do not fall at corresponding points. The fluctuations range from 10 to 40 mg. per 100 cc. (or even more) in 15 or 20 minute periods and are not due to the activity of microorganisms. Further studies on the source, identity, and behavior of this reducing substance are in progress.

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Value of Hexuronic Acid in the Treatment of Graves' Disease with Suprarenal Cortex.

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In 1921[1] and in 1924[2] we reported 20 cases of Graves' disease treated with a glycerol extract of fresh ox suprarenal cortex. This treatment produced very striking improvement in 12 to 15 days in the following particulars, namely (1) a gain in body weight, (2) a gain in muscle strength, (3) disappearance of diarrhea, (4) control of excessive menstrual flow and (5) a marked decrease in the metabolic rate, approaching normal after 2 to 4 months.

During the past 6 years we have treated approximately 50 additional cases by this method with the same general results.

In 1928 Szent-Györgyi[3] isolated a hexuronic acid from suprarenal cortex which is easily destroyed by exposure to air. In the preparation of our suprarenal cortex emulsion any hexuronic acid present would probably be destroyed. We, therefore, thought that possibly more effective results might be obtained if our treatment with suprarenal cortex were supplemented by concentrates of freshly prepared hexuronic acid. The following are the results obtained to date:

Case 1. Female, married, age 32, No. 18012. Patient had acute rheumatic fever in 1926 and diphtheria in July, 1929. Following the diphtheria, the patient noted weakness, palpitation, swelling of the ankles and sweating. Thyroid enlargement was noted in August, 1929, for which she was treated with Lugol's solution for 3 weeks. On admission the patient had all the symptoms of a severe Graves' disease in addition to a rheumatic cardiac disability.

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1 Marine, D., and Shapiro, S., *Endocrinol.*, 1921, **5**, 699.

2 Shapiro, S., *Endocrinol.*, 1924, **8**, 666.

3 Szent-Györgyi, A., *Biochem. J.*, 1928, **22**, 1387.

During a preliminary rest period of 2 months there occurred the expected decrease of metabolism from +62% to +41%. Between January 4 and January 22, 300 mg. of hexuronic acid was administered daily with no further decrease of metabolism. Between January 22 and May 29, 12 to 24 cc. of suprarenal cortex emulsion was given daily by mouth. The basal metabolic rate decreased from +41 to +15%. Between May 29 and October 30, no further medication. The B.M.R. then was 0, the pulse rate had dropped from the admission rate of 112 to 68 and the weight had increased from 48 to 57 kg.

Case 2. Another patient treated in a similar way gave similar results.

Case 3. Female, Admission diagnosis of Graves' disease. Patient has palpitation, muscle weakness, loss of weight and thyroid enlargement. She thinks these symptoms began to appear about one year ago.

During a control period (2 weeks) of rest in bed, patient showed no change. Between April 3 and June 12, 12 cc. of the cortex emulsion was given daily by mouth, and the B.M.R. dropped from +77 to +42%. Between June 10 and July 2, 400 mg. of a hexuronic acid concentrate was given daily by mouth. The B.M.R was not measured during this period, but the pulse rate remained unchanged. Between July 2 and August 24, 24 cc. of the suprarenal cortex emulsion was given daily. The B.M.R. sharply dropped to +3. The pulse was 72, while the weight had increased from 40 to 53 kg.

Two additional patients were given about 200 mg. hexuronic acid plus 24 to 36 cc. suprarenal cortex emulsion daily. They improved at the same rate as patients treated with suprarenal cortex emulsion alone.

In a sixth patient, the effect of hexuronic acid alone was noted. This patient, male, age 43, No. 18567, was admitted with a diagnosis of Graves' disease, May 19, 1930. He states he has always been nervous and temperamental but that active symptoms of Graves' disease date from the stock market break in October, 1929.

A larger dose of hexuronic acid concentrate (400 mg. twice daily) was given by mouth. Between May 19 and June 14 the B.M.R. showed no change, remaining at +33%. Pulse rate dropped slightly from 96 to 81 while weight increased 2.5 kg. After a quiet summer his B.M.R. was +25. Pulse rate was 84 while his weight had increased 11 kg.

This evidence so far shows that hexuronic acid is not the agent

of the suprarenal cortex which is so strikingly beneficial in Graves' disease. It is possible, however, that parenteral administration of hexuronic acid may be effective.

This evidence strongly supports the conclusion reported in our previous papers that (1) a symptom-complex essentially identical with Graves' disease, in its physiological and pathological aspects, can be produced by sublethal injury of the suprarenal cortex of rabbits and cats;[4, 5] (2) a glycerol extract of suprarenal cortex consistently causes strikingly beneficial effects in Graves' disease; (3) this suprarenal cortex extract as shown in 1926[6] lowers the metabolism of rabbits when thyroids are intact and (4) when hexuronic acid from suprarenal cortex is substituted for the glycerol extract of suprarenal cortex, no beneficial effects occur. We are convinced that the primary etiological factor in Graves' disease is the deficiency of the internal secretion of the suprarenal cortex.*

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On the Nature of the Dye Penetrating Nitella from Cresyl Blue.

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(1) Measurements of the sap of *Nitella B* with the glass electrode made with actively growing cells collected in early summer confirmed those formerly obtained[1, 2] and showed that there were no seasonal changes affecting the results. Living cells were placed in cresyl blue solution at pH 9 until 0.07% dye had penetrated the vacuole, causing an increase of about 0.4 pH in the sap. This corresponded to the increase when 0.07% dye base was dissolved in the sap *in vitro,* but not to the behavior of the dye salt which did not raise the pH value. These results show that the dye does not penetrate as a salt (undissociated DCl or $D^+ + Cl^-$).

[4] Marine, D., and Baumann, Emil J., *Am. J. Physiol.*, 1922, **59**, 353.

[5] Scott, W. J. M., *J. Exp. Med.*, 1922, **36**, 199.

[6] Marine, D., Baumann, Emil J., and Cipra, A., *Am. J. Physiol.*, 1925, **72**, 248.

* There is abundant evidence that the gonads contain a similar substance.

[1] Through the kindness of Dr. D. A. MacInnes and Dr. M. Dole the applicability of the glass electrode method to the studies of single cells was tested. *J. Gen. Physiol.*, 1928-29, **12**, 805.

[2] Irwin, M., PROC. SOC. EXP. BIOL. AND MED., 1929, **27**, 132; *J. Gen. Physiol.*, 1930-31, **14**, 1.