SECTION V.

'Growth' in relation to the Diabetogenic and Pancreotropic Actions of Anterior Pituitary Extract.

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Young (1941), on the basis of his experimental work with dogs, has suggested that the pre-diabetic increase of height and weight in children and adults respectively is due to excessive function of the anterior pituitary gland compensated by increased activity of the pancreatic islets, and that failure of this balanced mechanism from inability of the islets to maintain their overactive condition ultimately results in diabetes mellitus. The purpose of the present paper is to adduce further experimental evidence in favour of such a theory.

METHODS

Extract. A crude saline extract of fresh ox anterior pituitary glands was prepared after the method of Young (1938), so that 2 c.c. were equivalent to 1 g. of gland. The extract was stored at a low temperature without freezing, used within 6 days of preparation, and injected by the subcutaneous route. The injections consisted either of a constant amount of 1.5 g. of gland per kg. body weight or of a quantity which was increased by 0.5 g. of gland per kg. at invervals of 5 or 6 days from an initial 1 g. of gland per kg. to a final 2.5 g. of gland per kg. body weight./

weight.

Animals. The animals investigated were English rabbits, eight males and seven females, and weighed between 1615 and 2211 g., averaging 1983 g. They were kept in metabolism cages and given daily 100 g. of a mixture of 40% oats, 30% bran and 30% maize, 300 g. cabbage, 25 g. hay (four animals only), and water ad lib. The energy value of this diet was calculated by analysing its constituents as regards carbohydrate, protein and fat and applying the usual factors 4.1 x 9.3. Daily measurements included body weight, food consumption, urinary volume, and, when present, urinary sugar and ketones. The ten control rabbits used to estimate the pancreatic islet tissue were also English, seven males and three females, and weighed between 1530 and 2380 g., averaging 1947 g.

Estimations. Urinary sugar was estimated by Cole's method, urinary ketones by the Van Slyke-Denigès method, and the pancreatic islet tissue after the method described by Ogilvie (1937). The A- and B- cells of the islet tissue were differentially stained by Heidenhain's haematoxylin.

RESULTS.

(1) Clinical Data. The fifteen animals so far as their body weight was concerned reacted to extract treatment in one or other of three ways and/

and were consequently divisible into three groups. Group 1 consisting of Rabbits 7, 9, 11, 12, 13, 21 and 26 (Figs. 1, 2, 4, 5, 6, 9 & 12) increased in weight. Group 2 included Rabbits 14, 22, 30 and 32. Rabbit 14 (Fig. 7) continued to lose weight and Rabbit 32 (Fig. 15) to gain weight at the same rate as each respectively lost or gained weight under control, while Rabbits 22 and 30 (Figs. 10 & 14) more or less remained at their original level. These animals were conveniently regarded as a group since on the average they maintained a constant weight. Group 3 made up of Rabbits 10, 15, 25 and 29 (Figs. 3, 8, 11 & 13) decreased in weight. The details of the body weight will now be considered in relation to the other clinical aspects of the three groups and entire series (Table 1).

Group 1. The average results of the seven rabbits in this group are illustrated in Fig. 16. The periods of control, treatment and after-treatment amounted to 10, 15 and 4 days respectively and treatment consisted in the administration of 43.5 g. of gland in average daily quantities of 2.9 g. During the control period, the body weight fluctuated slightly about 1920 g. on a more or less constant food value of 295 calories per day, while the daily urine volume remained in the region of 147 c.c. The body weight throughout treatment rose steadily from 1939 g. to 2049 g. This amounted to an average daily increase/

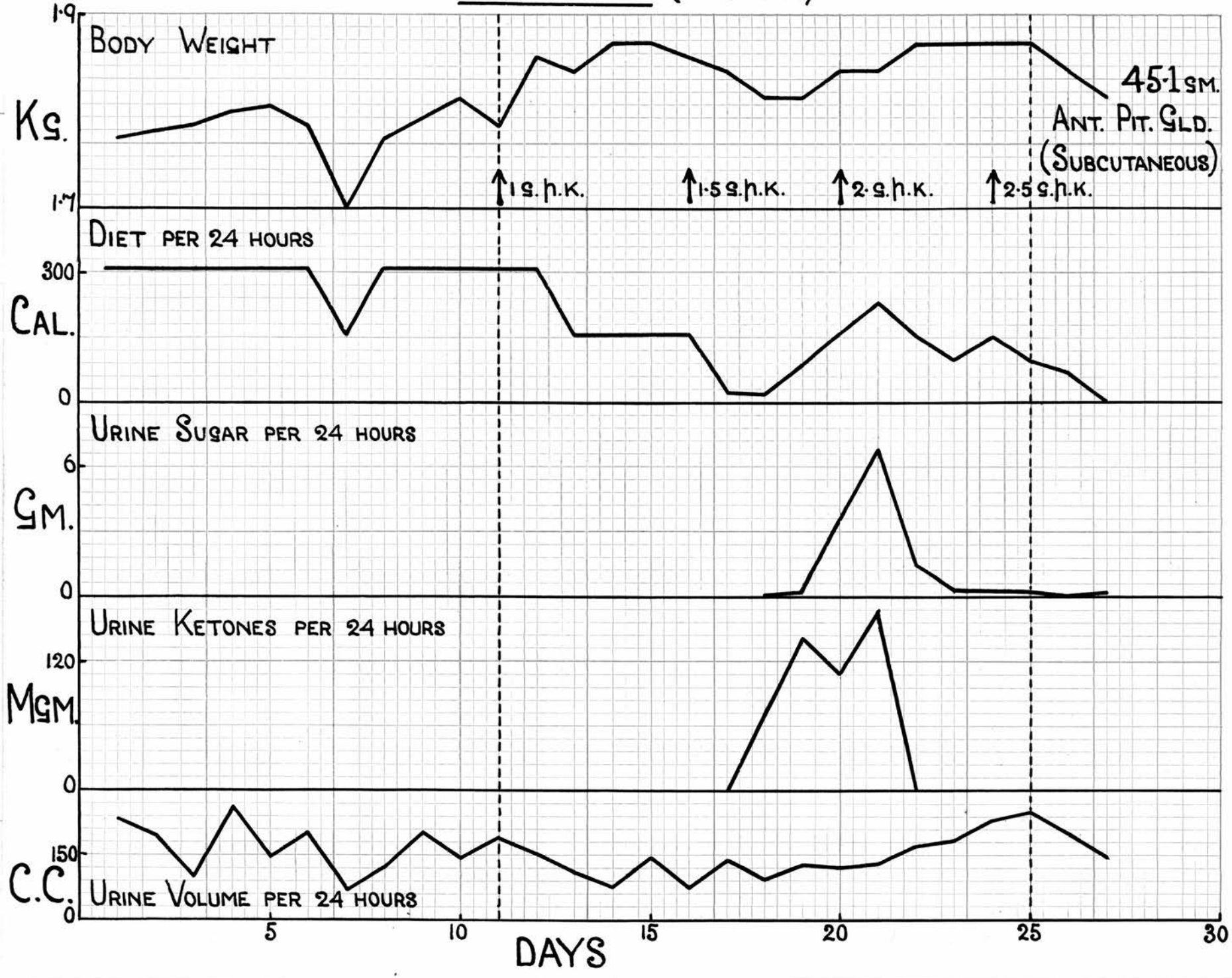
RABBIT 7 (MALE)
BODY WEIGHT
KG.
1·9
1·7
45·1 SM.
ANT. PIT. GLD.
(SUBCUTANEOUS)
1 G.H.K.
1·5 G.H.K.
2·G.H.K.
2·5 G.H.K.
DIET PER 24 HOURS
CAL.
300
0
URINE SUGAR PER 24 HOURS
GM.
6
0
URINE KETONES PER 24 HOURS
MGM.
120
0
C.C.
150
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 1.

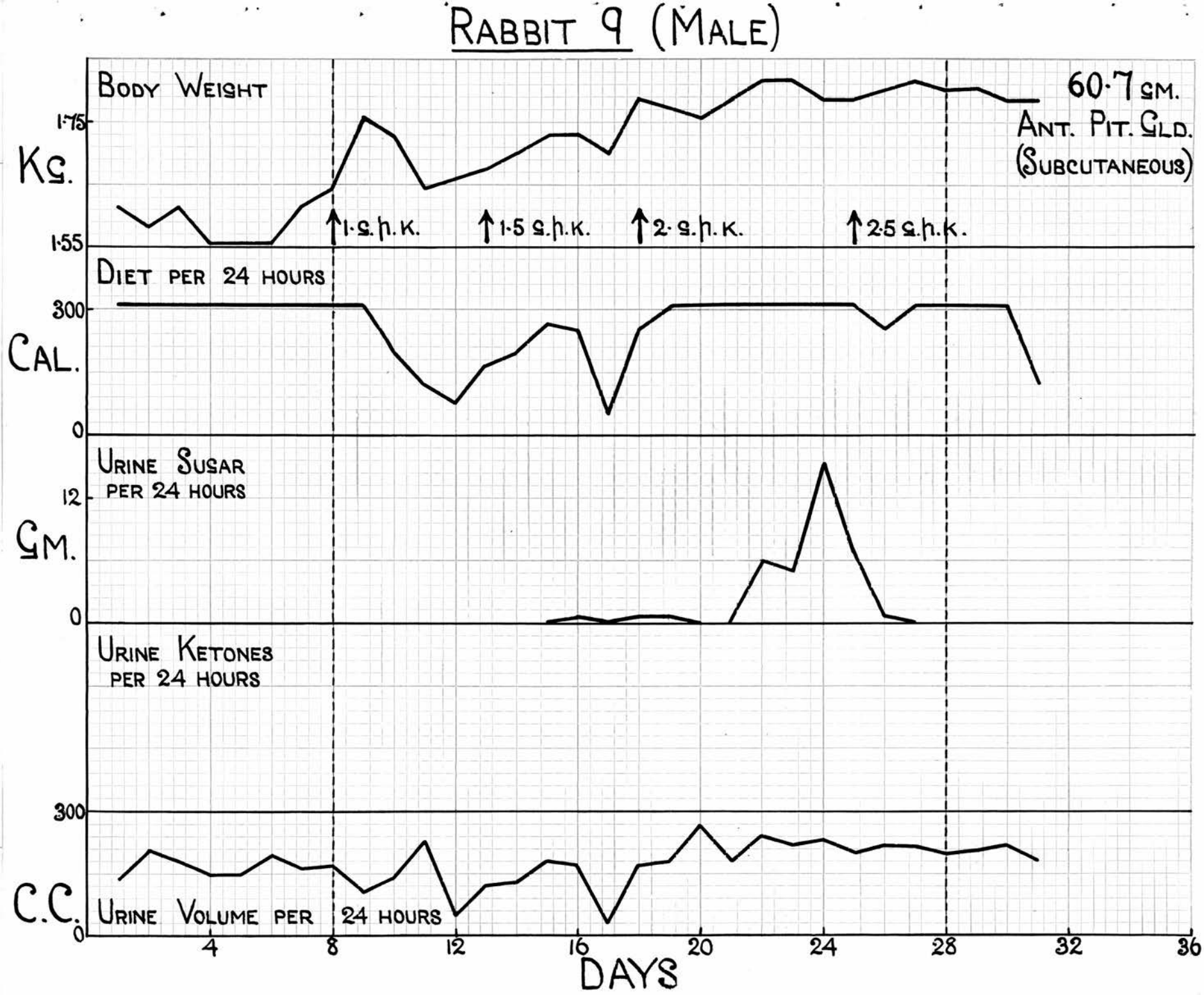
RABBIT 9 (MALE)
BODY WEIGHT
60·7 GM.
ANT. PIT. GLD.
(SUBCUTANEOUS)
1·75
KG.
1·55
↑1·5 G.H.K.
↑1·5 G.H.K.
↑2· G.H.K.
↑2·5 G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR
PER 24 HOURS
12
GM.
0
URINE KETONES
PER 24 HOURS
300
C.C.
0
URINE VOLUME PER 24 HOURS
4
8
12
16
20
24
28
32
36
DAYS

Figure 2.

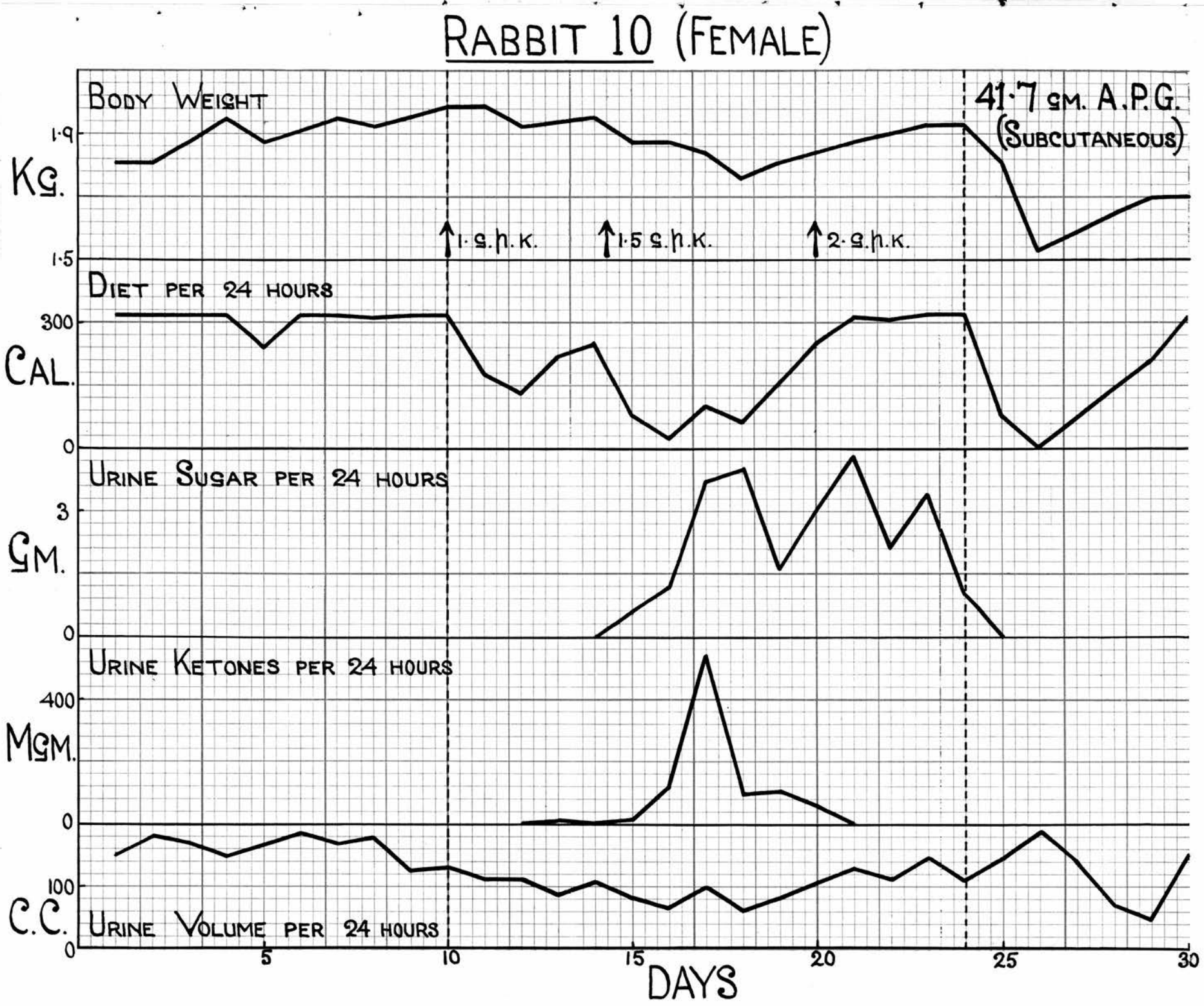
RABBIT 10 (FEMALE)
BODY WEIGHT
41·7 GM. A.P.G.
(SUBCUTANEOUS)
KG.
1·9
1·5
1·5 G.H.K.
2·G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR PER 24 HOURS
3
GM.
0
URINE KETONES PER 24 HOURS
400
MGM.
0
100
C.C.
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 3.

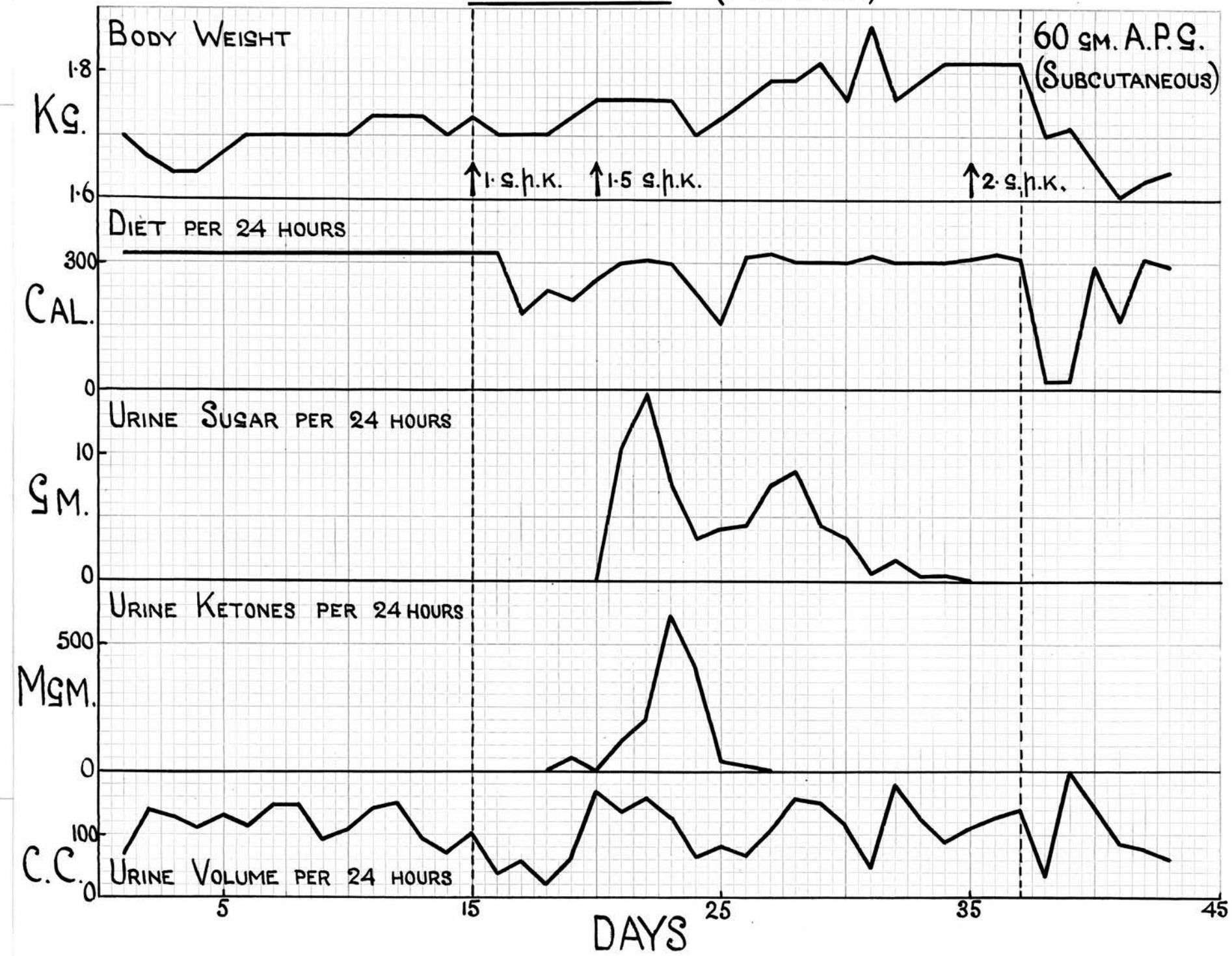
RABBIT 11 (FEMALE)
BODY WEIGHT
60 GM. A.P.G. (SUBCUTANEOUS)
KG.
1·8
1·6
↑1·G.h.K.
↑1·5 G.h.K.
↑2·G.h.K.
DIET PER 24 HOURS
CAL.
300
0
URINE SUGAR PER 24 HOURS
GM.
10
0
URINE KETONES PER 24 HOURS
MGM.
500
0
C.C.
100
0
URINE VOLUME PER 24 HOURS
5
15
25
35
45
DAYS

Figure 4.

