898-99, **23**, 178.

2 Salter, W. T., and Pearson, O. H., *J. Biol. Chem.*, 1936, **112**, 579.

administered suggests that its basis is a simple chemical mechanism which can be reproduced directly *in vitro*.

To this end we investigated the outcome of the hydrolysis of a nondescript iodoprotein so conducted as to favor condensation or synthesis. The procedure of Abelin[3] was modified to favor greater condensation (by mass-action) of split-products of hydrolyzed iodoprotein. The starting material was mammalian blood serum iodin-

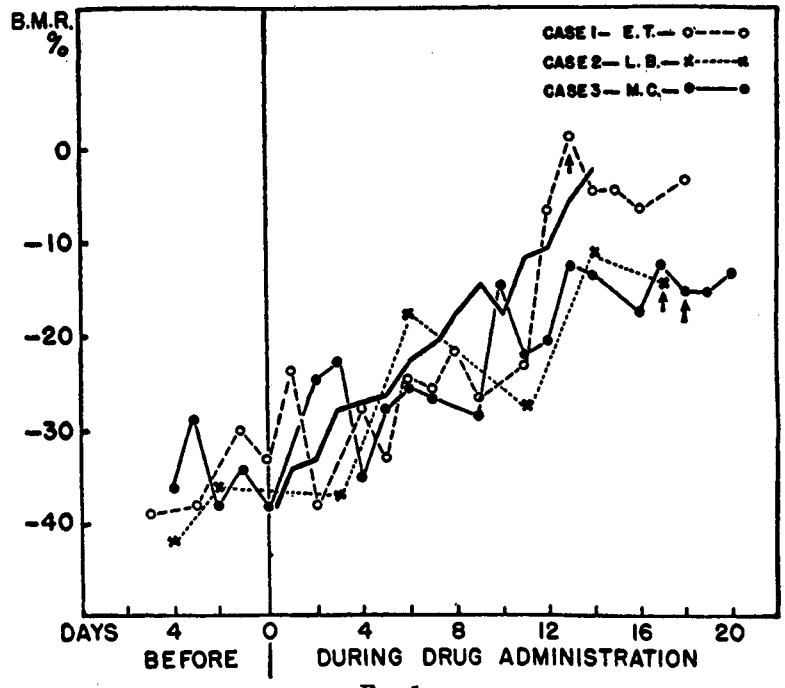

FIG. 1.

The metabolic response of 2 patients with myxedema and one with cretinism receiving the material described in the text. The arrows indicate omission of medication. The heavy solid line is our curve of reference and represents the metabolic response to the daily administration of thyroxin polypeptide containing 0.5 mg. of iodine.

ated by the procedure of Wormall.[4] For each liter of blood serum there resulted about 1.2 gm. of material containing 24% iodine. From this a fraction containing 47% iodine was readily obtained, which approximates the composition of diiodothyronine (48%).

Since human myxedema and cretinism offer the best test objects available for identifying thyroid activity, this material was tested clinically in 6 patients. In 3 of these, sufficient metabolic data have

[3] Abelin, I., *Arch. f. exp. Path. u. Pharmakol.*, 1936, **181**, 250.

[4] Wormall, A., *J. Exp. Med.*, 1930, **51**, 295.

been obtained to date to permit charting, as shown in Fig. 1. The fourth patient (after this chart went to press) made a standard metabolic response up to plus 16, on a daily dose of material containing 25 mg. of iodine. The data in the other 2 are incomplete.

Case 1. E. T., No. 77797, a 57-year-old woman, had myxedema for 20 years. The basal metabolic rate level was minus 36, pulse 50-54, and weight 72.5 kg. The plasma cholesterol was 284 mg./100 cc. She received material containing 5 mg. of iodine daily for 4 doses, 10 mg. for 4 doses, 20 mg. for 3 doses, and 30 mg. for 2 doses. Definite metabolic response started with the 10 mg. dosage. The subsequent metabolic response was rapid and persisted for a week after medication was stopped. She lost almost 4 kilograms in weight and had a definite diuresis. Clinically she became normal.

Case 2. L. B.,† No. 8702, a 25-year-old female cretin, was first seen by Dr. Fritz Talbot in 1915. The basal metabolic rate was minus 42 and minus 36, and weight averaged 36 kg. Plasma cholesterol was 331 mg./100 cc. She received material containing 5 mg. of iodine daily for 17 days. Coincident with the metabolic rise, she lost 4.5 kg. in weight and she appeared brighter and more animated.

Case 3. M. C., No. 3620, a 59-year-old woman, with typical myxedema of 3 years' duration, had a basal metabolic rate level of minus 37, pulse 60, and weight 74.5 kg. Plasma cholesterol was 390 mg./100 cc. She received material containing 15 mg. of iodine daily for 18 days. Her metabolism rose to a level of minus 14 and she lost 6 kg. in weight. There was a slight but definite diuresis, and plasma cholesterol was reduced to 121 mg./100 cc. Clinically she approached normal appearance. An electroencephalogram, obtained by Dr. R. S. Schwab, before treatment showed an alpha rhythm of 7-7.5 per sec., and a reaction time of 0.4 sec. Both values are extremely slow. After treatment, they approached normal, the alpha rhythm being 9.3 per sec. and the reaction time 0.3-0.35 sec.

In general, the activity is distinctly less than that of thyroglobulin and more of the order of diiodothyronine reported by Abderhalden and Wertheimer,[5] when dosage is based on total iodine.

Conclusion. It is shown in 3 cases that a derivative of iodinated protein obtained entirely from extra-thyroidal sources exerts qualitatively the physiologic action of thyroid hormone in human myxedema.

† This case is reported in full in Means, J. H., *The Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Co., 1937, page 274.

[5] Abderhalden, E., and Wertheimer, E., *Z. f. d. ges. exp. Med.*, 1929, **68**, 563.