as little as 2.5γ of biotin. The scaly dermatosis was observed to be healed by the administration of the crystalline biotin ester. The minimum curative dose has not yet been determined and is probably less than 10γ.

It is apparent from the experiments as a whole that the chick can be employed in a quantitative biological assay of biotin. Such a procedure is certainly more time-consuming than, *e. g.*, a yeast growth technic,[7] but it is definitely more expedient than a bioassay with rats based upon a secondary[8] deficiency disease brought about by egg-white injury.

Conclusion. Biotin-deficiency is brought about in the chick reared on a heated ration of low biotin content (0.1γ/g). This deficiency is produced in the absence of dietary egg white which is essential for the development of the avitaminosis in the rat. Deficiency symptoms are completely cured by administration of crystalline biotin methyl ester. The chick can be used in a quantitative biological assay of biotin.

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Generalized Muscular Weakness as a Toxic Reaction to Digitalis.*

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Clark,[1] Cushny[2] and Neuschloss[3] demonstrated that the efficiency of a nerve muscle preparation could be markedly impaired if ex-

7 Snell, E. E., Eakin, R. E., and Williams, R. J., *J. Am. Chem. Soc.*, 1940, **62**, 175.

8 György, P., Rose, C. S., Eakin, R. E., Snell, E. E., and Williams, R. J., *Science*, 1941, **93**, 477.

* This paper comprises part of a thesis submitted to the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Medicine.

1 Clark, A. J., *Brit. Med. J.*, 1912, **2**, 687.

2 Cushny, A. R., The Action and Uses in Medicine of Digitalis and Its Allies, Longmans, Green and Co., London, 1925.

3 Neuschloss, S. M., *Pflugers Arch. f. d. ges. Phys.*, 1922, **197**, 235.

cessive amounts of a cardiac glycoside were added to the perfusing fluid. The work capacity of the skeletal muscle preparations was temporarily increased by small amounts of digitalis, reduced by excessive amounts, and returned to normal after the drug was removed.

The toxic reactions of patients to cardiac glycosides have been studied and documented since the publication of Withering's[4] monograph in 1785, but careful search of the literature has failed to reveal any described clinical instance of digitalis affecting skeletal muscle. The writer believes that the following case history illustrates toxic changes in skeletal muscle resulting from the administration of large amounts of digitalis.

Case History. A 23-year-old girl who had aortic insufficiency and mitral stenosis of rheumatic origin developed dyspnea and transient edema during September, 1935. In June, 1936, she was hospitalized and was given a total amount of 22 grains of USP X digitalis (1½ grain = 1 Hatcher-Brody cat unit) in 36 hours, followed by a maintenance dose of 3 to 4 1½ grain tablets. After leaving the hospital she continued to take the drug daily in this dosage until September, 1940. During this period, the digitalis was changed from USP X to USP XI potency, an increase of from 30 to 60%. This represents a maintenance dose 3 to 5 times greater than that usually given.

Except for moderate dyspnea on exertion, she was symptom free until June, 1939, when she first noticed severe cramping in the muscles of both legs. Soon after this she found that slight exertion was accompanied by marked fatigue and weakness and she was unable to climb a single flight of stairs without great effort. Weakness was most noticeable in the leg and back muscles, but she stated that her arms "felt heavy" and that she could not hold a book in one position for long. These symptoms were so marked that she could not return to college in the fall and was confined to the house most of the time. Cramping of the leg and back muscles occurred almost every day. In September, 1939, she experienced occasional episodes of double vision coming on in the evening or after prolonged use of her eyes.

Except for occasional brief remissions, these symptoms persisted until September, 1940, and were the only symptoms noticed by the

[4] Withering, W., An Account of the Foxglove and Some of Its Medical Uses: with Practical Remarks on Dropsy and Other Diseases, M. Swinney, Birmingham, 1785.

patient. There were no anorexia, nausea, emesis or palpitation during this 4-year period when she was taking 3 to 4 cat units of digitalis daily.

When the writer first examined the patient in September, 1940, the heart was generally enlarged, with an ml of 13.4 cm and an mr of 4.7 cm. The rhythm was regular at 42; the first sound was loud and snapping, followed by a rough, whistling systolic murmur. P_2 was split, accentuated and followed by a soft, high-pitched diastolic murmur best heard along the left sternal margin. The blood pressure was 130/70; the lungs were clear and resonant; the liver was not palpable and there was no peripheral edema.

The neurological examination was essentially within normal limits except for a demonstrable weakness of all the skeletal muscles. The grip was weak, the patient was unable to raise herself from a prone to a sitting position without the use of her hands and, despite firm, well-developed musculature, weakness was apparent in all muscle actions. She could not jump up and down on one foot or lift her weight by her arm and shoulder muscles. She was asked to climb one flight of 36 four-inch steps as rapidly as possible and this took 7½ minutes with frequent rest periods. The exertion was not accompanied by dyspnea, but the pulse rose to 56 and was irregular. The electrocardiogram showed complete heart block, auricular fibrillation and right axis deviation.

Digitalis was discontinued and the patient was examined twice daily. For 2 days she still noted muscle pain and weakness, but thought them somewhat less severe. On the third day she felt much stronger and had no pain. Four days after the discontinuance of digitalis, she climbed the same flight of stairs in one minute, and was able to jump up and down on one foot 10 times, could rise from her back to a sitting position without the help of her hands and had a much stronger grip. At the end of a week, she stated that she felt stronger than ever before in her life.

Heart block persisted for one week and was followed by an absolutely irregular ventricular rate (55-65) which lasted 2 weeks. Then the rate rose above 70 and lanatoside C (a crystalline cardiac glycoside) was given in dosage of one Hatcher-Brody cat unit (0.25 mg) daily. The patient returned to college in January, 1941, and has had no further symptoms.

The writer had previously noted[5] that experimental administration

[5] LaDue, J. S., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 651.

of daily intravenous doses of lanatoside C to dogs (1/5 to ½ cat unit per kilo) resulted in marked weakness after 2 to 3 weeks. This was interpreted as being due to starvation, since the animals had severe anorexia and vomited frequently. However, the case history reported here suggested a different interpretation of the muscular weakness of these animals and prompted further investigation.

Four dogs were trained to run on a treadmill until they were able to exercise for more than 30 minutes without any sign of fatigue. Then daily intravenous injections of 1/5 of a cat unit of lanatoside C per kilo of body weight were given.† After 2 weeks these animals exhibited increasing anorexia, occasional emesis, sialorrhea and progressive muscular weakness. On the 23rd day, one animal collapsed as soon as the treadmill was started, 2 could not run more than 5 minutes without falling on the 24th day of the experiment, and the remaining dog was unable to exercise on the 25th day. The drug was then discontinued and food was withheld. Within 4 days, the dogs were again able to exercise 20 to 30 minutes. Feedings were resumed and within 2 days the animals were able to exercise as well as at the beginning of the experiment.

Summary and Conclusions. 1. A case history illustrating generalized muscular weakness as a toxic effect of digitalis is presented. 2. Four dogs given daily injections of a cardiac glycoside developed generalized muscular weakness. Four days after discontinuance of the drug, the animals were able to exercise without fatigue. 3. With the present trend towards increased digitalis dosage, it is possible that this syndrome may be encountered by other investigators.

† This dosage was equivalent to about twice the maintenance dose which the patient had been taking.