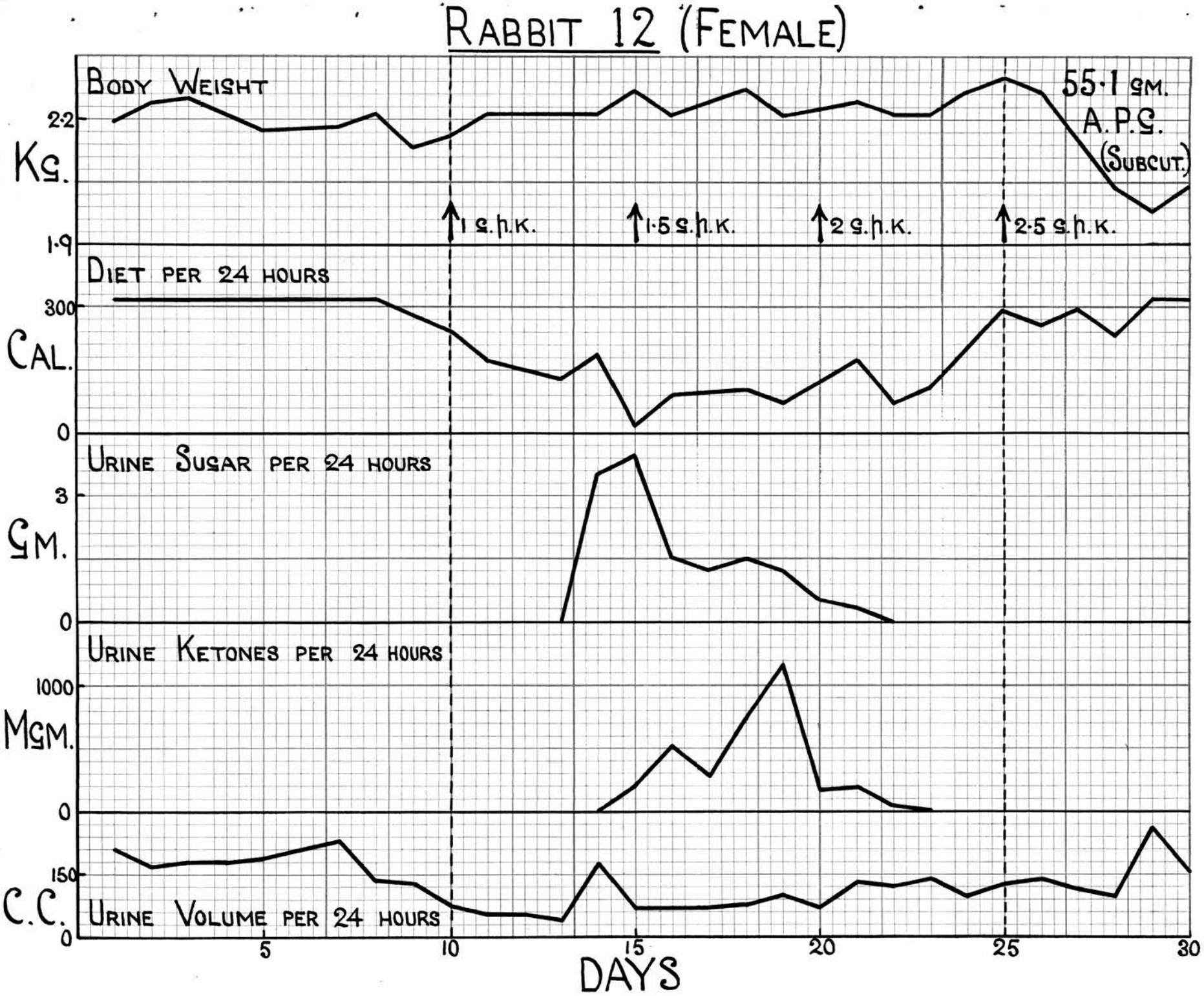
RABBIT 12 (FEMALE)
BODY WEIGHT
55·1 GM.
A.P.G.
(SUBCUT.)
KG.
2·2
1·9
1 G.H.K.
1·5 G.H.K.
2 G.H.K.
2·5 G.H.K.
DIET PER 24 HOURS
CAL.
300
0
URINE SUGAR PER 24 HOURS
GM.
3
0
URINE KETONES PER 24 HOURS
MGM.
1000
0
C.C.
150
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 5.

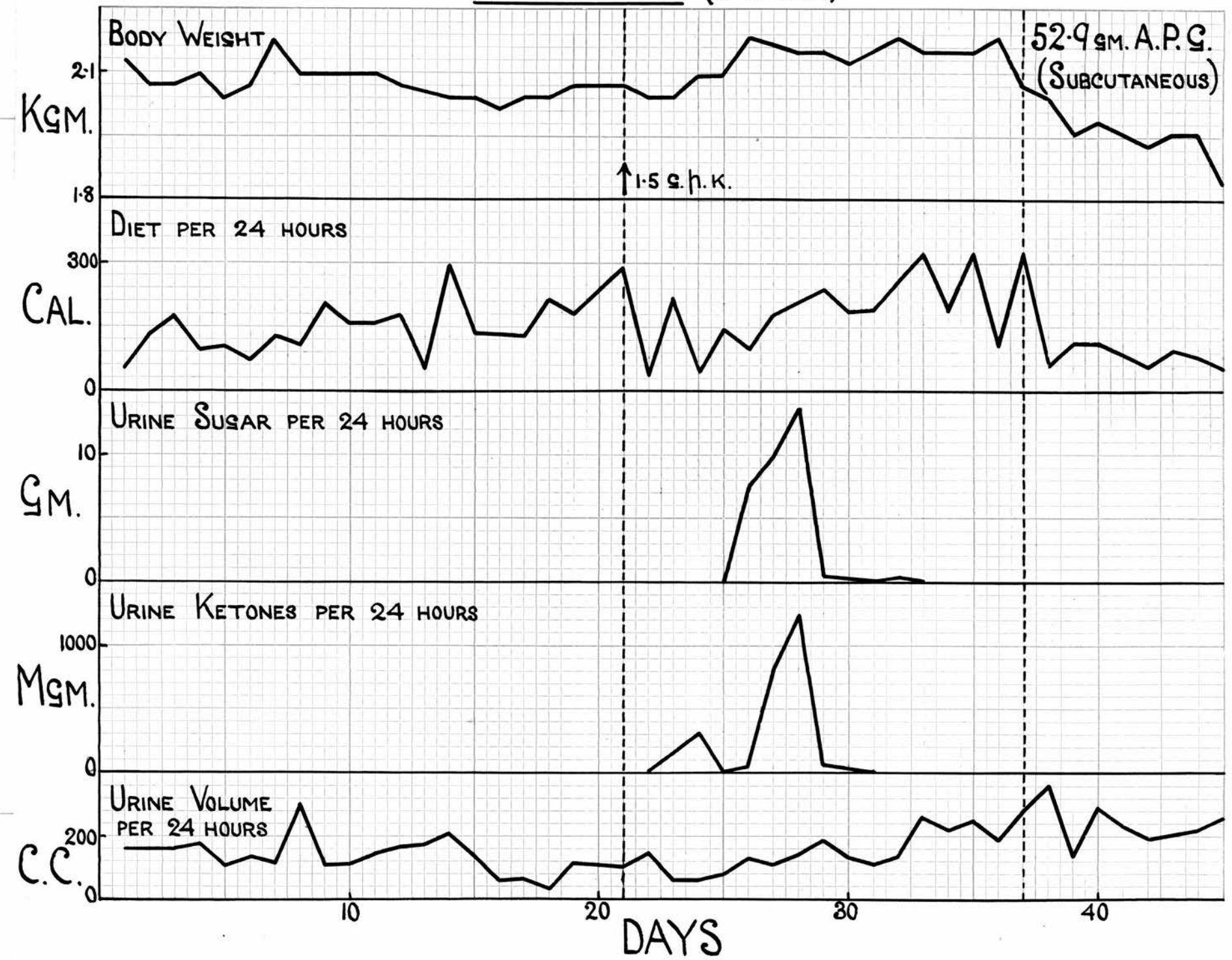
RABBIT 13 (MALE)
BODY WEIGHT
KGM.
2·1
1·8
52·9 GM. A.P.G.
(SUBCUTANEOUS)
1·5 G. H. K.
DIET PER 24 HOURS
CAL.
300
0
URINE SUGAR PER 24 HOURS
GM.
10
0
URINE KETONES PER 24 HOURS
MGM.
1000
0
URINE VOLUME
PER 24 HOURS
C.C.
200
0
10
20
30
40
DAYS

Figure 6.

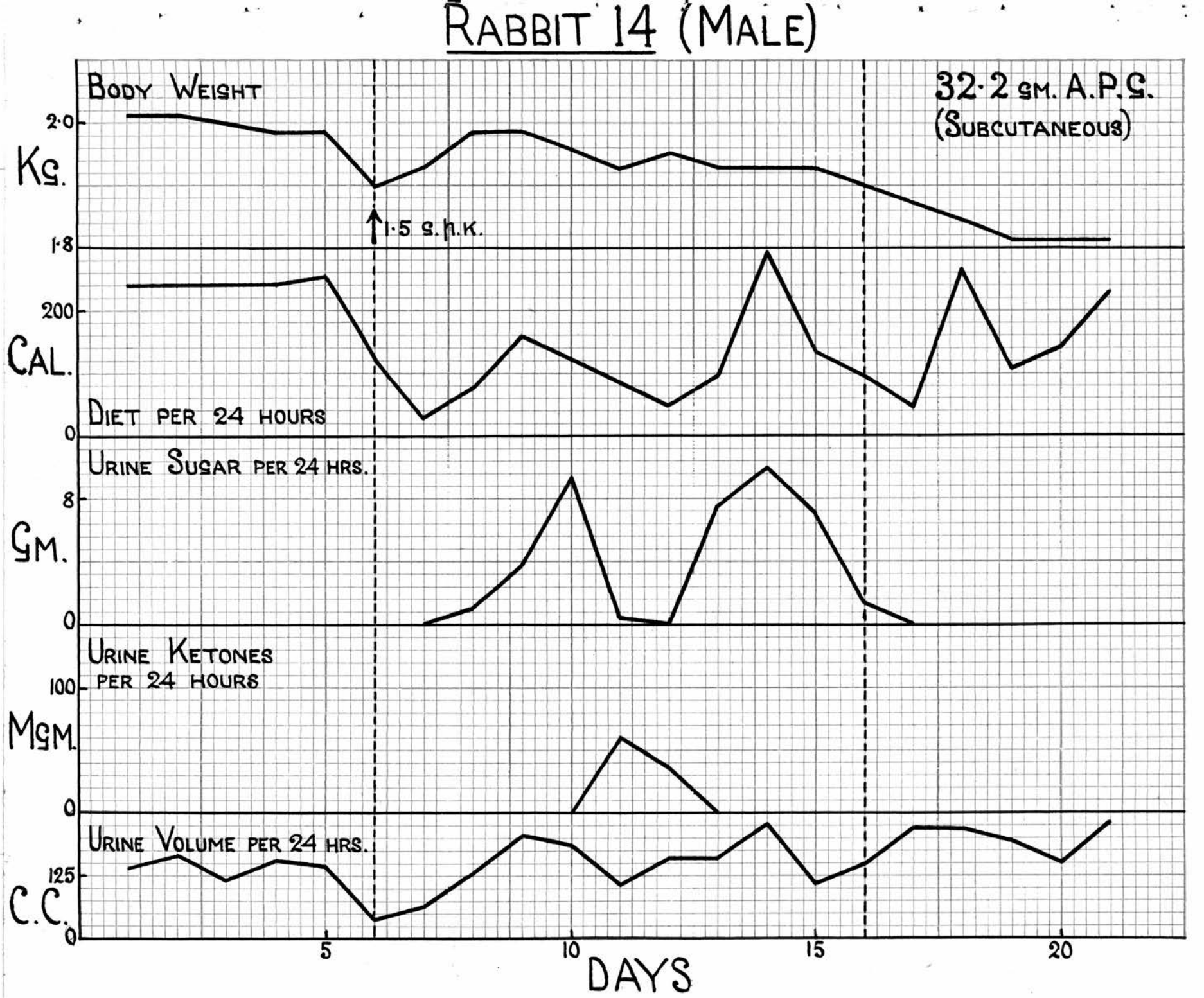
RABBIT 14 (MALE)
BODY WEIGHT
32·2 GM. A.P.S.
(SUBCUTANEOUS)
2·0
KG.
1·8
1·5 S.H.K.
200
CAL.
DIET PER 24 HOURS
0
URINE SUGAR PER 24 HRS.
8
GM.
0
URINE KETONES
PER 24 HOURS
100
MGM.
0
URINE VOLUME PER 24 HRS.
125
C.C.
0
5
10
15
20
DAYS

Figure 7.

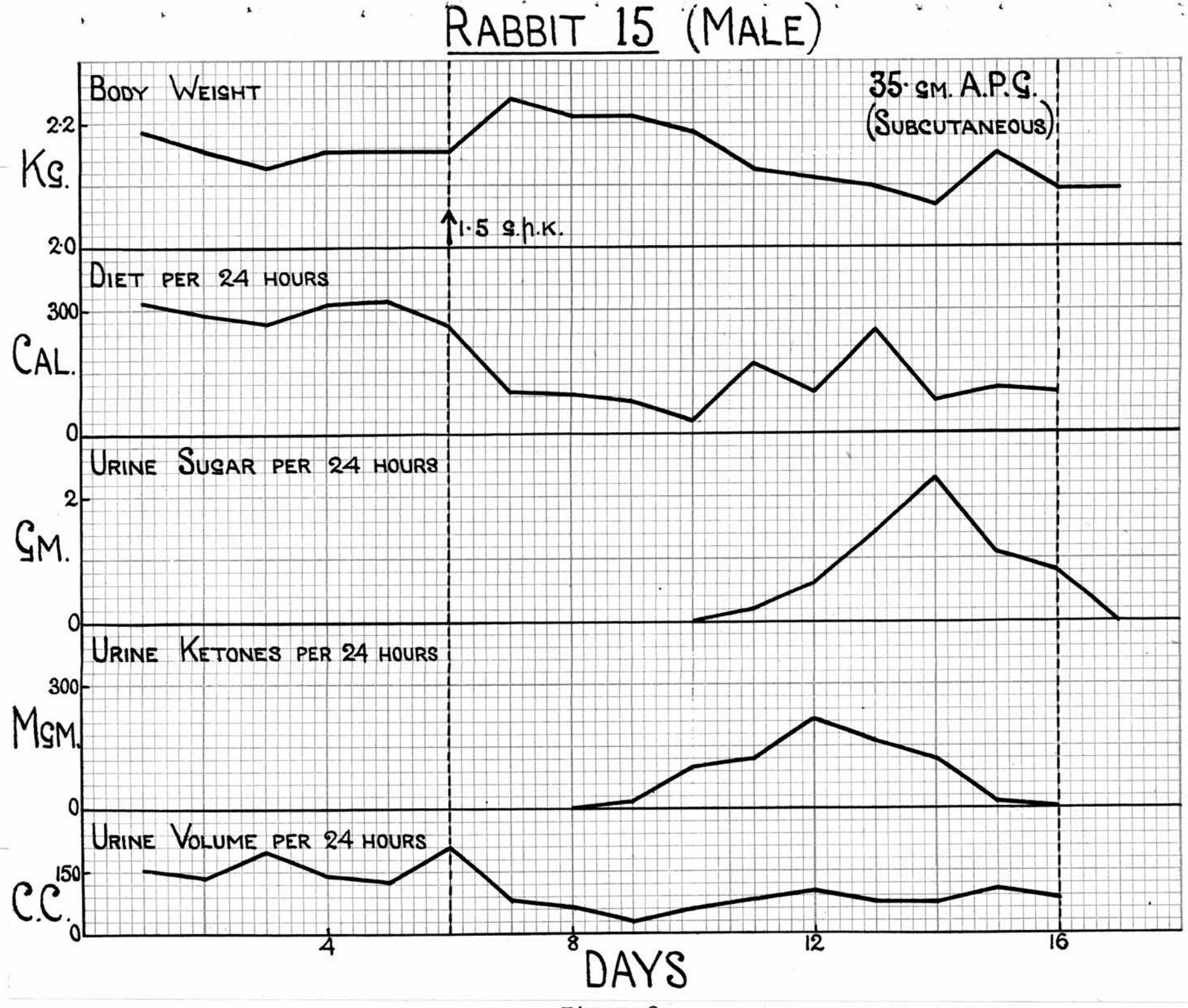
RABBIT 15 (MALE)
BODY WEIGHT
35·0 GM. A.P.C.
(SUBCUTANEOUS)
2·2
KG.
2·0
1·5 G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR PER 24 HOURS
2
GM.
0
URINE KETONES PER 24 HOURS
300
MGM.
0
URINE VOLUME PER 24 HOURS
150
C.C.
0
4
8
12
16
DAYS

Figure 8.

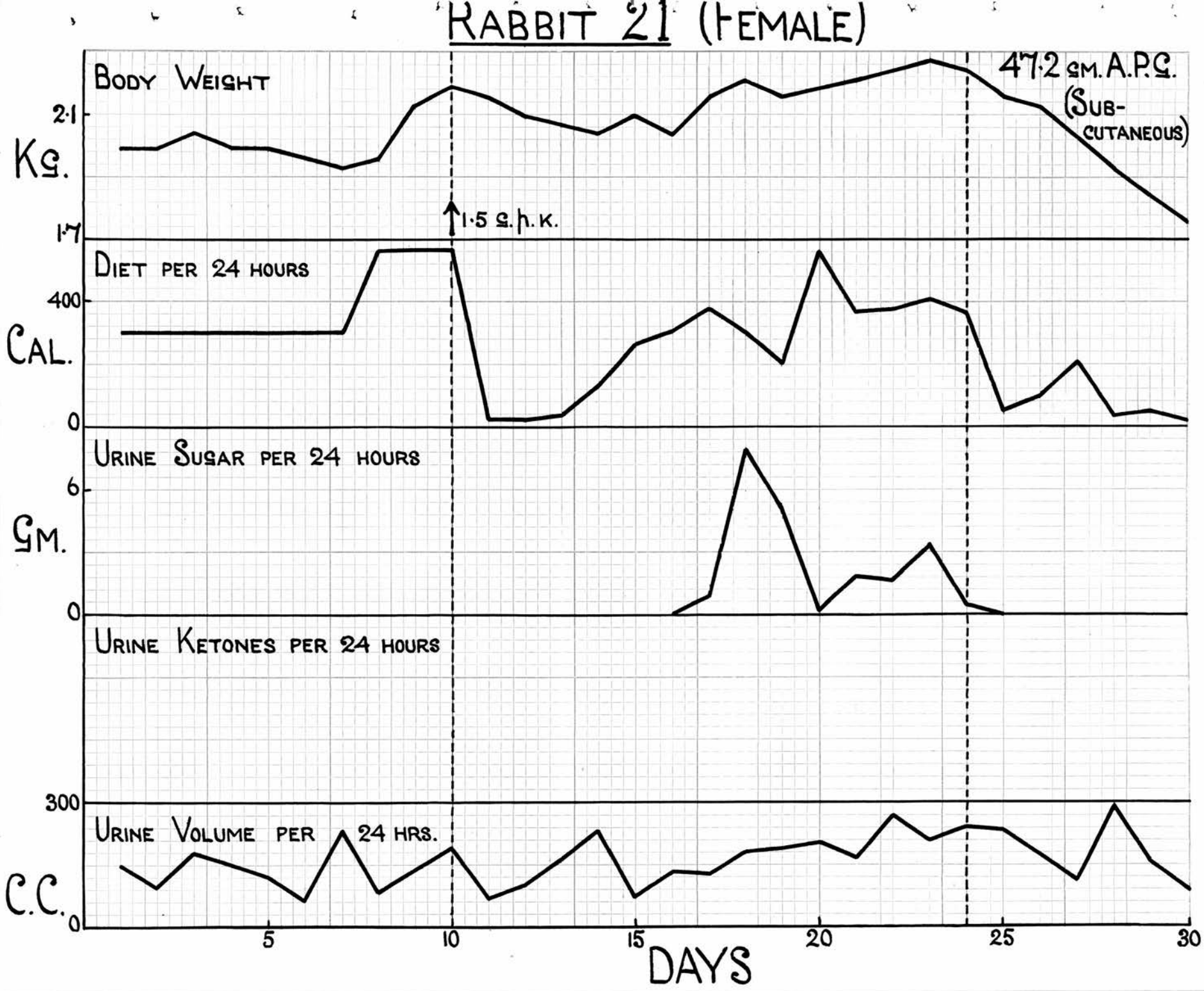
RABBIT 21 (FEMALE)
BODY WEIGHT
47·2 GM. A.P.G.
(SUB-CUTANEOUS)
2·1
KG.
1·7
1·5 G.H.K.
DIET PER 24 HOURS
400
CAL.
0
URINE SUGAR PER 24 HOURS
6
GM.
0
URINE KETONES PER 24 HOURS
300
URINE VOLUME PER 24 HRS.
C.C.
0
5
10
15
20
25
30
DAYS

Figure 9.

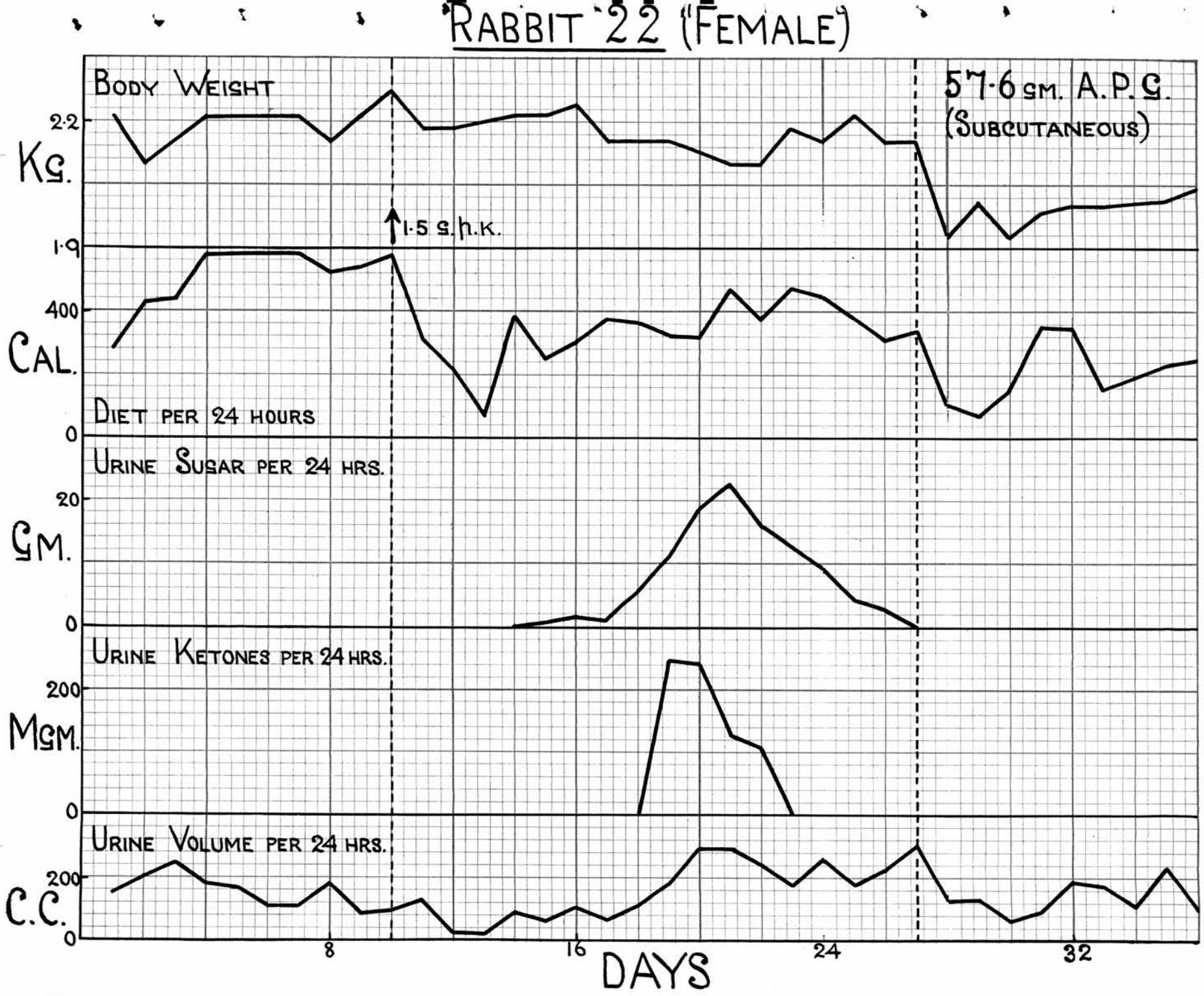
RABBIT 22 (FEMALE)
BODY WEIGHT
57·6 GM. A.P.G.
(SUBCUTANEOUS)
2·2
KG.
1·5 G.H.K.
1·9
400
CAL.
DIET PER 24 HOURS
0
URINE SUGAR PER 24 HRS.
20
GM.
0
URINE KETONES PER 24 HRS.
200
MGM.
0
URINE VOLUME PER 24 HRS.
200
C.C.
0
8
16
24
32
DAYS

Figure 10.

