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The action of iletin (insulin) on the blood sugar of pigeons.

By HANNAH ELIZABETH HONEYWELL and OSCAR RIDDLE.

[From the Department of Physiology, Columbia University, New York City, and the Carnegie Station for Experimental Evolution, Cold Spring Harbor, N. Y.]

The recent preparation of relatively pure and standardized extracts of the sugar reducing principle of the pancreas has been accompanied by measurements of the time and extent of the hypoglycemia resulting from its administration to the rabbit and to man.[1, 2] These earlier studies already permit the employment of such extracts with confidence in their power temporarily to reduce the blood sugar level in the higher animals. We present here the result of 120 sugar determinations made after subcutaneous injection of the extract into 35 pigeons of two species and of a third (ataxic) variety. It was usually considered unnecessary to make determinations of the sugar before injection since the birds were handled in groups and the group averages are known from extensive earlier work. These normal averages are: 185 mgms. per 100 c.c. blood (or .185 per cent.) for common pigeons[3]; 161 for ataxics; 150 for ring doves (unpublished data).

In a paper[4] accompanying this communication a pancreatic extract of the standardized type (iletin; or insulin, Lilly) was used continuously over a prolonged period in a test of its capacity to suppress ovulations in the pigeon. Large doses were also used to test the resistance of the bird to the extract. At the close of that study the same group of birds and the same pancreatic extracts were used for the purposes of the present study. One-half of the blood samples were obtained by needle-puncture of the heart and the other half by light bleeding from the upper beak. MacLean's micro-method of sugar determination was

1 Banting, Best, Collip, Macleod and Noble, *Amer. Jour. Physiol.*, 1922 lxii, 163.

2 Sutter and Murlin, PROC. SOC. EXP. BIOL. AND MED., 1922, xx, 68.

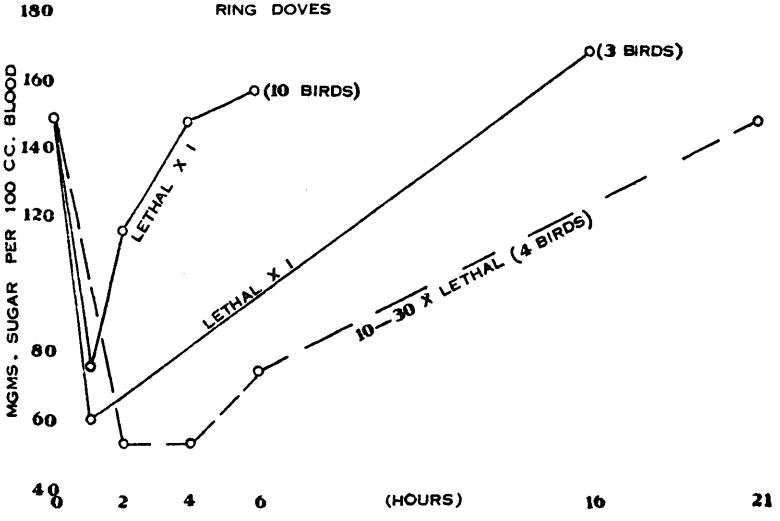
3 Scott and Honeywell, *Amer. Jour. Physiol.*, 1921, lv, 363.

4 Riddle, PROC. SOC. EXP. BIOL. AND MED., 1923, xx, 5.

used. Very few duplicate determinations were made. Further data concerning the extracts and dosages are given in the accompanying paper.

The curves of Figure 1 show the chief results obtained on ring-doves. In these very tame birds one can obtain samples probably unaffected by emotional glycemia resulting from handling or sampling at one-hour intervals. This is not equally possible with common pigeons and the extent of the fall of the sugar value at one hour after injection was not there measured (Figure 2). But comparison of the curves of the two groups clearly suggests that the maximum effect, of the lighter dosage at least, is reached in less than two hours in the common pigeon as is proved to be the case in the ring dove; probably this limit is attained within one hour.

FIGURE 1

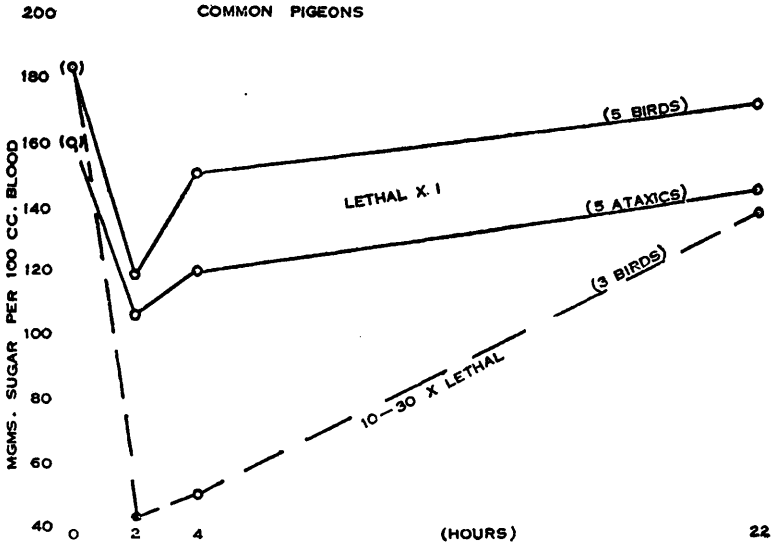


It is notable that in neither of the two groups of common pigeons given light dosage did the sugar return to a normal value at the end of four hours as it clearly did in the ring doves; nor was it at the apparent normal level after 22 hours, but our failure to obtain the normal for these particular birds before injection leaves the point uncertain. It is clear, however, that in the group of 10 ring doves (Figure 1) which at the time of sampling and during preceding weeks was being injected twice daily (9:00 A. M.; 7:00 P. M.) the blood sugar was again