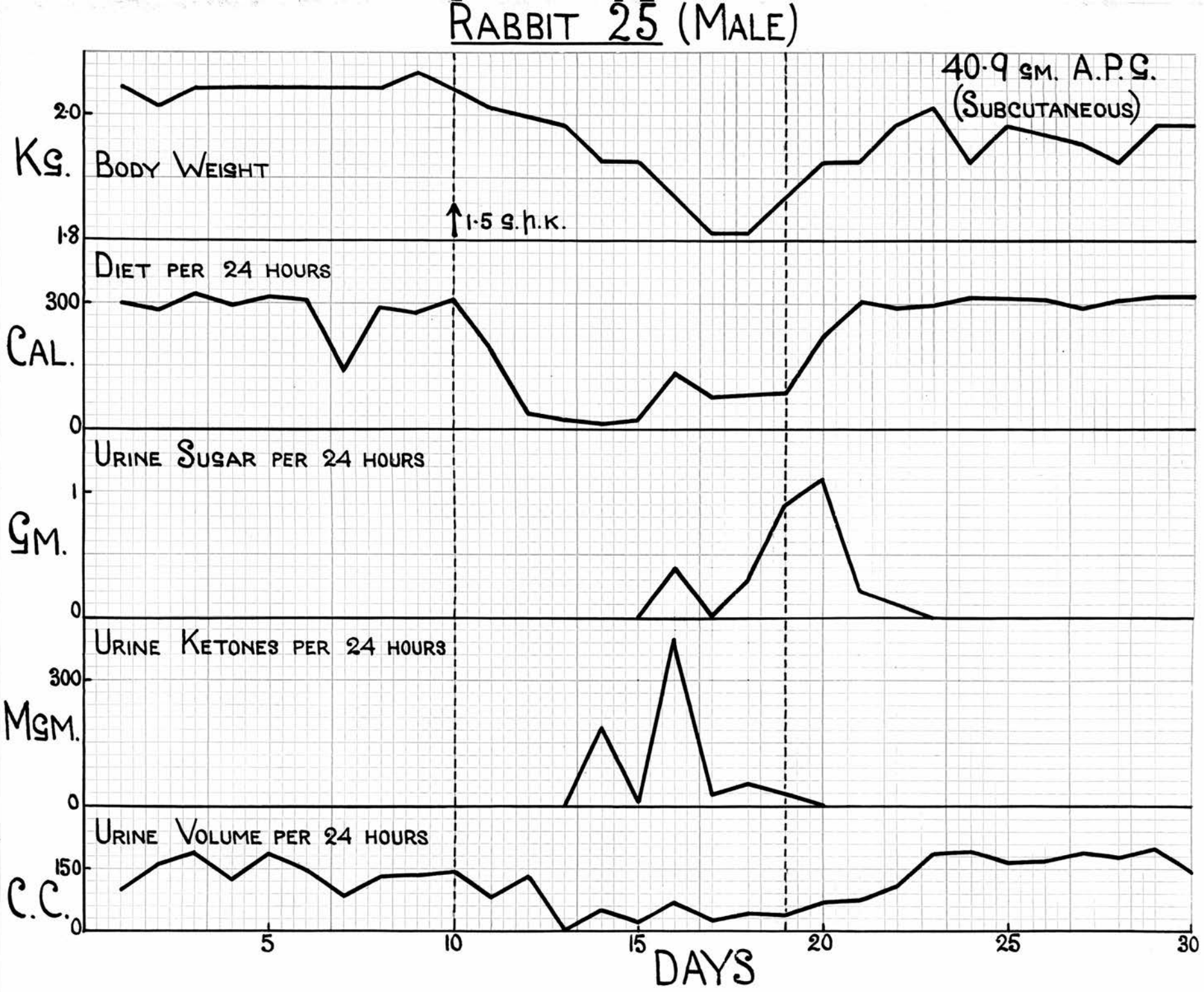
RABBIT 25 (MALE)
40·9 GM. A.P.G.
(SUBCUTANEOUS)
2·0
KG.
BODY WEIGHT
1·8
1·5 G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR PER 24 HOURS
1
GM.
0
URINE KETONES PER 24 HOURS
300
MGM.
0
URINE VOLUME PER 24 HOURS
150
C.C.
0
5
10
15
20
25
30
DAYS

Figure 11.

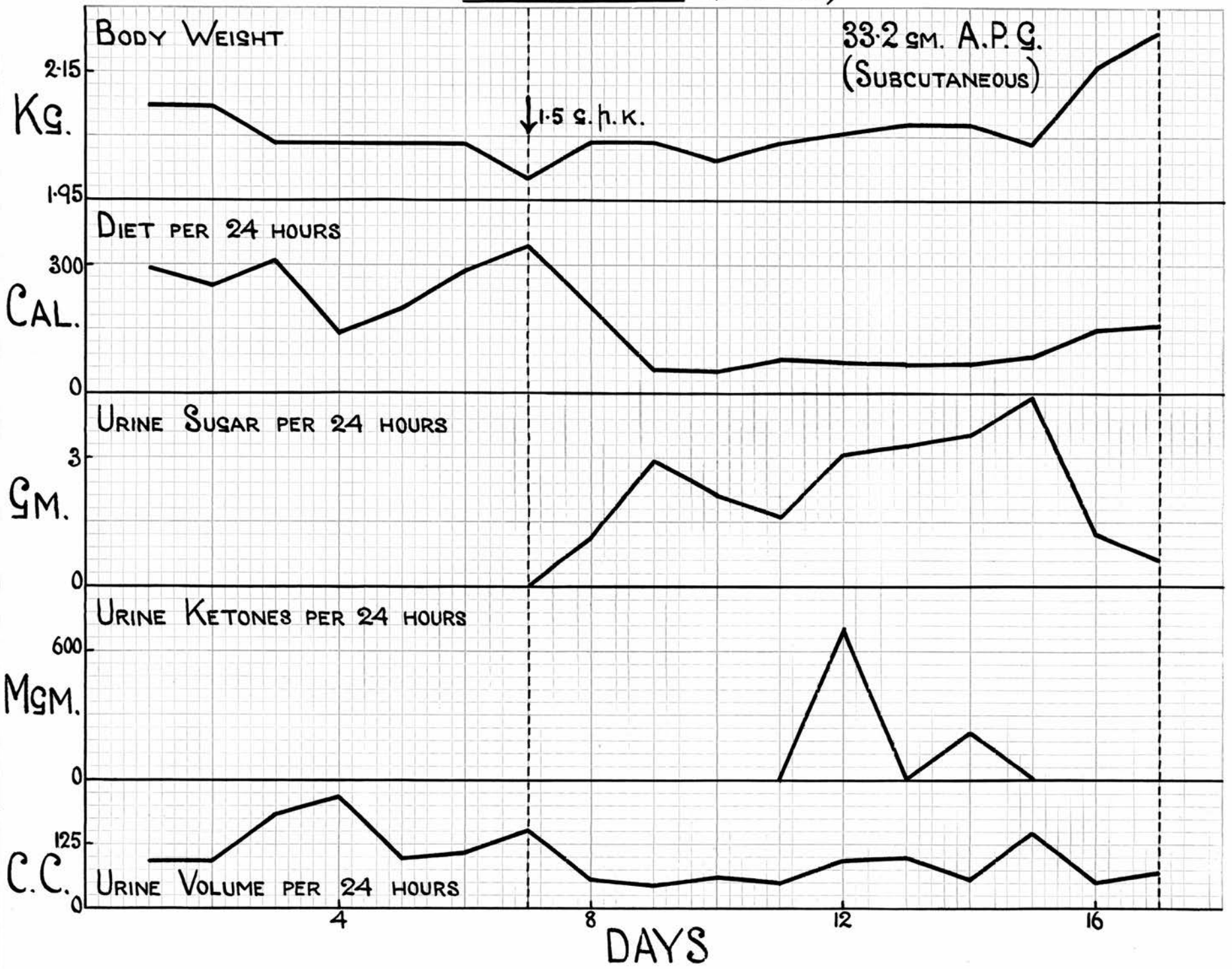
RABBIT 26 (MALE)
BODY WEIGHT
33·2 GM. A.P.G.
(SUBCUTANEOUS)
↓1·5 G. H.K.
2·15
KG.
1·95
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR PER 24 HOURS
3
GM.
0
URINE KETONES PER 24 HOURS
600
MGM.
0
125
C.C.
0
URINE VOLUME PER 24 HOURS
4
8
12
16
DAYS

Figure 12.

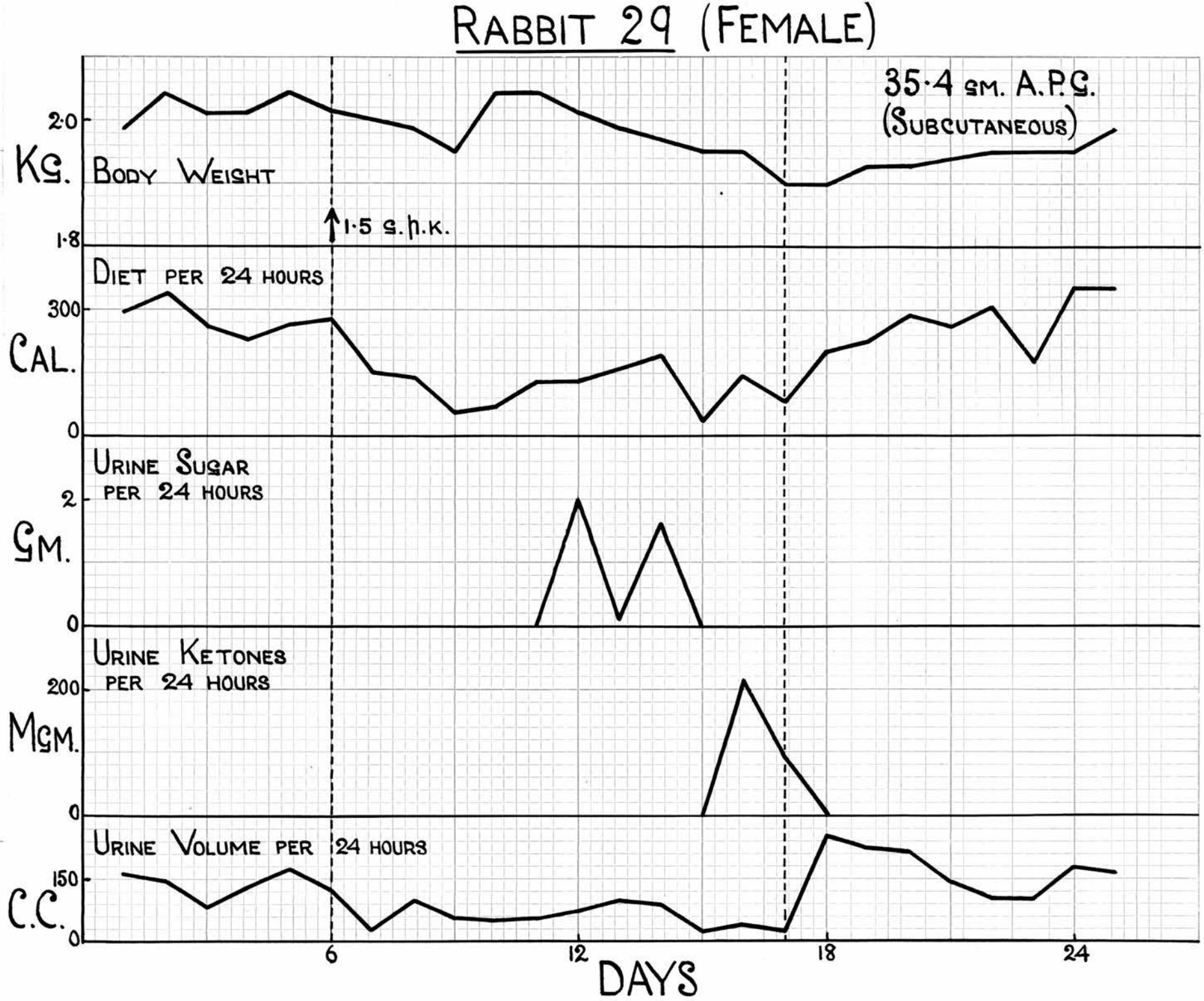
RABBIT 29 (FEMALE)
35·4 GM. A.P.G.
(SUBCUTANEOUS)
2·0
KG.
BODY WEIGHT
1·8
1·5 G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR
PER 24 HOURS
2
GM.
0
URINE KETONES
PER 24 HOURS
200
MGM.
0
URINE VOLUME PER 24 HOURS
150
C.C.
0
6
12
18
24
DAYS

Figure 13.

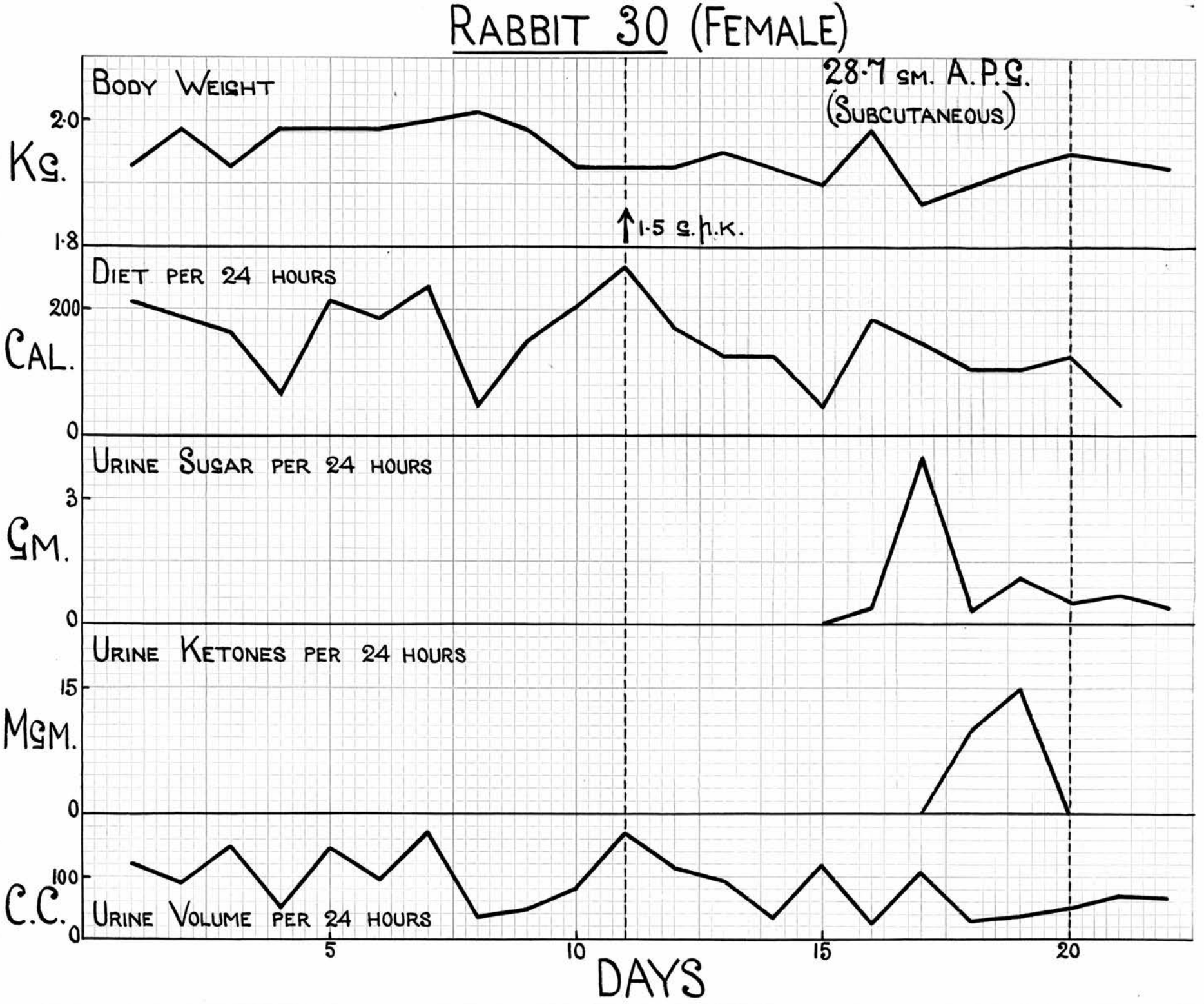
RABBIT 30 (FEMALE)
BODY WEIGHT
28·7 SM. A.P.S.
(SUBCUTANEOUS)
2·0
KG.
1·8
1·5 S.H.K.
DIET PER 24 HOURS
200
CAL.
0
URINE SUGAR PER 24 HOURS
3
GM.
0
URINE KETONES PER 24 HOURS
15
MGM.
0
100
C.C.
0
URINE VOLUME PER 24 HOURS
5
10
15
20
DAYS

Figure 14.

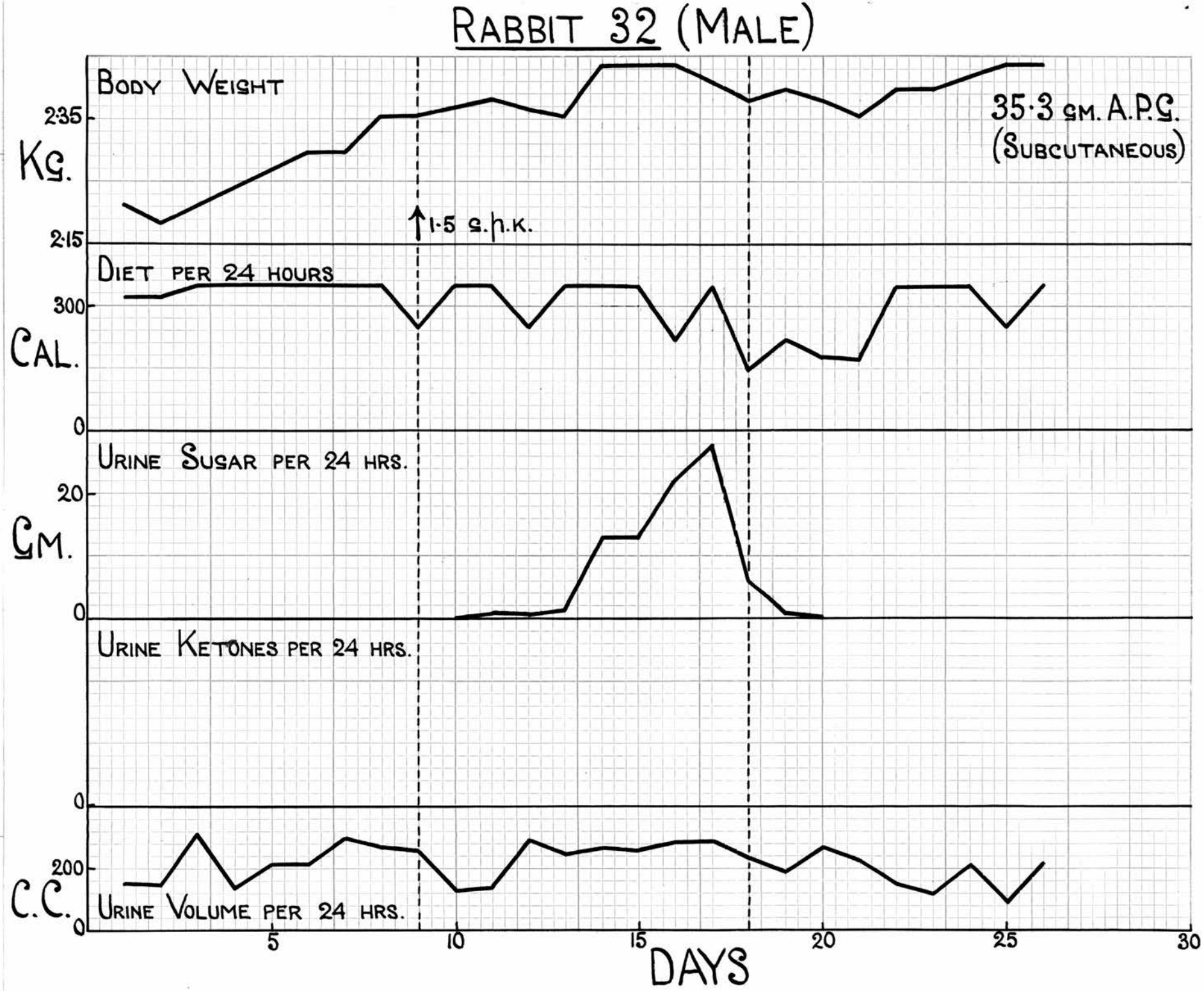
RABBIT 32 (MALE)
BODY WEIGHT
235
KG.
215
35·3 GM. A.P.G.
(SUBCUTANEOUS)
1·5 G.H.K.
DIET PER 24 HOURS
300
CAL.
0
URINE SUGAR PER 24 HRS.
20
GM.
0
URINE KETONES PER 24 HRS.
0
200
C.C.
0
URINE VOLUME PER 24 HRS.
5
10
15
20
25
30
DAYS

Figure 15.

TABLE I.

		Group 1	Group 2	Group 3	Entire Series
umber of animals		7	4	4	15
uration of treatment		15 days	10 days	10 days	12 days
verage amount of A.P.G.* per animal		43.5 g.	31.5 g.	28.6 g.	36.3 g.
ody ight.	Av. per day	+7.3 g.	±0 g.	-12.1 g.	+1.8 g.
	Total	+ 5.7 %	±0 %	- 5.9 %	+1.1 %
verage caloric intake per day relative to control.		65 %	65 %	39 %	58 %
verage urinary volume per day relative to control.		87 %	90 %	47 %	77 %
ycos-ria	No. of animals	7	4	4	15
	Duration	9 days	9 days	7 days	9 days
	Maximum	9.6 g. per day	16.0 g. per day	2.4 g. per day	9.4 g. per day
ton-ia	No. of animals	5	3	4	12
	Duration	6 days	3 days	6 days	5 days
	Maximum	757 mg. per day	109 mg. per day	340 mg. per day	456 mg. per day

* Anterior pituitary gland.

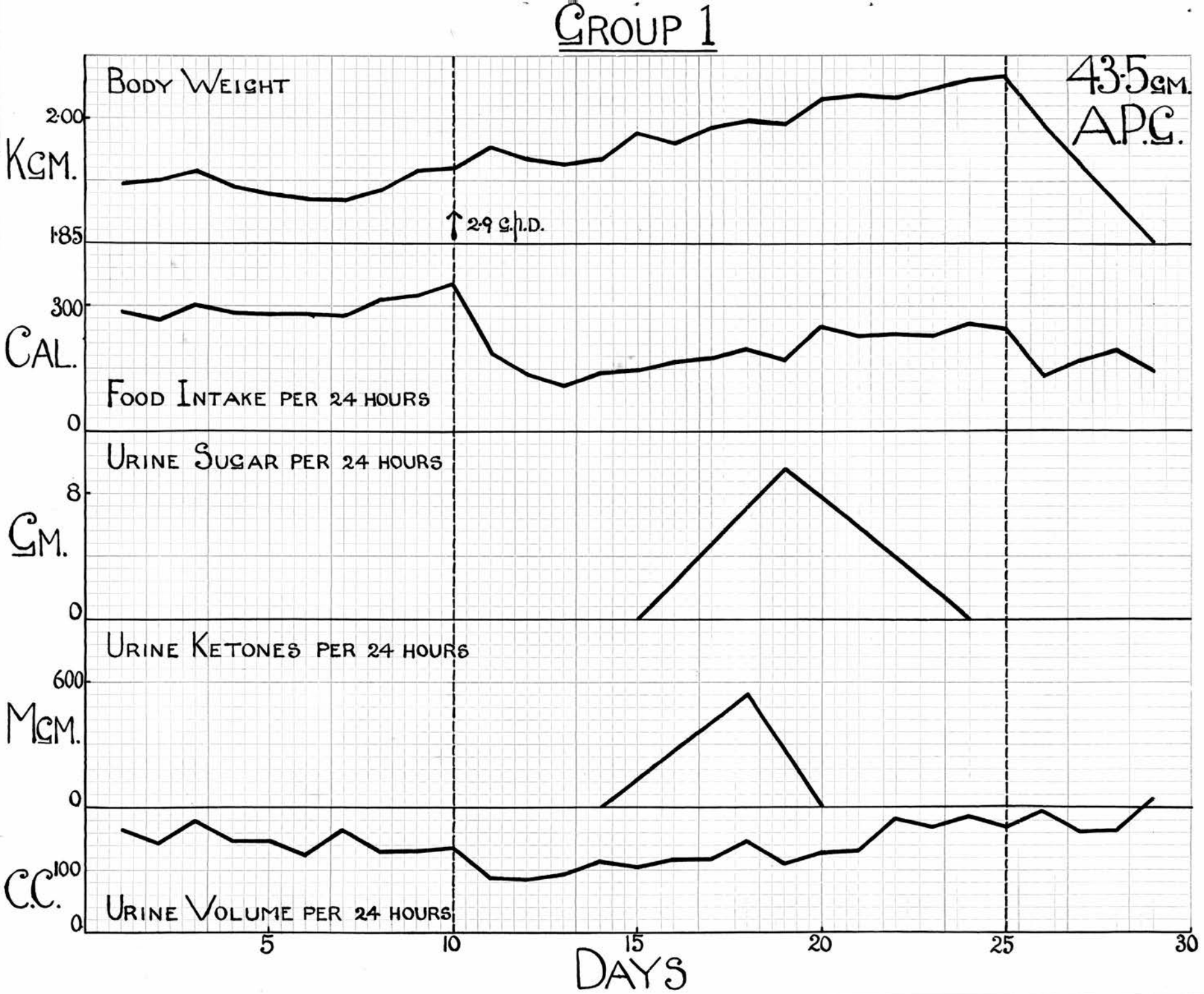
GROUP 1
BODY WEIGHT
43.5 GM.
A.P.C.
200
KGM.
185
2.9 G.h.D.
300
CAL.
FOOD INTAKE PER 24 HOURS
0
URINE SUGAR PER 24 HOURS
8
GM.
0
URINE KETONES PER 24 HOURS
600
MGM.
0
100
C.C.
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 16.

increase of 7.3 g. and a total increase of 5.7 per cent. The caloric intake fell sharply after the start of injections and then rose slowly, but was still subnormal at the end of treatment. It averaged 192 calories per day or 65 per cent of the daily control intake. Each of the seven animals, while being treated, showed transitory glycosuria and also in five cases temporary ketonuria. Glycosuria appeared on the seventh day, reached a maximum of 9.6 g. per 24 hr. on the tenth day and lasted 9 days. It varied inversely as the body weight in two animals. Ketonuria showed itself on the sixth day, attained a peak of 757 mg. per 24 hr. on the ninth day and disappeared after 6 days. The urine volume fell moderately with the start of injections, but by the end of treatment had risen to a high normal. The average excretion was 128 c.c. per day or 87 per cent of the daily control output. The body weight in the period after treatment fell abruptly and markedly and this was accompanied by a moderate reduction in energy intake and a slight increase in urine volume.

Group 2. The average results of the 4 rabbits forming this group are shown in Fig. 17. The stages of control, treatment and after-treatment lasted 10, 10 and 5 days respectively and treatment lay in the administration of 31.5 g. of gland in average amounts of 3.2 g. per day. The body weight under control turned moderately about

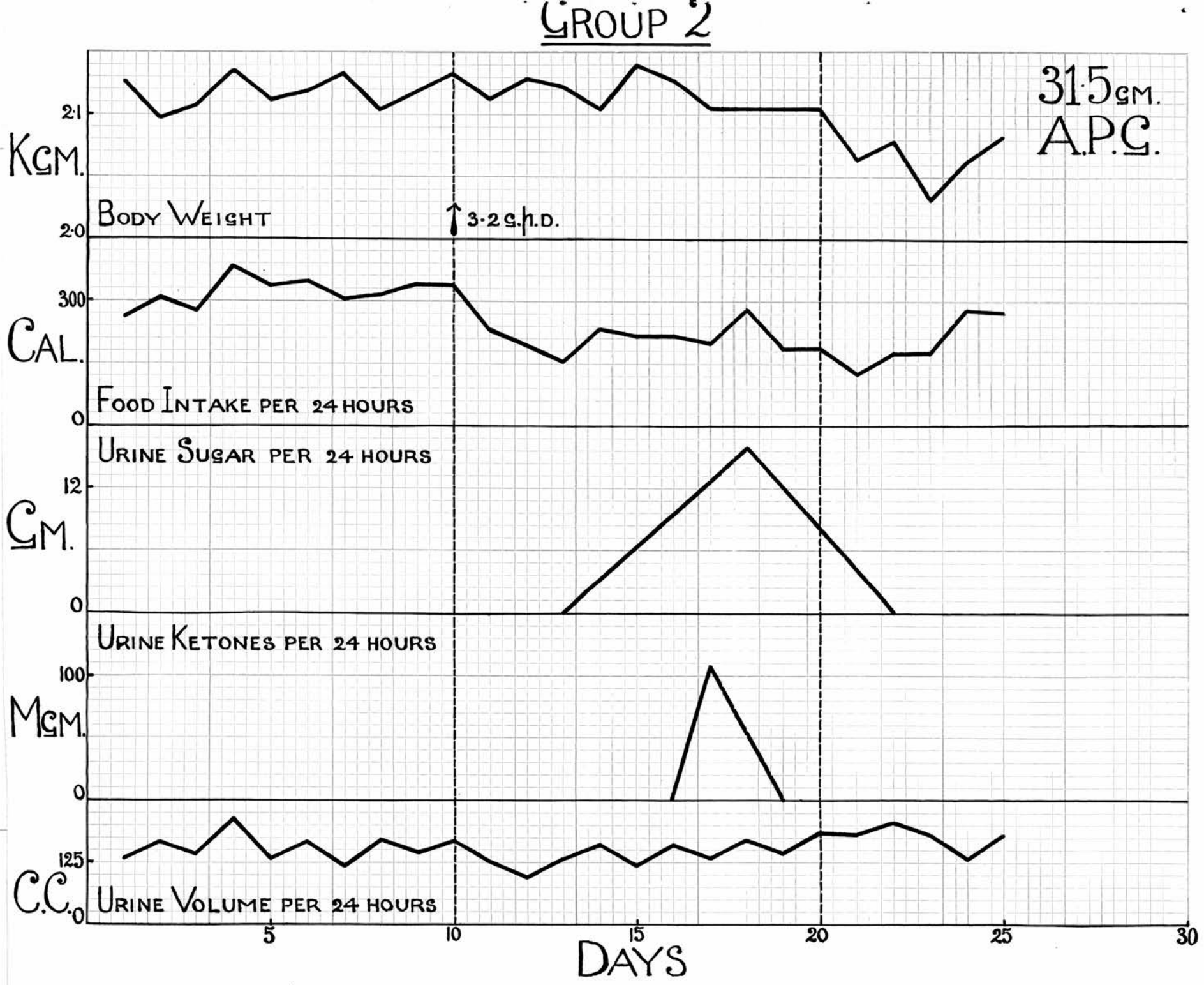
GROUP 2
315 GM.
A.P.G.
KGM.
2·1
2·0
BODY WEIGHT
3·2 G.H.D.
CAL.
300
0
FOOD INTAKE PER 24 HOURS
URINE SUGAR PER 24 HOURS
GM.
12
0
URINE KETONES PER 24 HOURS
MGM.
100
0
C.C.
125
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 17.

2119 g. on a food value of 320 calories per day, while the daily urine volume was in the neighbourhood of 156 c.c. The body weight during treatment averaged 2115 g. and thus maintained its control level. The caloric intake with the initiation of injections fell more or less abruptly at first and then recovered to some extent, but nevertheless remained definitely depressed. It amounted to an average of 207 calories per day or 65 per cent of the daily control value. Each of the 4 rabbits as a result of treatment showed transitory glycosuria and also in three cases temporary ketonuria. Glycosuria came on the fifth day, rose to a peak of 16.0 g. per 24 hr. on the ninth day and disappeared after 9 days. It varied inversely as the body weight in two animals. Ketonuria started on the eighth day, reached a maximum of 109 mg. per 24 hr. on the eighth day and lasted 3 days. The urine volume fell moderately after the start of injections and then rose gradually so as to reach normal by the end of treatment. The average output of urine was 141 c.c. per day and therefore 90 per cent of the daily control excretion. The body weight after treatment fell sharply at first and then partially recovered, while the energy intake after a slight initial decline rose to low normal. The urine at the same time was on the average slightly raised above the control excretion level.

Group 3. The average results of the 4 animals comprising this group are illustrated in Fig. 18. The/

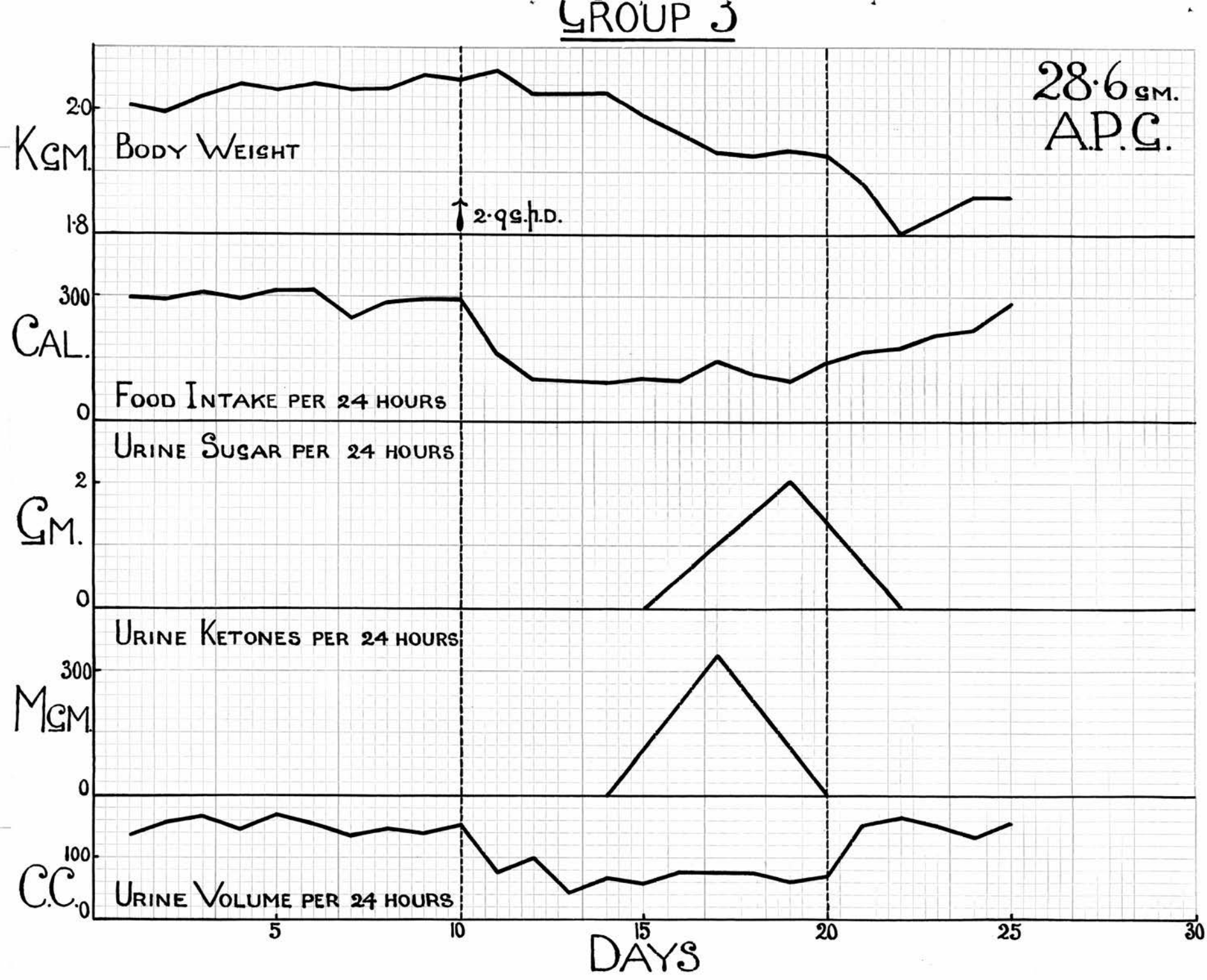
GROUP 3
28·6 GM.
A.P.G.
2·0
KGM.
1·8
BODY WEIGHT
2·9 S.H.D.
300
CAL.
0
FOOD INTAKE PER 24 HOURS
URINE SUGAR PER 24 HOURS
2
GM.
0
URINE KETONES PER 24 HOURS
300
MGM.
0
100
C.C.
0
URINE VOLUME PER 24 HOURS
5
10
15
20
25
30
DAYS

Figure 18.

The stages of control, treatment and after-treatment amounted to 10, 10 and 5 days respectively and treatment consisted in the injection of 28.6 g. gland in average quantities of 2.9 g. per day. The body weight in the control period followed a fairly even course about an average of 2031 g. on a more or less constant food value of 293 calories per day, while the daily urine volume varied only slightly and averaged 149 c.c. During treatment, the body weight remained within normal range for the first few days, but thereafter fell to become stabilised at a lower level. The loss amounted to 12.1 g. per day and a total of 5.9 per cent. The caloric intake incidentally fell to slightly less than 100 calories per day on the second day of treatment and thereafter continued almost constantly at that level to the end of injections. The food value for the period averaged 113 calories per day or 39 per cent of the normal intake. Each of the animals during treatment exhibited transitory glycosuria and ketonuria. Glycosuria appeared on the seventh day of treatment, reached a maximum of 2.4 g. per 24 hr. on the tenth day and lasted 7 days. Ketonuria began on the sixth day, rose to 340 mg. per 24 hr. on the eighth day and disappeared after 6 days. The urine volume after the start of treatment fell more or less abruptly and continued at a definitely depressed level until the end of treatment. The urine output averaged 70 c.c. per day or 47 per cent of the normal daily excretion. The period after treatment was characterised/

characterised by a sudden, marked fall followed by a partial recovery in body weight, a steadily increasing energy intake and a return of the urine volume to normal.

Average of Entire Series. The average results of the 15 animals are shown in Graph 19. The periods of control, treatment and after-treatment lasted respectively 10 days, 12 days and 5 days and treatment consisted in the administration of 36.3 g. gland in daily injections of 3.0 g. Under control, the body weight, energy intake and urine volume were respectively 2002 g., 301 calories and 150 c.c. During treatment the body weight was 2024 g. or 1.1 per cent greater than the control, while the food value fell to 175 calories or 58 per cent of the normal and the urine excretion to 116 c.c. or 77 per cent of the control. Each of the 15 animals in this period showed transitory glycosuria and in 12 cases also temporary ketonuria. Glycosuria began on the sixth day, reached a maximum of 9.4 g. per 24 hr. on the tenth day and lasted 9 days. Ketonuria started on the sixth day, attained a peak of 456 mg. on the ninth day and disappeared after 5 days. After treatment (omitting 4 animals owing to insufficient data) the body weight, energy intake and urine volume were respectively 1940 g., 187 calories and 172 c.c.

(2) Pancreatic Islet Tissue. The weight of islet tissue and the average weight and number of the islets in the 15 injected rabbits and also in 10 control animals are given in Tables 2 and 3.

The/

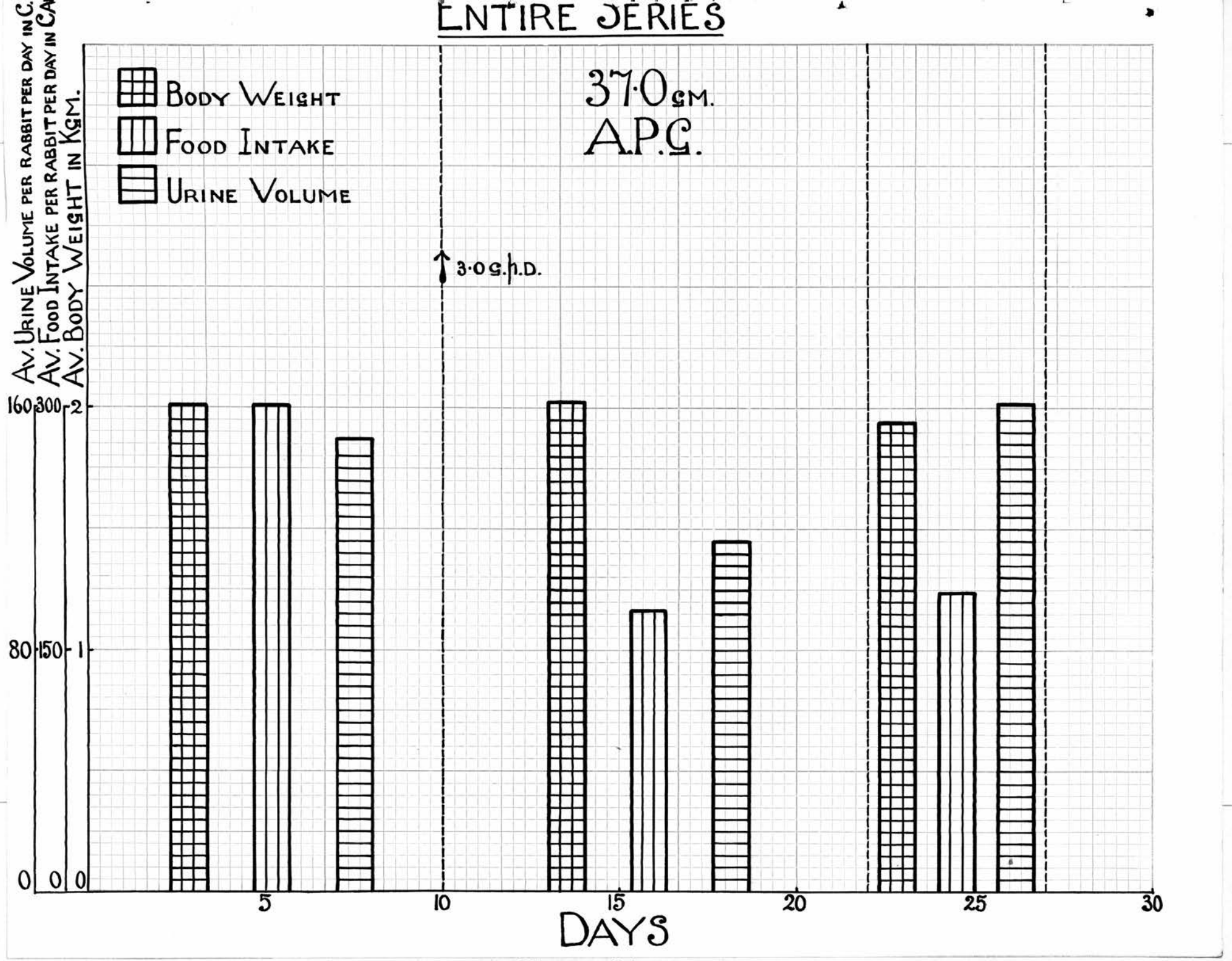
ENTIRE SERIES
BODY WEIGHT
FOOD INTAKE
URINE VOLUME
37·0 GM.
A.P.G.
3·0 G.h.D.
AV. URINE VOLUME PER RABBIT PER DAY IN C.
AV. FOOD INTAKE PER RABBIT PER DAY IN CA
AV. BODY WEIGHT IN KGM.
160
300
2
80
150
1
0
0
0
5
10
15
20
25
30
DAYS

Figure 19.