normal after four hours and probably above normal after six hours. Our samples from this group were drawn after the morning injection so that the last previous dosage was thus 14 hours removed. That such previous injection did not affect the sugar values as obtained under this lighter dosage is indicated by the curve itself. This point is further checked by results from the group of 3 birds given only a single injection and whose sugar tested normal or above normal at 16 hours. This group of three ring doves, each injected with one-sixth unit of a very fresh and somewhat more potent extract (Lot 2) than that given to the group of 10 ring doves, gave lower values after one hour (62 mgms.) than did eight birds (82) of the other group which were injected with Lot 1.

Four ring doves given 10 to 30 times the "lethal" dose for the rabbit (Lot 2 used) lowered the sugar value (55) at two hours much more than did the smaller (lethal X 1) dosage (97). Moreover, with the heavy dosage the sugar remained low (55) at four and at six hours. After 21 hours the curve indicates (148) a return to normal value (150); but the figures obtained from the individual birds show that neither of the seven birds for which data for this 19-21 hour period are available was even approximately normal; the figures obtained were: 25, 45, 95, 110, 230, 235, 240 mgms. per 100 c.c. of blood. The four lower values were obtained from birds given the highest dosage —30 times lethal; the three higher values were from birds given 10 (2 cases) or 20 times the lethal dose. The sugar was not determined at the one-hour period in these heavily dosed birds. The low values (20 and 30 mgms.) shown by two birds at the two-hour interval, and the wide difference between the values obtained from low and high dosage at the two-hour interval, together with the demonstrated lower level at one hour than at two, where both were measured strongly suggest that extremely low sugar values obtain at this one-hour period under high dosage. At this particular period, however, the heavily dosed bird shows few or no wide departures from the normal in appearance or behavior. Only one of this group of birds died (after 28-34 hours); its sugar value after 21 hours was 25 mgms. Nearly all of our data from ring doves indicate that heavy insulin dosage causes a very rapid and nearly complete depletion of the blood sugar—to a point not higher than one-sixth its normal value; that this is usually followed by a some-

FIGURE 2



what slower and less complete rise; and that the short period of nearly complete absence of sugar is a period of little danger to the life of the bird.

The upper and lower curves of Figure 2 give for normal common pigeons the sugar measurements obtained from low and high dosage respectively. The much lower values from and the prolonged effect of the heavy dosage are apparent; they are also quite similar to the differences obtained with ring doves. The five ataxic pigeons figured on the middle curve were earlier known to have lower sugar values than normal pigeons. They maintained this lower level when under equivalent dosage. All these birds had a body weight of about one-third kilogram and received therefore in the "lethal X 1" dosage about one-third unit of iletin. In the "10 to 30 X lethal" dosage they received 3 to 10.5 units of iletin. Besides having a lower body weight which results in a saving of injected material the ring doves offer several advantages over the more commonly used pigeon for laboratory studies involving the determination of blood sugar.

The blood sugar was measured in a few instances at intervals longer than 24 hours after injections. For five of these birds the sugar was not measured soon after injection and are there-

fore not represented on the curves noted above. Three ring doves at 34, 35 and 36 days after injection with 1 unit (6 X lethal) gave normal average values of 143, 145 and 155 for these three days; one dove given 4.5 units showed a normal value (155) at 48 hours, but less (110) at 74 hours. One common pigeon (18 X lethal) gave values of 165 after 48 hours and of only 70 after 74 hours; this bird showed only 15 mgms. sugar after two hours and survived the treatment. Another common pigeon given 3.4 units (10 X lethal) gave a normal value (185) at 32 hours and less than one-half normal (70) at 58 hours. Some of these heavily dosed birds whose sugars were low at advanced periods had probably taken no food during a considerable preceding interval..

The fact that many of the ring doves and common pigeons given heavy dosage of insulin were not permitted to take food during about 20 hours preceding dosage, and that sugar samples representing values recorded in the curves were taken as much as 22 hours after injection, raises a question as to the bearing of this circumstance upon the sugar values obtained. Concerning this point it is noted that earlier studies[5] have indicated that inanition during 48 hours is practically without effect on the normal blood sugar of the pigeon. Only 7 of the 30 birds included in the curves presented (10-30 x lethal) were in any way restricted in their feeding either before or after injection of the extracts.

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Experimental production of streptococcus endocarditis with glomerular nephritis.

By RALPH A. KINSELLA and C. C. SHERBURNE.

[*From the Medical Clinic, Barnes Hospital, Washington University School of Medicine, St. Louis, Mo.*]

In human patients subacute streptococcus endocarditis is a fatal disease. No authentic report of a recovery has even been published. The mechanism of production of this disease in

[5] Honeywell, *Amer. Jour. of Physiol.*, 1921, lviii, 152.