TABLE II.

No.	Injected Rabbits		
	Wt. of Islet Tissue in g.	Average Wt. of Islets in γ	Number of Islets
1.	0.04	0.380	95,000
2.	0.07	0.471	143,000
3.	0.15	0.496	308,000
4.	0.05	0.302	153,000
5.	0.08	0.633	119,000
6.	0.02	0.380	63,000
7.	0.06	0.220	276,000
8.	0.16	0.447	361,000
9.	0.05	0.302	165,000
10.	0.17	0.447	385,000
11.	0.36	0.793	452,000
12.	0.30	1.103	272,000
13.	0.10	0.284	335,000
14.	0.07	0.663	106,000
15.	0.02	0.496	46,000
Average	0.113	0.494	218,000
Standard Error.	±0.026	±0.059	±34,000

TABLE III.

No.	Control Rabbits.		
	Wt. of Islet Tissue in g.	Average Wt. of Islets in γ	Number of Islets
1.	0.06	0.359	176,000
2.	0.04	0.122	363,000
3.	0.06	0.154	396,000
4.	0.06	0.220	266,000
5.	0.05	0.206	247,000
6.	0.03	0.179	186,000
7.	0.07	0.302	220,000
8.	0.09	0.402	229,000
9.	0.03	0.220	130,000
10.	0.04	0.235	166,000
Average	0.053	0.240	238,000
Standard Error.	±0.006	±0.028	±27,000

The injected series had on the average more than twice as much islet tissue by weight as the control group, while the islets of the injected animals compared with those of the control rabbits were on the average more than twice as much by weight (Fig.20) and within similar range as regards number. Finally, the islets of the injected animals apart from their increased size were normal architecturally and in their proportion of A- and B- cells.

DISCUSSION

The animals in this investigation responded to treatment with crude anterior pituitary extract by increasing actually or relatively in weight on a distinctly smaller caloric intake than that normally required for the maintenance of constant body weight. Such an observation is in agreement with the results of previous investigators. Thus, Lee and Schaffer (1934) and Lee (1938) found that when restricted to the same food intake normal rats treated with anterior pituitary extract gained significantly more weight than controls. The same finding was obtained in hypophysectomised rats by Marx, Simpson, Reinhardt and Evans (1941-2), who also noted that the internal organs except the thymus grew at approximately the same rate as the body as a whole. Again, Young (1941-2, 1942) has shown that on a constant daily amount of food just sufficient to maintain its body weight a normal dog or cat treated with pituitary extract increases in weight despite the occurrence of/

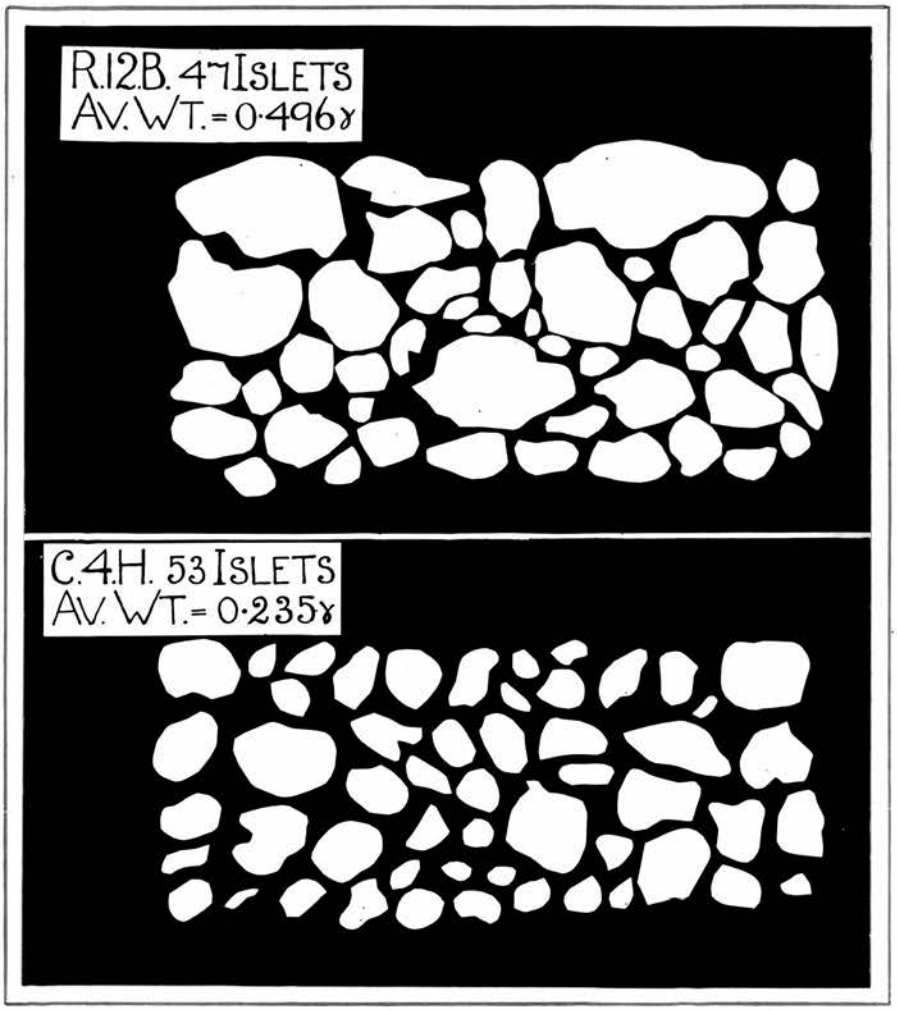

Figure 20. Comparison of islet tissue in injected and control rabbits. The average weight (0.496 γ) of the upper group of forty-seven islets from the body of the pancreas of injected rabbit 12 approximates closely to the average weight (0.494 γ) of the islets of the entire injected series, while the average weight (0.235 γ) of the lower group of fifty-three islets from the head of the pancreas of control rabbit 4 approximates closely to the average weight (0.240 γ) of the islets of the entire control series. The islets of the upper group are on the average more than twice the size of those in the lower group.

of glycosuria. These investigations and the present thus justify the conclusion that anterior pituitary extracts probably lead to reduced catabolism or increased anabolism or even to both of these phenomena concurrently.

A combination of reduced catabolism and increased anabolism with a consequent rise in body weight is indeed comprehensible in the light of some of the known actions of anterior pituitary extract. Thus, the oxidation of carbohydrate as emphasised by Russell (1938) is suppressed by its diabetogenic property, while an equally important effect according to Mirsky (1938, 1939) is a diminution of protein catabolism. Such an action on protein metabolism is in Mirsky's opinion mediated through the secretion of insulin by the pancreas. Twice the amount of insulin, moreover, can be extracted after the same treatment with anterior pituitary extract as produces double the quantity of pancreatic islet tissue (Marks & Young, 1940). Accordingly, the hypertrophied islets here observed may be regarded not only as a manifestation of the pancreotropic action of the extract (Ogilvie, 1944), but also as a source of additional insulin and, by reason thereof, part of the mechanism whereby the extract reduces protein catabolism. Now, another effect of the augmented pancreatic islet tissue and insulin would naturally be to increase the anabolic processes controlled thereby with the result that the carbon and nitrogen conserved through the reduced catabolism/

catabolism of carbohydrate and protein would be synthesised respectively into more carbohydrate and possibly fat (Rony, 1940) and into more protein (Mirsky, 1938, 1939). The outcome would be an increase in body weight. The transitory glycosuria which constantly accompanied this rise in body weight is explained by a temporary excess of the diabetogenic action of the extract over pancreatic islet activity, but the already noted increase of the islets in size and functional capacity induced by the pancreotropic property of the extract always ensued to neutralise the diabetogenic effect and cause subsidence of the condition. The fact that the glycosuria sometimes varied inversely as the body weight agrees with the observation of Young (1942) in the dog and was probably due to the loss of carbon and nitrogen incurred by the diabetes. Briefly, the reduced catabolism of carbohydrate and protein brought about by anterior pituitary extract can thus be ascribed to a combination of its diabetogenic and pancreotropic properties, while its pancreotropic influence is also responsible for the increased anabolism of protein and possibly fat. The consequent rise in body weight, in other words, may be regarded as due to the diabetogenic activity of the extract balanced by increased pancreatic islet function induced through the pancreotropic action of the extract. Relatively excessive diabetogenic action or similarly decreased islet function, on the other hand, results in diabetes and ultimately/

ultimately in a loss of weight.

Such experimental results throw suggestive light on the genesis of human diabetes mellitus. As initially stated, the children who develop diabetes are often abnormally tall, while the majority of adult diabetic cases are or have been obese. Obese subjects at the same time do not increase in weight continuously, but acquire most of their overweight in the first few years and thereafter maintain a state of more or less equilibrium (Dunlop & Murray-Lyon, 1931). They finally lose weight with the onset of diabetes. Further, Ogilvie (1935), assuming sugar tolerance to be an index of pancreatic islet activity, believes that the islets in a proportion of obese diabetic subjects pass through phases of increased, normal, and decreased function, while the fact that the islets in a considerable percentage of obese subjects are compensatorily hypertrophied (Ogilvie, 1933, 1935) also suggests that these structures are overactive at first and later depressed. Finally, Rabinowitch (1938), having observed that diabetic subjects on caloric intakes definitely below theoretical requirements either maintain their weight or lose very much less weight than the anticipated amount, has thereby shown that the diabetic condition is characterised by reduced catabolism or increased anabolism or both. Now, all these phenomena - increase and decrease in body weight, parallel phases of pancreatic islet function, hypertrophy of the pancreatic islets, and associated/

associated reduced catabolism and increased anabolism - also obtained in the present pituitary-treated rabbits, and a mechanism similar to that described in these animals may consequently be assumed for their correlation in the human diabetic subject. In other words, the prediabetic increase of height and weight in children and adults respectively, as Young (1941) has stated, may be regarded as due to excessive anterior pituitary activity with the diabetogenic action thereof temporarily compensated by increased pancreatic islet function induced through the pancreotropic influence of the gland. Failure of the balance of this mechanism throught islet exhaustion would ultimately result in diabetes mellitus.

SUMMARY AND CONCLUSIONS.

1. Fifteen English rabbits maintaining an almost constant body weight and urinary volume on a practically fixed caloric intake were intensively trated with crude ox anterior pituitary extract.

2. The animals as a result of this treatment increased actually or relatively in weight on a definitely reduced caloric intake. The diminution in food value was due mainly to loss of appetite, but also partly to dissipation of energy through temporary glycosuria and ketonuria.

3. The pancreatic islets of the treated animals, while numerically normal, were on the average more than twice as heavy as those of a control/

control series.

4. The actual or relative increase in body weight of the injected rabbits on a reduced food value indicates that anterior pituitary extract leads to reduced catabolism and increased anabolism. These effects are attributed to the diabetogenic action of the extract on the one hand and on the other to increased pancreatic islet function induced through the pancreotropic property of the preparation.

5. The above observations support the suggestion of Young (1941) that the prediabetic excess of height and weight in children and adults respectively is due to an elevated hypophysial-pancreatic balance, failure of which through islet exhaustion results in diabetes mellitus.

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Protocols.

Rabbit 7 (Male).

te.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals.* per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
10.40	1771	236	100 g.bran 250 g.cab.	308	-	-	-	-	-
10.40	-	196	100 g.bran 250 g.cab.	308	-	-	-	-	-
10.40	1785	101	100 g.bran 250 g.cab.	308	-	-	-	-	-
10.40	1799	258	100 g.bran 250 g.cab.	308	-	-	-	-	-
10.40	1806	147	100 g.bran 250 g.cab.	308	-	-	Blank - 20**	-	-
,10.40	1785	200	100 g.bran 250 g.cab.	308	-	-	-	-	-
,10.40	1700	67	50 g.bran 125 g.cab.	154	-	-	-	-	-
,10.40	1771	120	100 g.bran 2 50 g.cab.	308	-	-	-	-	-
,10.40	-	200	100 g.bran 250 g.cab.	308	-	-	-	-	-
.10.40	1814	139	100 g.bran 250 g.cab.	308	-	-	-	-	-
.10.40	1785	191	100 g.bran 250 g.cab.	308	-	-	-	-	1.0 g.per kg. (3.6 c.c.)
.10.40	1857	151	100 g.bran 250 g.cab.	308	-	-	-	-	1.0 g.per kg. (3.8 c.c.)
.10.40	1842	110	50 g.bran 125 g.cab.	154	-	-	-	-	1.0 g.per kg. (3.8 c.c.)
11.40	1871	76	50 g.bran 125 g.cab.	154	-	-	-	-	1.0 g.per kg. (3.8 c.c.)
11.40	1871	144	50 g.bran 125 g.cab.	154	-	-	-	-	2.5 g.per kg. (9.6 c.c.)
11.40	-	74	50 g.bran 125 g.cab.	154	-	-	-	-	-

* = Calories

** = Blank has not been deducted from either percentage or total ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
1.40	1842	141	0 g.bran 125 g.cab.	23	-	-	-	-	1.5 g.per kg. (5.8 c.c.)
1.40	1814	91	0 g.bran 100 g.cab.	19	-	-	100	91	1.5 g.per kg. (5.4 cc.)
1.40	1814	125	20 g.bran 190 g.cab.	88	0.1	0.1	134	168	1.5 g.per kg. (5.4 c.c.)
1.40	1842	121	50 g.bran 165 g.cab.	162	3.0	3.6	109	132	2.0 g.per kg. (7.6 c.c.)
1.40	1842	133	60 g.bran 200 g.cab.	231	5.5	7.3	154	205	2.0 g.per kg. (7.6 c.c.)
1.40	1871	172	40 g.bran 250 g.cab.	151	0.8	1.4	-	-	2.0 g.per kg. (7.6 c.c.)
11.40	-	183	20 g.bran 250 g.cab.	99	0.1	0.2	-	-	2.0 g.per kg. (7.6 c.c.)
11.40	1871	233	40 g.bran 250 g.cab.	151	0.1	0.2	-	-	2.5 g.per kg. (9.5 c.c.)
11.40	1871	248	20 g.bran 250 g.cab.	99	0.1	0.1	-	-	2.45 g.per kg. (9.1 c.c.)
11.40	1842	198	10 g.bran 250 g.cab.	73	-	-	-	-	-
11.40	1814	145	-	-	0.2	0.2	-	-	-

DIED.

21.

Rabbit 9. (Male)

e	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
11.40	1615	138	100 g.bran 250 g.cab.	308	-	-	-	-	-
11.40	1587	208	100 g.bran 250 g.cab.	308	-	-	-	-	-
11.40	1615	178	100 g.bran 250 g.cab.	308	-	-	-	-	-
11.40	1558	148	100 g.bran 250 g.cab.	308	-	-	-	-	-
.2.40	-	150	100 g.bran 250 g.cab.	308	-	-	-	-	-
.2.40	1558	194	100 g.bran 250 g.cab.	308	-	-	-	-	-
.2.40	1615	164	100 g.bran 250 g.cab.	308	-	-	-	-	-
.2.40	1643	169	100 g.bran 250 g.cab.	308	-	-	-	-	1.0 g. per kg. (3.2 c.c.)
.2.40	1757	108	100 g.bran 250 g.cab.	308	-	-	-	-	1.0 g. per kg. (3.6 c.c.)
12.40	1729	143	50 g.bran 220 g.cab.	195	-	-	-	-	1.0 g. per kg. (3.4 c.c.)
12.40	1643	230	30 g.bran 220 g.cab.	119	-	-	-	-	2x 1 g. per kg. (6.4 c.c.)
.2.40	-	50	20 g.bran 115 g.cab.	74	-	-	-	-	-
12.40	1672	120	50 g.bran 200 g.cab.	168	-	-	-	-	1.5 g. per kg. (5.2 c.c.)
12.40	1700	128	60 g.bran 210 g.cab.	196	-	-	-	-	1.5 g. per kg. (5.2 c.c.)
12.40	1729	181	85 g.bran 240 g.cab.	267	-	-	-	-	1.5 g. per kg. (5.2 c.c.)
12.40	1729	170	80 g.bran 230 g.cab.	252	0.3	0.6	-	-	1.5 g. per kg. (5.2 c.c.)
12.40	1700	31	Fasting	50	-	-	-	-	1.5 g. per kg. (5.2 c.c.)
12.40	1785	169	80 g.bran 250 g.cab.	256	0.4	0.6	-	-	2.0 g. per kg. (7.2 c.c.)

;e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
,12.40	-	180	100 g.bran 250 g.cab.	308	0.3	0.6	-	-	-
,12.40	1757	265	100 g.bran 250 g.cab.	308	-	-	-	-	2.0 g. per kg. (6.8 c.c.)
,12.40	1785	180	100 g.bran 250 g.cab.	308	-	-	-	-	2.0 g. per kg. (7.2 c.c.)
,12.40	1814	241	100 g.bran 250 g.cab.	308	2.5	6.0	-	-	2.0 g. per kg. (7.2 c.c.)
,12.40	1814	221	100 g.bran 250 g.cab.	308	2.3	5.1	-	-	2.0 g. per kg. (7.2 c.c.)
.12.40	1785	232	100 g.bran 250 g.cab.	308	6.6.	15.3	-	-	2.0 g. per kg. (7.2 c.c.)
.12.40	1785	205	100 g.bran 250 g.cab.	308	3.3	6.8	-	-	2.5 g. per kg. (9 c.c.)
.12.40	-	218	80 g.bran 250 g.cab.	256	0.3	0.7	-	-	2.5 g. per kg. (9 c.c.)
.12.40	1814	217	100 g.bran 250 g.cab.	308	-	-	-	-	2.5 g. per kg. (9 c.c.)
.12.40	1799	201	100 g.bran 250 g.cab.	308	-	-	-	-	2.5 g. per kg. (9 c.c.)
.12.40	1806	209	100 g.bran 250 g.cab.	308	-	-	-	-	-
.12.40	1785	218	100 g.bran 250 g.cab.	308	-	-	-	-	-
.12.40	1785	182	30 g.bran 250 g.cab.	125	-	-	-	KILLED.	

Rabbit 10. (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
12.40	1814	152	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1814	180	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1871	174	100 g.bran 300 g.cab.	318	-	-	Blank - 35*	-	-
..40	1956	151	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1871	170	70 g.bran 290 g.cab.	237	-	-	-	-	-
..40	-	185	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1956	173	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1927	181	100 g.bran 280 g.cab.	314	-	-	-	-	-
..40	1956	122	100 g.bran 300 g.cab.	318	-	-	-	-	-
..40	1984	131	100 g.bran 300 g.cab.	318	-	-	-	-	1.0 g.per kg. (4 c.c.)
1.40	1984	109	50 g.bran 250 g.cab.	177	-	-	-	-	1.0 g. per kg. (4 c.c.)
1.40	1927	110	30 g.bran 270 g.cab.	129	-	-	-	-	2 x 1 g.per kg. (7.6 c.c.)
1.40	-	83	70 g.bran 190 g.cab.	219	-	-	12	10	-
1.40	1956	106	80 g.bran 200 g.cab.	247	-	-	-	-	1.0 g. per kg. (3.8 c.c.)
1.40	1871	80	20 g.bran 150 g.cab.	80	0.7	0.6	10	8	1.5 g. per kg. (5.8 c.c.)
1.40	1871	65	0 g.bran 150 g.cab.	28	1.8	1.2	184	120	1.5 g. per kg. (5.8 c.c.)
1.40	1842	101	30 g.bran 100 g.cab.	97	3.7	3.7	539	544	1.5 g. per kg. (5.8 c.c.)

* = Blank has been deducted from both percentage and total ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
1.40	1757	60	fasting	? 60	6.7	4.0	159	95	1.5 g.per kg. (5.4 c.c.)
1.40	1814	80	40 g.bran 240 g.cab.	149	2.0	1.6	131	105	1.5 g.per kg. (5.4 c.c.)
1.40	-	106	80 g.bran 180 g.cab.	243	2.8	3.0	54	57	1.5 g.per kg. (5.4 c.c.)
1.40	1871	129	100 g.bran 250 g.cab.	308	3.3	4.3	-	-	2.0 g.per kg. (7.6 c.c.)
1.40	1899	110	100 g.bran 220 g.cab.	303	1.9	2.1	-	-	2.0 g.per kg. (7.6 c.c.)
1.40	1927	146	100 g.bran 300 g.cab.	318	2.3	3.4	-	-	2.0 g.per kg. (7.6 c.c.)
1.40	1927	114	100 g.bran 300 g.cab.	318	0.9	1.0	-	-	2.0 g.per kg. (7.6 c.c.)
1.40	1814	143	20 g.bran 150 g.cab.	80	-	-	-	-	-
1.40	1530	190	0	0	-	-	-	-	-
1.40	-	140	-	-	-	-	-	-	-
1.40	1643	72	-	-	-	-	-	-	-
1.40	1700	47	70 g.bran 150 g.cab.	211	-	-	-	-	-
1.40	1700	143	100 g.bran 270 g.cab.	312	-	-	-	-	-

Rabbit 11. (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
1.41	1700	68	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1672	140	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1643	130	100 g.bran 300 g.cab.	318	-	-	Blank = 40*	-	-
1.41	1643	111	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	-	133	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	115	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	146	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	151	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	94	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	106	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1729	142	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	-	151	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1729	95	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1700	72	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.41	1729	100	100 g.bran 300 g.cab.	318	-	-	-	-	1.0 g. per kg (3.4 c.c.)
1.41	1700	38	100 g.bran 300 g.cab.	318	-	-	-	-	1.0 g.per kg. (3.4 c.c.)
1.41	1700	58	50 g.bran 260 g.cab.	179	-	-	-	-	1.0 g.per kg. (3.4 c.c.)

* = Blank has been deducted from total, but not from percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg. %	Total Urine Ketones per 24 hr. in mg.	A.P.E.
2.41	1700	20	70 g.bran 22 g.hay	235	-	-	-	-	2 x 1.0 g. per kg. (6.8 c.c.)
2.41	-	61	70 g.bran 150 g.cab.	211	-	-	124	51	-
2.41	1757	170	80 g.bran 300 g.cab.	265	-	-	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1757	136	100 g.bran 200 g.cab.	300	7.7	10.5	129	121	1.5 g. per kg. (5.4 c.c.)
2.41	1757	157	100 g.bran 230 g.cab.	305	9.4	14.8	232	201	1.5 g. per kg. (5.4 c.c.)
2.41	1757	125	100 g.bran 200 g.cab.	300	6.0	7.5	527	609	1.5 g. per kg. (5.4 c.c.)
2.41	1700	63	fasting	-	5.3	3.3	701	404	1.5 g. per kg. (5.4 c.c.)
2.41	1729	80	50 g.bran 150 g.cab.	159	5.0	4.0	86	37	1.5 g. per kg. (5.4 c.c.)
2.41	-	64	100 g.bran 250 g.cab.	309	6.7	4.3	55	10	1.5 g. per kg. (5.4 c.c.)
2.41	1785	105	100 g.bran 300 g.cab.	318	7.0	7.4	30	-	1.5 g. per kg. (5.4 c.c.)
2.41	1785	156	100 g.bran 200 g.cab.	300	5.5	8.6	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1814	152	100 g.bran 200 g.cab.	300	2.8	4.3	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1757	116	100 g.bran 200 g.cab.	300	3.0	3.5	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1871	51	100 g.bran 270 g.cab.	313	1.1	0.6	-	-	1.5 g. per kg. (5.8 c.c.)
2.41	1757	181	100 g.bran 200 g.cab.	300	0.9	1.6	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	-	127	100 g.bran 200 g.cab.	300	0.04	0.1	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1814	87	100 g.bran 200 g.cab.	300	0.5	0.4	-	-	1.5 g. per kg. (5.4 c.c.)
2.41	1814	111	100 g.bran 250 g.cab.	309	-	-	-	-	2.0 g. per kg. (7.2 c.c.)

ıte	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
2.41	1814	128	100 g.bran 300 g.cab.	318	-	-	-	-	2.0 g. per kg. (7.2 c.c.)
2.41	1814	139	100 g.bran 250 g.cab.	309	-	-	-	-	2.0 g. per kg. (7.2.c.c.)
2.41	1700	35	0 g.bran 100 g.cab.	19	-	-	-	-	-
2.41	1714	200	0 g.bran 100 g.cab.	19	-	-	-	-	-
2.41	-	143	100 g.bran 165 g.cab.	293	-	-	-	-	-
2.41	1601	86	50 g.bran 150 g.cab.	159	-	-	-	-	-
2.41	1629	76	100 g.bran 250 g.cab.	309	-	-	-	-	-
2.41	1643	60	100 g.bran 180 g.cab.	295	-	-	-	-	-
2.41	1587	43	-	-	-	-	-	-	-
2.41	1587	35	-	-	-	-	-	-	-

Rabbit 12. (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
2.41	2197	210	100 g.bran 300 g.cab.	318	-	-	-	-	-
2.41	2239	172	100 g.bran 300 g.cab.	318	-	-	-	-	-
2.41	2253	181	100 g.bran 300 g.cab.	318	-	-	-	-	-
2.41	2211	180	100 g.bran 300 g.cab.	318	-	-	Blank = 14*	-	-
3.41	2168	191	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.41	-	11	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.41	2183	232	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.41	2211	130	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.41	2126	124	fasting	-	-	-	-	-	-
3.41	2154	72	80 g.bran 150 g.cab.	237	-	-	-	-	1.0 g. per kg. (4.2 c.c.)
3.41	2211	50	50 g.bran 200 g.cab.	168	-	-	-	-	1.0 g. per kg. (4.4 c.c.)
3.41	2211	54	50 g.bran 250 g.cab.	177	-	-	-	-	2x 1.0 g.per kg. (8.8 c.c.)
3.41	-	40	30 g.bran 250 g.cab.	125	-	-	-	-	-
.3.41	2211	174	50 g.bran 300 g.cab.	187	2.0	3.5	-	-	1.0 g. per kg. (4.4.c.c.)
.3.41	2267	68	0 g.bran 100 g.cab.	19	5.8	4.0	330	215	1.5 g. per kg. (6.8 c.c.)
.3.41	2211	66	20 g.bran 200 g.cab.	89	2.3	1.5	798	518	1.5 g. per kg. (6.4 c.c.)
.3.41	2239	67	-	-	1.8	1.2	413	267	1.5 g. per kg. (6.6 c.c.0
.3.41	2267	75	20 g.bran 250 g.cab.	99	2.0	1.5	985	728	1.5 g.per kg. (6.4 c.c.)

* Blank has been deducted from total, but not from percentage ketones

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
3.41	2211	102	10 g.bran 250 g.cab.	73	1.2	1.2	1040	1047	1.5 g. per kg. (6.4 c.c.)
3.41	-	67	-	-	0.7	0.5	98	56	2.0 g. per kg. (8.8 c.c.)
3.41	2239	131	50 g.bran 250 g.cab.	177	0.2	0.3	58	58	2.0 g. per kg. (8.8 c.c.)
3.41	2211	120	10 g.bran 250 g.cab.	73	-	-	20	7	2.0 g. per kg. (8.8 c.c.)
3.41	2211	138	20 g.bran 280 g.cab.	104	-	-	-	-	2.0 g. per kg. (8.8 c.c.)
3.41	2267	92	60 g.bran 240 g.cab.	202	-	-	-	-	2.0 g. per kg. (9.0 c.c.)
3.41	2295	125	95 g.bran 220 g.cab.	290	-	-	-	-	2.5 g. per kg. (11.2 c.c.)
3.41	2267	138	80 g.bran 250 g.cab.	256	-	-	-	-	-
3.41	-	116	95 g.bran 266 g.cab.	298	-	-	-	-	-
3.41	2041	93	70 g.bran 260 g.cab.	232	-	-	-	-	-
3.41	1984	260	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.41	2041	153	100 g.bran 300 g.cab.	318	-	-	-	-	-

Rabbit 13 (Male)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
3.41	2126	159	0 g.bran 290 g.cab.	54	-	-	-	-	-
3.41	2069	162	30 g.bran 260 g.cab.	127	-	-	-	-	-
3.41	2069	160	50 g.bran 240 g.cab.	175	-	-	-	-	-
3.41	2097	172	30 g.bran 90 g.cab.	95	-	-	Blank= 28*	-	-
3.41	2041	112	20 g.bran 290 g.cab.	106	-	-	-	-	-
3.41	-	131	10 g.bran 250 g.cab.	73	-	-	-	-	-
3.41	2183	114	30 g.bran 240 g.cab.	123	-	-	-	-	-
3.41	2097	295	20 g.bran 300 g.cab.	108	-	-	-	-	-
3.41	2097	112	60 g.bran 230 g.cab.	200	-	-	-	-	-
3.41	2097	115	40 g.bran 270 g.cab.	155	-	-	-	-	-
3.41	2097	145	40 g.bran 280 g.cab.	157	-	-	-	-	-
3.41	2069	162	50 g.bran 260 g.cab.	179	-	-	-	-	-
3.41	-	170	0 g.bran 300 g.cab.	56	-	-	-	-	-
3.41	2041	203	90 g.bran 300 g.cab.	291	-	-	-	-	-
4.41	2041	136	30 g.bran 300 g.cab.	134	-	-	-	-	-
4.41	2012	61	fasting	-	-	-	-	-	-
4.41	2041	64	30 g.bran 280 g.cab.	130	-	-	-	-	-
4.41	2041	35	60 g.bran 0 g.cab.	213	-	-	-	-	-

* = Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
.41	2069	116	50 g.bran 290 g.cab.	185	-	-	-	-	-
.41	-	-	-	-	-	-	-	-	-
.41	2069	104	100 g.bran 150 g.cab.	290	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
.41	2041	149	0 g.bran 190 g.cab.	35	-	-	-	-	1.0 g. per kg. (4.6 c.c.)
.41	2041	67	65 g.bran 230 g.cab.	213	-	-	260	155	1.5 g. per kg. (6.0 c.c.)
4.41	2097	59	0 g.bran 250 g.cab.	46	-	-	552	309	1.5 g. per kg. (6.3 c.c.)
4.41	2097	78	40 g.bran 215 g.cab.	145	-	-	20	0	1.5 g. per kg. (6.3 c.c.)
4.41	2183	123	20 g.bran 250 g.cab.	99	6.2	7.6	52	30	1.5 g. per kg. (6.6 c.c.)
4.41	-	112	50 g.bran 260 g.cab.	179	8.8	9.9	750	809	1.5 g. per kg. (6.6 c.c.)
4.41	2154	139	fasting	-	9.8	13.6	932	1257	1.5 g. per kg. (6.3 c.c.)
4.41	2154	187	70 g.bran 290 g.cab.	237	0.2	0.3	53	47	1.5 g. per kg. (6.3 c.c.)
4.41	2126	130	50 g.bran 285 g.cab.	184	0.1	0.1	34	8	1.5 g. per kg. (6.3 c.c.)
4.41	2154	110	50 g.bran 300 g.cab.	187	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2183	132	fasting	-	0.2	0.3	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2154	260	100 g.bran 300 g.cab.	318	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	-	221	50 g.bran 300 g.cab.	187	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2154	246	100 g.bran 300 g.cab.	318	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2183	192	20 g.bran 300 g.cab.	108	-	-	-	-	1.5 g. per kg. (6.3 c.c.)

e.	Body Weight in f.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Urine Urine Ketones per 24 hr. in mg.	A.P.E.
4.41	2069	279	100 g.bran 300 g.cab.	318	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2041	360	0 g.bran 300 g.cab.	56	-	-	-	-	-
4.41	1956	136	20 g.bran 300 g.cab.	108	-	-	-	-	-
4.41	1984	286	20 g.bran 300 g.cab.	108	-	-	-	-	-
4.41	1956	235	-	-	-	-	-	-	-
4.41	1927	196	0 g.bran 300 g.cab.	56	-	-	-	-	-
4.41	1955	202	20 g.bran 230 g.cab.	95	-	-	-	-	-
4.41	1955	215	10 g.bran 300 g.cab.	82	-	-	-	-	-
5.41	1842	253	0 g.bran 300 g.cab.	56	-	-	-	-	-

Rabbit 14 (Male)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
4.41	2012	140	70 g.bran 300 g.cab.	239	-	-	-	-	-
4.41	2012	167	70 g.bran 300 g.cab.	239	-	-	-	-	-
4.41	-	115	70 g.bran 300 g.cab.	239	-	-	Blank = 9*	-	-
4.41	1984	155	70 g.bran 300 g.cab.	239	-	-	-	-	-
4.41	1984	148	80 g.bran 240 g.cab.	254	-	-	-	-	-
4.41	1899	37	fasting	?120	-	-	-	-	1.5 g. per kg. (6 c.c.)
.41	1927	66	0 g.bran 150 g.cab.	28	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
.41	1984	130	10 g.bran 270 g.cab.	76	0.9	1.1	-	-	1.5 g. per kg. (6 c.c.)
.41	1984	203	40 g.bran 290 g.cab.	159	1.9	3.9	-	-	1.5 g. per kg. (6 c.c.)
.41	-	188	-	-	5.0	9.4	-	-	1.5 g. per kg. (6 c.c.)
.41	1927	110	fasting	-	0.4	0.4	64	61	1.5 g. per kg. (5.8 c.c.)
.41	1956	160	0 g.bran 260 g.cab.	48	-	-	32	37	1.5 g. per kg. (5.8 c.c.)
.41	1927	160	20 g.bran 240 g.cab.	97	4.7	7.5	-	-	1.5 g. per kg. (5.8 c.c.)
.41	1927	226	90 g.bran 300 g.cab.	291	4.4	10.0	-	-	1.5 g. per kg. (5.8 c.c.)
.41	1927	115	30 g.bran 300 g.cab.	134	6.2	7.1	-	-	1.5 g. per kg. (5.8 c.c.)
5.41	1899	148	20 g.bran 230 g.cab.	95	0.9	1.3	-	-	1.5 g. per kg. (5.7 c.c.)
5.41	-	220	0 g.bran 250 g.cab.	46	-	-	-	-	-

* - Blank has been deducted from total, but not percentage ketones.

;e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
,5.41	1842	220	80 g.bran 300 g.cab.	265	-	-	-	-	-
,5.41	1814	197	20 g.bran 300 g.cab.	108	-	-	-	-	-
,5.41	1814	151	30 g.bran 330 g.cab.	140	-	-	-	-	-
,5.41	1814	228	60 g.bran 388 g.cab.	229	-	-	-	-	-

Rabbit 15. (Male)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
5.41	2183	152	100 g.bran 290 g.cab.	316	-	-	-	-	-
5.41	2154	135	90 g.bran 280 g.cab.	288	-	-	-	-	-
5.41	2126	198	80 g.bran 290 g.cab.	263	-	-	Blank- 20*	-	-
5.41	2154	140	100 g.bran 270 g.cab.	312	-	-	-	-	-
5.41	-	122	100 g.bran 300 g.cab.	318	-	-	-	-	-
5.41	2154	210	80 g.bran 275 g.cab.	261	-	-	-	-	1.5 g. per kg. (6 c.c.)
5.41	2239	80	20 g.bran 260 g.cab.	101	-	-	-	-	1.5 g. per kg. (6.6 c.c.)
5.41	2211	62	20 g.bran 220 g.cab.	93	-	-	-	-	1.5 g. per kg. (6.6 c.c.)
5.41	2211	27	20 g.bran 140 g.cab.	78	-	-	78	16	1.5 g. per kg. (6.6 c.c.)
5.41	2183	59	5 g.bran 100 g.cab.	32	-	-	190	100	1.5 g. per kg. (6.6.c.c.)
5.41	2126	80	50 g.bran 200 g.cab.	168	0.3	0.2	148	118	1.5 g. per kg. (6.3 c.c.)
5.41	-	97	20 g.bran 250 g.cab.	99	0.6	0.6	238	212	1.5 g. per kg. (6.3 c.c.)
5.41	2097	72	80 g.bran 220 g.cab.	250	1.9	1.4	249	165	1.5 g. per kg. (6.3 c.c.)
5.41	2069	68	10 g.bran 275 g.cab.	77	3.3	2.3	195	119	1.5 g. per kg. (6.3 c.c.)
5.41	2154	103	20 g.bran 300 g.cab.	108	1.1	1.1	32	12	1.5 g. per kg. (6.0 c.c.)
5.41	2097	87	fasting	? 100	0.9	0.8	-	-	1.5 g. per kg. (6.3 c.c.)
5.41	2097	-	-	-	-	-	-	-	-

= Blank has been deducted from total, but not percentage ketones.

Rabbit 21 (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
9.41	1984	149	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	1984	94	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	2041	178	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	1984	151	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	1984	123	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	-	62	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	1927	230	100 g.bran 200 g.cab.	299	-	-	-	-	-
9.41	1956	83	200 g.bran 200 g.cab.	561	-	-	-	-	-
0.41	2126	120	200 g.bran 200 g.cab.	561	-	-	-	-	-
0.41	2183	194	200 g.bran 200 g.cab.	561	-	-	-	-	1.5 g. per kg. (6.8 c.c.)
0.41	2154	68	0 g.bran 135 g.cab.	25	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
0.41	2097	98	0 g.bran 90 g.cab.	18	-	-	-	-	1.5 g. per kg. (6.2 c.c.)
0.41	-	159	0 g.bran 200 g.cab.	37	-	-	-	-	1.5 g. per kg. (6.2 c.c.)
0.41	2041	233	35 g.bran 190 g.cab.	127	-	-	-	-	1.5 g. per kg. (6.0 c.c.)
0.41	2097	73	84 g.bran 200 g.cab.	260	-	-	-	-	1.5 g. per kg. (6.2 c.c.)
0.41	2041	129	105 g.bran 160 g.cab.	305	-	-	-	-	1.5 g. per kg. (6.0 c.c.)
0.41	2154	125	135 g.bran 120 g.cab.	376	0.7	0.9	-	-	1.5 g. per kg. (6.0 c.c.)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
10.41	2211	179	100 g.bran 200 g.cab.	299	4.4	7.9	-	-	1.5 g. per kg. (6.6 c.c.)
10.41	2154	187	fasting	?200	2.8	5.1	-	-	1.5 g. per kg. (6.0 c.c.
10.41	-	199	200 g.bran 200 g.cab.	561	0.1	0.2	-	-	1.5 g. per kg. (6.0 c.c.)
10.41	2211	164	125 g.bran 200 g.cab.	365	1.1	1.8	-	-	1.5 g. per kg. (6.2 c.c.)
10.41	2239	269	130 g.bran 200 g.cab.	378	0.6	1.7	-	-	1.5 g. per kg. (6.6 c.c.)
10.41	2267	209	140 g.bran 200 g.cab.	404	1.6	3.3	-	-	1.5 g. per kg. (6.6 c.c.)
10.41	2239	240	120 g.bran 250 g.cab.	361	0.2	0.5	-	-	1.5 g. per kg. (6.6 c.c.)
10.41	2154	235	0 g.bran 250 g.cab.	46	-	-	-	-	-
10.41	2126	-	20 g.bran 230 g.cab.	95	-	-	-	-	-
10.41	-	112	60 g.bran 250 g.cab.	204	-	-	-	-	-
10.41	1927	295	0 g.bran 200 g.cab.	37	-	-	-	-	-
10.41	1842	255	0 g.bran 255 g.cab.	47	-	-	-	-	-
10.41	1757	89	0 g.bran 100 g.cab.	19	-	-	-	-	-

Rabbit 22. (Female)

;e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
10.41	2211	158	100 g.bran 110 g.cab.	282	-	-	-	-	-
10.41	2097	205	150 g.bran 200 g.cab.	430	-	-	-	-	-
10.41	2154	244	150 g.bran 250 g.cab.	439	-	-	-	-	-
10.41	2211	186	200 g.bran 300 g.cab.	580	-	-	-	-	-
,10.41	2211	166	200 g.bran 300 g.cab.	580	-	-	-	-	-
.10.41	-	112	200 g.bran 300 g.cab.	580	-	-	Blank- 20*	-	-
.10.41	2211	115	200 g.bran 300 g.cab.	580	-	-	-	-	-
.10.41	2154	179	180 g.bran 265 g.cab.	521	-	-	-	-	-
.10.41	2211	82	190 g.bran 230 g.cab.	540	-	-	-	-	-
.10.41	2267	98	200 g.bran 300 g.cab.	580	-	-	-	-	1.5 g. per kg. (6.8 c.c.)
.10.41	2183	130	110 g.bran 120 g.cab.	310	-	-	-	-	1.5 g. per kg. (6.4 c.c.)
.10.41	2183	21	75 g.bran 160 g.cab.	226	-	-	-	-	1.5 g. per kg. (6.4 c.c.)
.10.41	-	13	20 g.bran 115 g.cab.	74	-	-	-	-	1.5 g. per kg. (6.4 c.c.)
.10.41	2211	93	130 g.bran 210 g.cab.	380	-	-	-	-	1.5 g. per kg. (6.6 c.c.)
.10.41	2211	57	80 g.bran 170 g.cab.	241	0.06	0.03	-	-	1.5 g. per kg. (6.6 c.c.)
.10.41	2239	108	100 g.bran 210 g.cab.	301	1.3	1.4	-	-	1.5 g. per kg. (6.6 c.c.)
.10.41	2154	62	120 g.bran 300 g.cab.	370	1.4	0.9	-	-	1.5 g. per kg. (6.3 c.c.)

* = Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
10.41	2154	112	130 g.bran 100 g.cab.	359	4.7	5.3	-	-	1.5 g. per kg. (6.3 c.c.)
1.41	2154	171	110 g.bran 170 g.cab.	320	6.2	10.6	166	250	1.5 g. per kg. (6.3 c.c.)
1.41	-	285	100 g.bran 300 g.cab.	318	6.6	18.7	105	242	1.5 g. per kg. (6.3 c.c.)
1.41	2097	282	162 g.bran 260 g.cab.	473	8.0	22.6	65	127	1.5 g. per kg. (6.2 c.c.)
1.41	2097	237	120 g.bran 300 g.cab.	370	6.7	15.8	65	107	1.5 g. per kg. (6.2 c.c.)
1.41	2183	171	160 g.bran 300 g.cab.	475	7.2	12.2	-	-	1.5 g. per kg. (6.3 c.c.)
1.41	2154	271	150 g.bran 300 g.cab.	449	3.3	9.0	-	-	1.5 g. per kg. (6.3 c.c.)
.1.41	2211	170	120 g.bran 290 g.cab.	368	2.4	4.1	-	-	1.5 g. per kg. (6.6 c.c.)
.1.41	2154	226	90 g.bran 380 g.cab.	306	1.3	2.9	-	-	1.5 g. per kg. (6.3 c.c.)
.1.41	-	310	100 g.bran 400 g.cab.	336	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
11.41	1927	124	30 g.bran 160 g.cab.	108	-	-	-	-	-
11.41	2012	127	10 g.bran 270 g.cab.	76	-	-	-	-	-
11.41	1927	120	40 g.bran 270 g.cab.	155	-	-	-	-	-
11.41	1984	92	120 g.bran 210 g.cab.	353	-	-	-	-	-
11.41	2041	194	70 g.bran 350 g.cab.	248	-	-	-	-	-
11.41	2041	170	40 g.bran 255 g.cab.	152	-	-	-	-	-
11.41	-	109	-	-	-	-	-	-	-
11.41	2012	230	110 g.bran 240 g.cab.	332	-	--	-	-	-
11.41	2041	99	75 g.bran 275 g.cab.	247	-	-	-	-	-

Rabbit 25.(Male)

-e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
2.42	2041	96	100 g.bran 200 g.cab.	299	-	-	-	-	-
2.42	2012	157	90 g.bran 270 g.cab.	286	-	-	-	-	-
2.42	2041	186	100 g.bran 300 g.cab.	318	-	-	-	-	-
2.42	2041	122	100 g.bran 185 g.cab.	296	-	-	Blank = 28 *	-	-
2.42	-	183	100 g.bran 280 g.cab.	314	-	-	-	-	-
2.42	2041	149	100 g.bran 240 g.cab.	306	-	-	-	-	-
2.42	2041	84	40 g.bran 180 g.cab.	138	-	-	-	-	-
2.42	2041	130	90 g.bran 295 g.cab.	290	-	-	-	-	-
2.42	2069	135	90 g.bran 240 g.cab.	280	-	-	-	-	-
2.42	2041	142	100 g.bran 220 g.cab.	303	-	-	-	-	1.5 g. per kg. (6 c.c.)
2.42	2012	82	60 g.bran 190 g.cab.	194	-	-	-	-	1.5 g. per kg. (6 c.c.)
3.42	-	126	0 g.bran 180 g.cab.	33	-	-	-	-	1.5 g. per kg. (6 c.c.)
3.42	1984	-	0 g.bran 100 g.cab.	19	-	-	-	-	1.5 g. per kg. (6 c.c.)
3.42	1927	53	0 g.bran 70 g.cab.	13	-	-	379	186	1.5 g. per kg. (5.7 c.c.)
3.42	1927	18	0 g.bran 100 g.cab.	19	-	-	70	8	1.5 g. per kg. (5.7 c.c.)
3.42	1871	66	40 g.bran 100 g.cab.	123	0.6	0.4	620	391	1.5 g. per kg. (5.6 c.c.)
3.42	1814	27	10 g.bran 110 g.cab.	77	-	-	129	27	1.5 g. per kg. (5.6 c.c.)
3.42	1814	43	fasting	-	0.7	0.3	143	50	1.5 g. per kg. (5.6 c.c.)

= Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
.42	-	34	20 g.bran 190 g.cab.	88	2.6	0.9	110	28	1.5 g. per kg. (5.6 c.c.)
.42	1927	70	70 g.bran 220 g.cab.	224	1.6	1.1	-	-	-
3.42	1927	74	100 g.bran 225 g.cab.	304	0.3	0.2	-	-	-
3.42	1984	110	100 g.bran 160 g.cab.	292	0.1	0.1	-	-	-
3.42	2012	183	100 g.bran 200 g.cab.	299	-	-	-	-	-
3.42	1927	194	100 g.bran 285 g.cab.	315	-	-	-	-	-
3.42	1984	168	100 g.bran 270 g.cab.	312	-	-	-	-	-
3.42	-	170	100 g.bran 260 g.cab.	310	-	-	-	-	-
3.42	1956	185	95 g.bran 250 g.cab.	295	-	-	-	-	-
3.42	1927	178	100 g.bran 250 g.cab.	308	-	-	-	-	-
3.42	1984	195	100 g.bran 300 g.cab.	318	-	-	-	-	-
3.42	1984	145	100 g.bran 300 g.cab.	318	-	-	-	-	-

Rabbit 26 (Male)

-e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
.42	2097	92	85 g.bran 200 g.cab. 20 g.hay	290	-	-	-	-	-
.42	2097	92	70 g.bran 190 g.cab. 20 g.hay	249	-	-	-	-	-
.42	2041	181	90 g.bran 230 g.cab. 20 g.hay	308	-	-	-	-	-
.42	2041	217	30 g.bran 170 g.cab. 20 g.hay	140	-	-	Blank = 50*	-	-
.42	-	98	50 g.bran 200 g.cab. 20 g.hay	198	-	-	-	-	-
.42	2041	103	80 g.bran 250 g.cab. 20 g.hay	286	-	-	-	-	-
.42	1984	150	100 g.bran 270 g.cab. 20 g.hay	342	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	2041	53	50 g.bran 200 g.cab. 20 g.hay	198	2.1	1.1	-	-	1.5 g. per kg. (6 c.c.)
.42	2041	44	0 g.bran 130 g.cab. 20 g.hay	54	6.7	2.9	-	-	1.5 g. per kg. (6 c.c.)
.4.42	2012	56	0 g.bran 100 g.cab. 20 g.hay	49	3.8	2.1	-	-	1.5 g. per kg. (6 c.c.)
.4.42	2041	47	0 g.bran 250 g.cab. 20 g.hay	76	3.4	1.6	-	-	1.5 g. per kg. (6 c.c.)
.4.42	-	89	0 g.bran 220 g.cab. 20 g.hay	71	3.5	3.1	820	695	1.5 g. per kg. (6 c.c.)

Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
4.42	2069	98	0 g.bran 175 g.cab. 20 g.hay	62	3.4	3.3	-	-	1.5 g. per kg. (6 c.c.)
4.42	2069	54	0 g.bran 170 g.cab. 20 g.hay	62	6.5	3.5	450	216	1.5 g. per kg. (6 c.c.)
4.42	2041	147	0 g.bran 290 g.cab. 20 g.hay	84	3.0	4.4	-	-	1.5 g. per kg. (6 c.c.)
4.42	2154	50	25 g.bran 275 g.cab. 20 g.hay	146	2.3	1.2	-	-	1.5 g. per kg. (6 c.c.)
4.42	2211	66	30 g.bran 250 g.cab. 20 g.hay	155	0.8	0.6	-	-	1.5 g. per kg. (6.3 c.c.)

Rabbit 29. (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
4.42	1984	160	80 g.bran 300 g.cab. 20 g.hay	295	-	-	-	-	-
4.42	2041	147	100 g.bran 230 g.cab. 20 g.hay	335	-	-	Blank = 41*	-	-
4.42	2012	83	70 g.bran 270 g.cab. 20 g.hay	263	-	-	-	-	-
4.42	2012	125	65 g.bran 160 g.cab. 20 g.hay	230	-	-	-	-	-
.42	2041	175	70 g.bran 280 g.cab. 20 g.hay	265	-	-	-	-	-
.42	2012	126	75 g.bran 255 g.cab. 20 g.hay	274	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	-	28	35 g.bran 150 g.cab. 20 g.hay	150	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	1984	96	35 g.bran 100 g.cab. 20 g.hay	140	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	1956	56	0 g.bran 130 g.cab. 20g.hay	54	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
.42	2041	50	0 g.bran 200 g.cab. 20 g.hay	67	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	2041	57	30 g.bran 120 g.cab. 20 g.hay	131	-	-	-	-	1.5 g. per kg. (6 c.c.)
.42	2012	75	30 g.bran 130 g.cab. 20 g.hay	133	2.7	2.0	-	-	1.5 g. per kg. (6 c.c.)

Blank has been deducted from the total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
.42	1984	94	fasting	-	0.1	0.1	-	-	1.5 g. per kg. (6 c.c.)
5.42	-	89	50 g.bran 150 g.cab. 20 g.hay	189	1.8	1.6	-	-	1.5 g. per kg. (6 c.c.)
5.42	1956	22	0 g.bran 20 g.cab. 20 g.hay	34	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
5.42	1956	34	40 g.bran 60 g.cab. 20 g.hay	146	-	-	667	213	1.5 g. per kg. (5.7 c.c.)
5.42	1899	26	10 g.bran 130 g.cab. 20 g.hay	80	-	-	390	91	1.5 g. per kg. (5.7 c.c.)
.5.42	1899	248	50 g.bran 200 g.cab. 20 g.hay	198	-	-	-	-	-
.5.42	1927	225	55 g.bran 270 g.cab. 20 g.hay	224	-	-	-	-	-
.5.42	1927	212	80 g.bran 250 g.cab. 20 g.hay	286	-	-	-	-	-
.5.42	-	143	70 g.bran 270 g.cab. 20 g.hay	263	-	-	-	-	-
.5.42	1956	103	90 g.bran 220 g.cab. 20 g.hay	307	-	-	-	-	-
.5.42	1956	101	40g.bran 220 g.cab. 20 g.hay	176	-	-	-	-	-
.5.42	1956	178	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
.5.42	1984	165	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-

Rabbit 30 (Female)

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
.42	1927	121	50 g.bran 260 g.cab. 20 g.hay	209	-	-	-	-	-
.42	1984	91	40 g.bran 270 g.cab. 20 g.hay	185	-	-	-	-	-
.42	1927	148	30 g.bran 275 g.cab. 20 g.hay	160	-	-	-	-	-
.42	1984	56	0 g.bran 175g.cab. 20 g.hay	62	-	-	Blank= 42*	-	-
.42	1984	142	50 g.bran 275 g.cab. 20 g.hay	212	-	-	-	-	-
.42	1984	95	40 g.bran 270 g.cab. 20 g.hay	185	-	-	-	-	-
5.42	-	170	60 g.bran 270 g.cab. 20 g.hay	237	-	-	-	-	-
5.42	2012	36	0 g.bran 85 g.cab. 20 g.hay	46	-	-	-	-	-
5.42	1984	47	35 g.bran 150 g.cab. 20 g.hay	150	-	-	-	-	-
.5.42	1927	79	50 g.bran 220 g.cab. 20 g.hay	202	-	-	-	-	-
.5.42	1927	169	70 g.bran 300 g.cab. 20 g.hay	269	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
.5.42	1927	114	40 g.bran 200 g.cab. 20 g.hay	172	-	-	-	-	1.5 g. per kg. (5.7 c.c.)

- Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
5.42	1956	92	25 g.bran 160 g.cab. 20 g.hay	125	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
5.42	-	34	20 g.bran 225 g.cab. 20 g.hay	124	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
5.42	1899	120	0 g.bran 70 g.cab. 20 g.hay	43	-	-	-	-	1.5 g. per kg. (5.7 c.c.)
5.42	1984	25	50 g.bran 130 g.cab. 20 g.hay	185	1.7	0.4	-	-	1.5 g. per kg. (6 c.c.)
5.42	1871	108	40 g.bran 60 g.cab. 20 g.hay	146	3.7	4.0	-	-	1.5 g. per kg. (5.6 c.c.)
5.42	1899	31	20 g.bran 120 g.cab. 20 g.hay	105	1.0	0.3	75	10	1.5 g. per kg. (5.7 c.c.)
5.42	1927	39	20 g.bran 120 g.cab. 20 g.hay	105	2.8	1.1	81	15	1.5 g. per kg. (5.7 c.c.)
5.42	1956	48	30 g.bran 100 g.cab. 20 g.hay	127	1.1	0.5	-	-	1.5 g. per kg. (5.8 c.c.)
5.42	-	70	0 g.bran 110 g.cab. 20 g.hay	50	0.9	0.7	-	-	-

Rabbit 32 (Male)

—e	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
5.42	2211	150	90 g.bran 300 g.cab.	321	-	-	-	-	-
5.42	2183	145	90 g.bran 300 g.cab.	321	-	-	-	-	-
5.42	-	313	100g. bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
5.42	2239	136	100 g.bran 300 g.cab. 20 g.hay	348	-	-	Blank = 34*	-	-
5.42	2267	210	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
5.42	2295	208	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
6.42	2295	293	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
6.42	2352	271	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
6.42	2352	253	fasting	? 250	-	-	-	-	1.5 g. per kg. (6.9 c.c.)
6.42	-	126	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	1.5 g. per kg. (6.9 c.c.)
6.42	2380	140	100 g.bran 300 g.cab. 20 g.hay	348	0.5	0.7	-	-	1.5 g. per kg. (7.1 c.c.)
6.42	2366	283	fasting	? 250	0.1	0.4	-	-	1.5 g. per kg. (6.9 c.c.)
.6.42	2352	240	100 g.bran 300 g.cab. 20 g.hay	348	0.5	1.1	-	-	1.5 g. per kg. (6.9 c.c.)
.6.42	2437	263	100 g.bran 300 g.cab. 20 g.hay	348	4.9	12.9	-	-	1.5 g. per kg. (7.2 c.c.)

* - Blank has been deducted from total, but not percentage ketones.

e.	Body Weight in g.	Urine Volume in c.c.	Diet per 24 hr.	Total Cals. per 24 hr.	Urine Sugar in g.%	Total Urine Sugar per 24 hr. in g.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
-6.42	2437	257	100 g.bran 300 g.cab. 20 g.hay	348	4.9	12.6	-	-	1.5 g. per kg. (7.2 c.c.)
-6.42	2437	282	50 g.bran 300 g.cab. 20 g.hay	217	7.8	21.9	-	-	1.5 g. per kg. (7.2 c.c.)
6.42	-	285	100 g.bran 300 g.cab. 20 g.hay	348	9.7	27.5	-	-	1.5 g. per kg. (7.2 c.c.)
6.42	2380	234	25 g.bran 270 g.cab. 20 g.hay	146	2.5	5.9	-	-	1.5 g. per kg. (7 c.c.)
6.42	2395	190	50 g.bran 300 g.cab. 20 g.hay	217	0.3	0.5	-	-	-
6.42	2380	265	35 g.bran 300 g.cab. 20 g.hay	177	-	-	-	-	-
6.42	2352	225	70 g.bran 300 g.cab. 20 g.hay	269	-	-	-	-	-
.6.42	2395	152	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
.6.42	2395	119	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
.6.42	-	210	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
.6.42	2437	99	70 g.bran 190 g.cab. 20 g.hay	249	-	-	-	-	-
.6.42	2437	218	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-

Section VI.

The Aetiology of Diabetes Mellitus.

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Section VI.

The Aetiology of Diabetes Mellitus.*

The unfolding of the aetiology of diabetes mellitus forms one of the most fascinating chapters in the history of medicine. Besides its interest historically, the search for the causes of this disease has been of value in that it has led not only to the elucidation of many problems directly connected with the condition, but also to much new knowledge concerning the intermediary metabolism of carbohydrates, proteins and fats and to a fuller appreciation of the function and interplay of the endocrine glands. Further, the names of such as von Mering and Minkowski, Banting and Best, Houssay and F. G. Young, who have contributed so outstandingly to the subject, will continue to live down the generations, yet the discoveries of even these men have sometimes been merely the logical sequence of the work of many previous investigators. In other words, the modern approach to diabetes mellitus so far as its aetiology is concerned stands as a monument to sustained, world-wide co-operation such as might well be emulated in other spheres of international life to-day.

The historical approach also indicates that the diabetic problem may most appropriately be considered in/

* A Honyman Gillespie Lecture delivered in the Royal Infirmary, 31st August 1944.

in five sections : (1) the pancreas; (2) the pituitary gland ; (3) a balance between the pancreas and pituitary gland ; (4) the other endocrine glands, especially the thyroid gland, adrenal glands, and ovaries, and (5) alloxan diabetes.

Pancreas

The relationship of the pancreas to diabetes was first established by von Mering and Minkowski (1890), who showed that absence of the pancreas produces hyperglycaemia, glycosuria, ketonuria, polyuria, emaciation and death in less than four weeks. Discussion thereafter ensued regarding the rôle of the pancreatic acinar and islet tissue respectively in the control of carbohydrate metabolism, but the residence of this control in the islet tissue ultimately crystallised upon the finding of Ssobolew (1900) and Schulze (1900) that obstruction of the pancreatic duct was characterised by atrophy of the acinar but not of the islet tissue and the non-development of any diabetic condition. Such focussing of attention on the pancreatic islets immediately led in the earliest years of this century to the detection of a variety of pathological changes in the islets of diabetic subjects. These changes are broadly divisible into qualitative and quantitative.

Qualitative Islet Changes.

The/

The qualitative changes as observed by Warren (1938) in a series of 484 diabetic cases are (1) hyaline degeneration (41 per cent.) ; (2) fibrosis (27 per cent.) ; (3) hydropic degeneration (5 per cent.) ; (4) lymphocytic infiltration (2 per cent.) ; (5) atrophy (personal addition) ; (6) haemochromatosis (2 per cent.) ; (7) hypertrophy (8 per cent.) ; (8) adenoma (0.2 per cent.) ; (9) normal (26 per cent.).

(1) Hyaline degeneration was first described by Opie (1900-01) and is the most typical of the degenerative changes affecting the islets in diabetes. It entails swelling of the epithelial cells and their replacement by homogeneous, translucent material which stains pink with eosin, royal blue with the aniline blue of Mallory's method (Fig. 1) and sometimes rose pink like amyloid with methyl violet. Cell outlines are at first retained, but each islet in the end consists merely of thick, hyaline strands and persisting capillaries. Marked involvement of the individual islets, moreover, is generally accompanied by the implication of many islets and vice versa. Of Warren's cases, 6 per cent. under 40 years of age showed hyaline degeneration of the islets compared with 45 per cent. over that age. Again, 50 per cent. of a series of cases known to have had diabetes for at least ten years showed hyalinisation. Hyaline degeneration of the islets is thus commonest in older subjects and in mild cases/

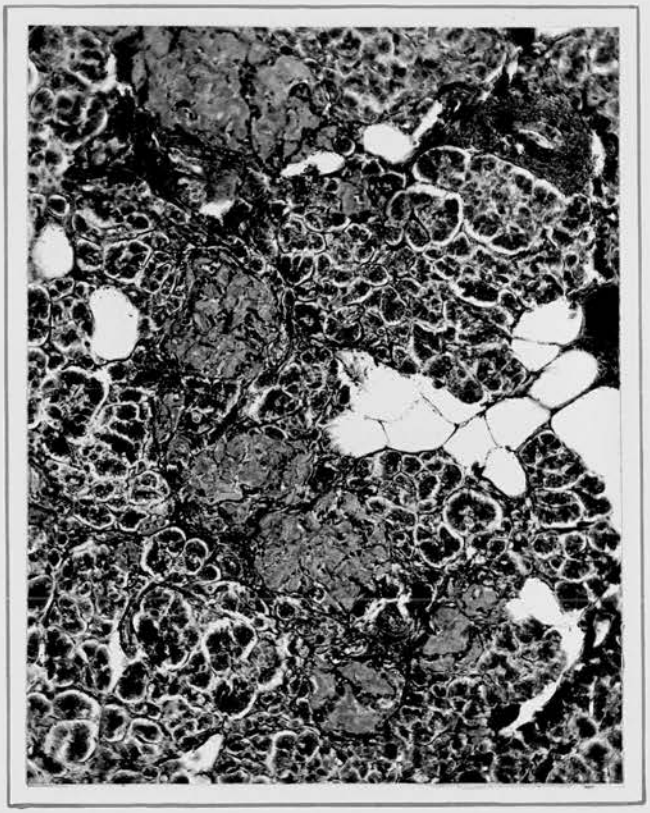


Fig.1. Pancreas. Male aged 84 years. Duration of diabetes unknown. The islets have been extensively replaced by hyaline material. Heidenhain's Azan Method. x 105.

cases of the disease. Rarely, hyalinisation is followed by calcification. Fischer (1915), for example, has reported the case of an eighteen-year-old boy who died in coma after typical juvenile diabetes and whose pancreas was studded with calcified, hyalinised islets.

(2) Fibrosis observed by Opie (1900 -01) varies in degree. The initial stage entails a thin fibrous capsule, some pericapillary fibrosis and early epithelial loss (Fig. 2), while gross encapsulation, marked fibrous replacement and corresponding epithelial reduction characterise the final phase. Slight implication of the individual islets is usually accompanied by the involvement of many islets and vice versa. The phenomenon in this respect is thus the reverse of hyalinisation. Fibrosis of the islets is one of the characteristic changes in children, but like hyalinisation occurs most commonly in older subjects and is then practically always accompanied by interlobular and interacinar fibrosis and thickening and hyalinisation of the arterioles (Fig. 3). The condition in older subjects consequently amounts to hypertensive arteriolosclerotic atrophy of the pancreas and is basically similar to the primary granular contracted kidney. Finally, the same pancreas sometimes shows both fibrosis and hyalinisation of the islets, and both types of degeneration are even occasionally observed in the same islet.

(3) Hydropic degeneration was first reported by Weichselbaum/

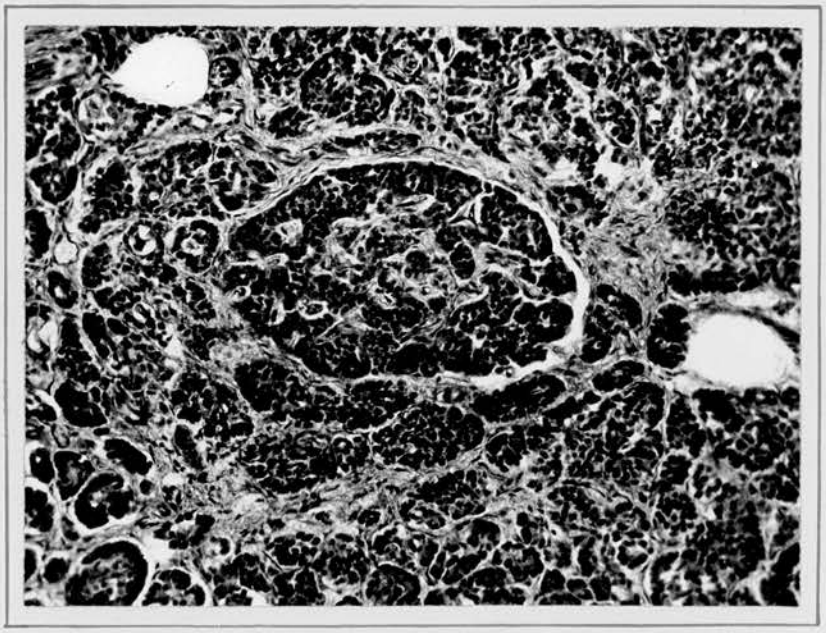


Fig. 2. Pancreas. Female aged 64 years. Diabetes for 8 years. The islet is enclosed by a thin fibrous capsule, while an excess of fibrous tissue surrounds its capillaries. The neighbouring acinar tissue is also atrophied and scarred. Masson's Method. x 150.

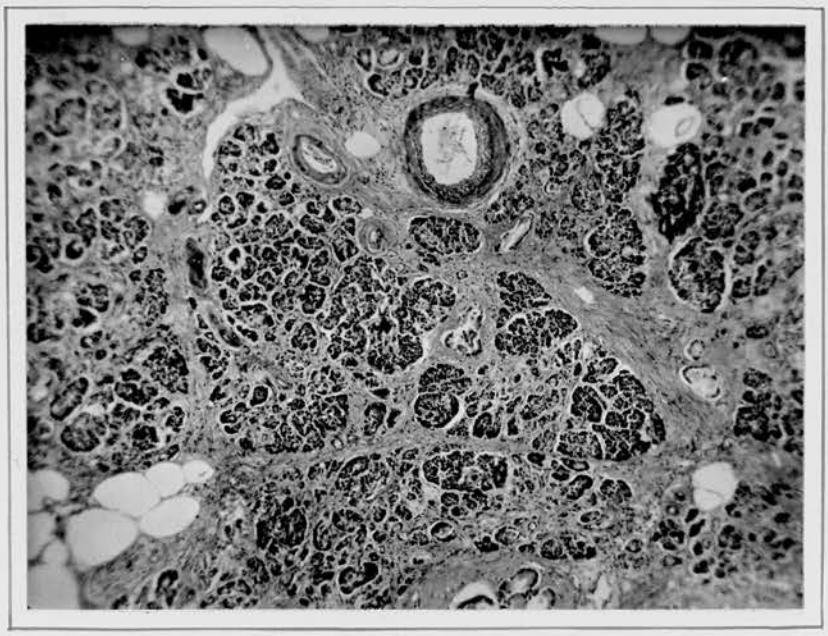


Fig. 3. Pancreas. Same case as in Fig. 2. The arteries and arterioles top and left are thickened and hyalinised and the fibrous tissue is increased both around and within the lobules. An islet immediately to left of centre is moderately fibrosed. Haematoxylin and Eosin. x 60.

Weichselbaum and Stangl (1901). The cells in the earlier stages of this condition are occupied by minute serous droplets and later distended by a single large globule, while their nucleus is pyknotic or lysed. The affection is apparently reversible in its slighter degrees, but in advanced measure is followed by absorption of the damaged cells. It occurs at all ages and most strikingly in fulminating cases. The condition is also noteworthy in that it was the first of the degenerative islet changes to be reproduced. Allen (1913) achieved this object by partial pancreatectomy and the subsequent administration of an excessively carbohydrate diet, and Homans (1914) then showed that the degeneration affected principally the beta cells. Consequently, the beta cells have since been regarded as the essential source of insulin.

(4) Lymphocytic infiltration, described by Warren and Root (1925), involves an over-running of the islets and sometimes of the peri-insular tissues with lymphocytes and rarely also endothelial cells (Fig. 4). It is particularly apt to be found in young subjects and in cases with a short history of the disease.

(5) Atrophy of the islets is a late result of duct obstruction produced by such conditions as calculus, carcinoma of the head of the pancreas, and duodenal diverticulum (Figs. 5 and 6). The obstruction before it leads to such intense atrophy of the islets as to cause diabetes must be long-standing/

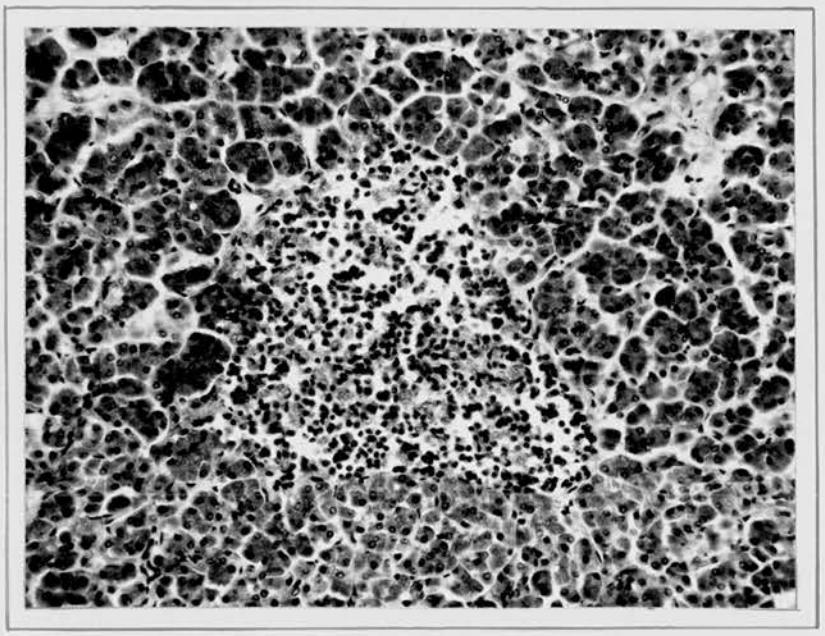


Fig. 4. Pancreas. Male aged 19 years. Diabetes for 11 months. The islet is diffusely infiltrated with small round cells. Haematoxylin and Eosin. x 170.

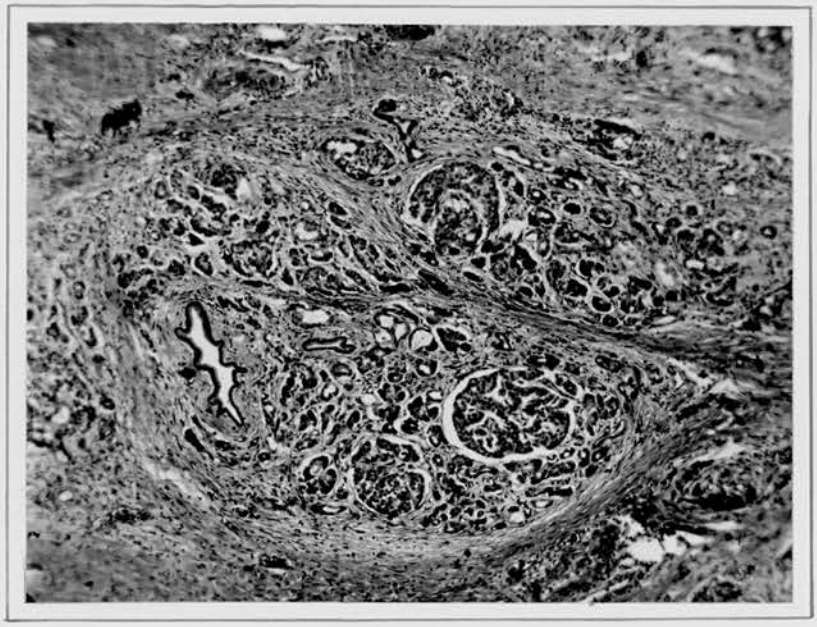


Fig. 5. Pancreas. Female aged 62 years. A carcinoma was present in the head of the pancreas. The acinar tissue consequent upon obstruction of the main duct by the tumour is atrophied and fibrosed, but the islets apart from being drawn together are normal. No diabetes. Haematoxylin and Eosin. x 70.

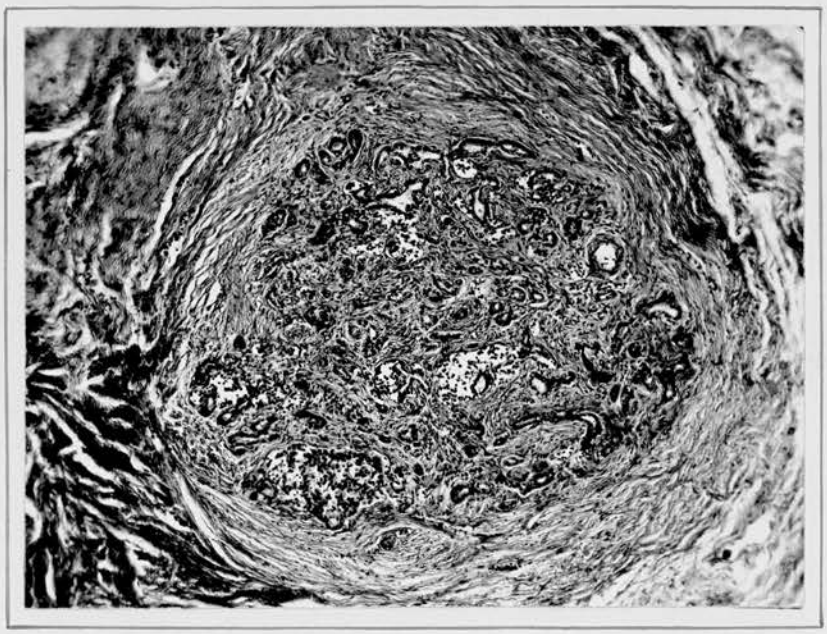


Fig. 6. Pancreas. Male aged 48 years. Diabetes for 5 years. A calculus was present in the main duct. The acinar tissue is markedly atrophied and fibrosed, especially at the margin. Many of the islets have disappeared and those remaining (represented by open, granular structures) are definitely atrophied. Heidenhain's Azan Method. x 70.

standing and severe, and a calculus is consequently the likeliest mechanism to achieve these demands. Such a case is characterised by more or less marked increase of the interlobular and interacinar fibrous tissue, while the islets being drawn together are very conspicuous and appear increased numerically. They are structurally normal even in moderately severe cases, but in advanced examples show marked atrophy, with perhaps some condensation of their stroma. Ultimately, many islets have disappeared in the generalised overgrowth of fibrous tissue. The condition produced by a pancreatic calculus is similar to that following experimental duct obstruction and is thereby historically interesting in that a case reported by Barron (1920) intrigued Banting (1929) and thus played a part in the preparation of insulin.

(6) Haemochromatosis involves the islets in association with the rest of the pancreas and many other organs (Fig. 7). Its salient features are fibrosis and pigmentation with haemosiderin and haemofuscin. According to Sheldon (1935), the islets have been involved in the fibrotic process in 24 per cent. of the reported cases, while 80 per cent. of the patients have shown pigmentation of the islets. Such pigmentation varies greatly in intensity not only as regards different cases, but also in relation to different islets and cells in the same case and islet respectively. The occurrence of/

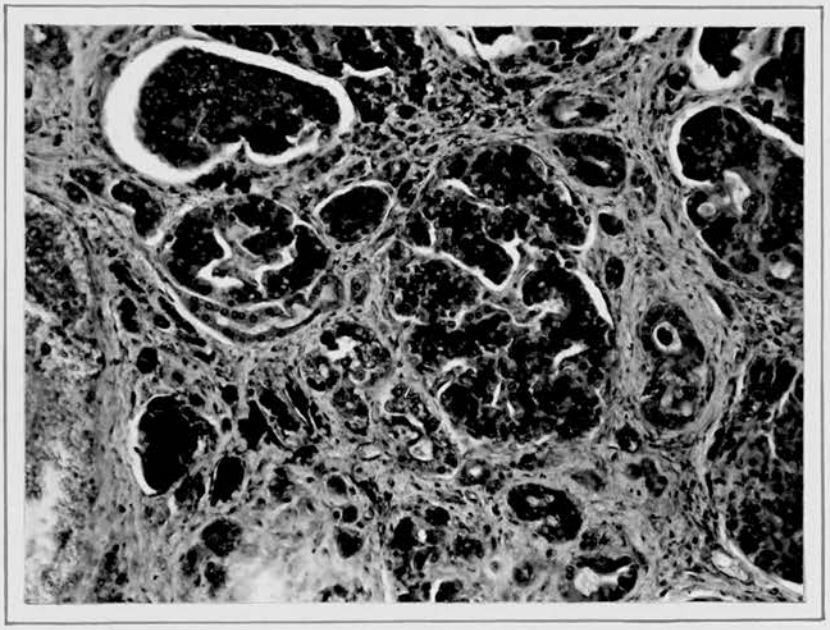


Fig. 7. Pancreas. Male aged 53 years. Haemochromatosis. Moribund on admission. No history of diabetes obtained. The acinar tissue is moderately atrophied and fibrosed. The islet to right of centre is heavily pigmented with haemosiderin and haemosiderosis is also present in the surrounding acinar and fibrous tissues. Prussian Blue Method. x 160.

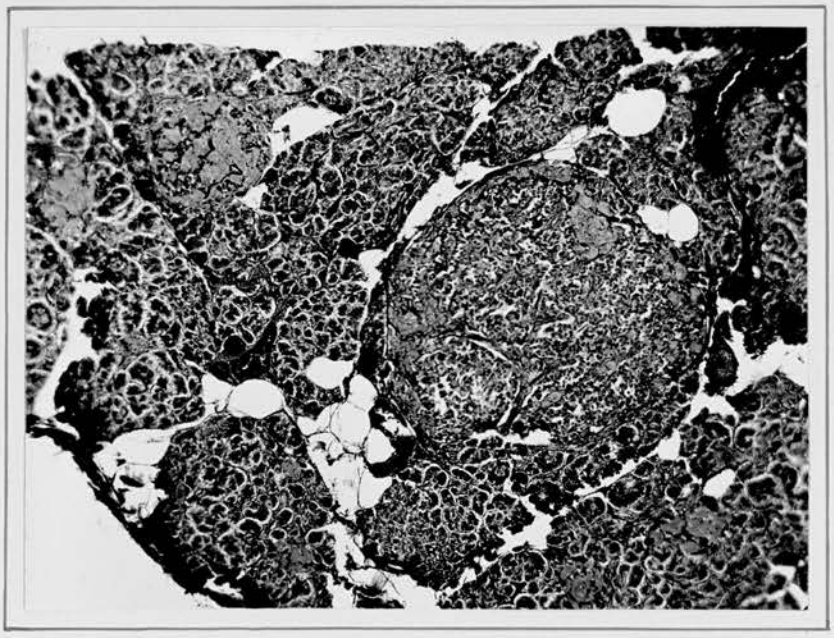


Fig. 8. Pancreas. Male aged 84. Duration of diabetes unknown. The islet to right of centre is markedly hypertrophied and focally hyalinised, but normal as regards its shape, architecture and polyhedral cells. A largely hyalinised islet of normal size is present at top left.
Heidenhain's Azan Method. x 70.

of diabetes depends on the implication of the islets. Thus, slight pigmentation of these structures is not accompanied by diabetes, but a diabetic state is always associated with severe involvement of the islets. This diabetes usually runs a rapid course and is particularly noteworthy in that it results from damage to the pancreatic islets by a known agent.

(7) Hypertrophy of the islets occurs in association with degeneration of other islets and also in the absence of any detectable insular change. Cecil (1909) pointed out that islet hypertrophy assumes two types. The islet in one variety is not unduly irregular and normal both in architecture and being composed of polyhedral cells (Fig. 8). The islet in the other type is often much more irregular than usual, while its cords are abnormally long and tortuous and consist of columnar cells with central nucleus (Figs. 9 & 10). Columnar cell hypertrophy is much less common than simple enlargement, and interesting in that it seems to represent a reversion to a duct-like type of epithelium. Hypertrophy usually affects only a moderate proportion of the islets, but the majority occasionally appear to show enlargement. The incidence of the condition bears no relation to the age of the patient or to the duration or severity of the diabetes.

(8) Adenoma of the islets is a rare finding in diabetes. Warren (1938) encountered it only once in his large series. It takes the form of a rounded/

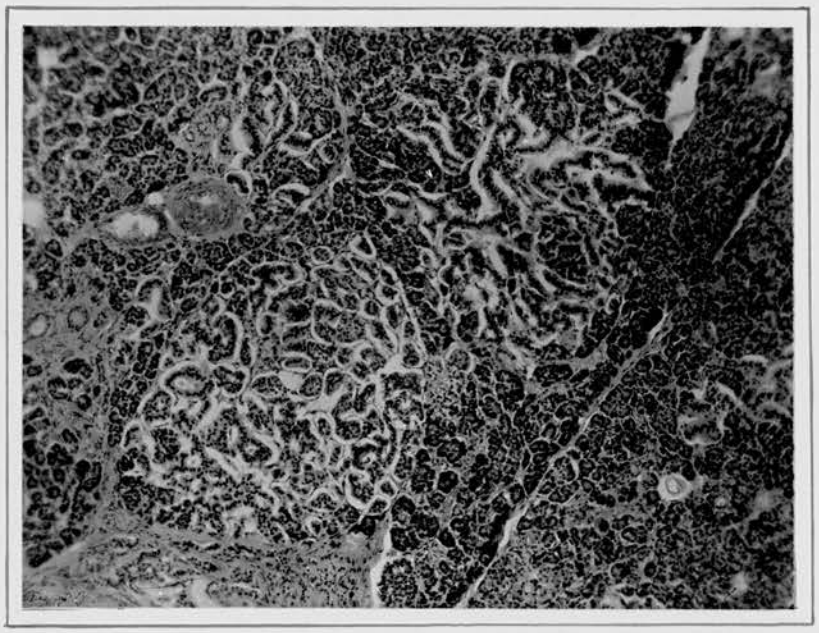


Fig. 9. Pancreas. Female aged 58 years. Diabetes for 3 years. The islets bottom left and top right are respectively of normal and irregular configuration, while both consist of abnormally long and tortuous cords of columnar epithelium. Haematoxylin and Eosin. x 70.

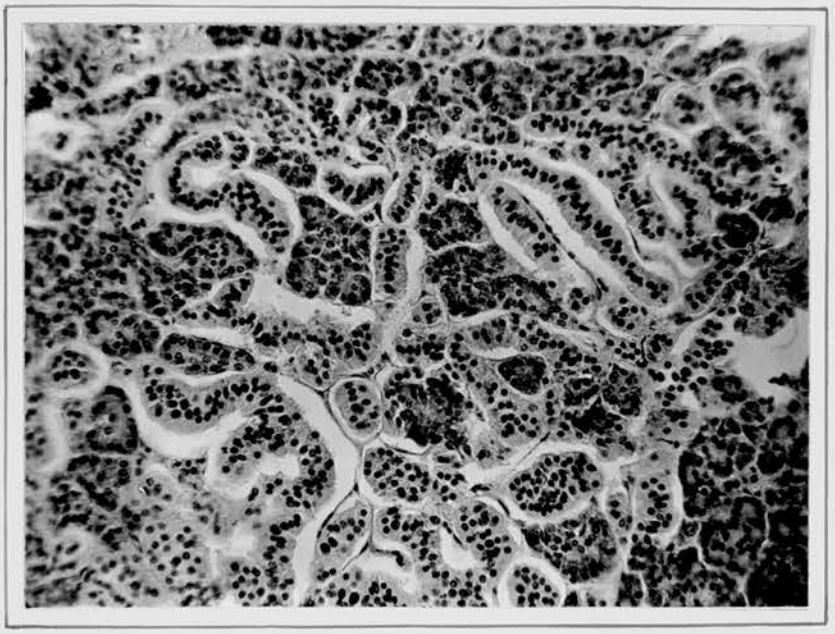


Fig. 10. Pancreas. Same case as in Fig. 9. The segment of hypertrophied islet illustrated consists of unusually long and tortuous cords of mostly columnar cells resembling duct epithelium. Haematoxylin and Eosin. x 190.

rounded, well-defined, encapsulated nodule which resembles normal islet tissue both architecturally and in the cells composing it.

(9) Universally normal islets or islets at least histologically normal were found by Warren (1938) in a considerable percentage of his diabetic subjects. This is an important negative observation, the significance of which will be mentioned shortly.

Quantitative Islet Changes

Reduction in the weight of the pancreas and the number of islets has often been noted in the pancreas of diabetic subjects. Enumeration of the islets in human material, however, can only be carried out by examining sections from various parts of the organ and any such technique is naturally exposed to many errors. The weight of the pancreas and the number of islets also vary within wide limits normally (Ogilvie, 1937). Consequently, any observation regarding reduction of these structures may be more apparent than real and rendered of still more doubtful significance by the fact that one-eighth of the pancreas has been found experimentally to be sufficient to avert the development of diabetes. Exceptions arerare cases of congenital hypoplasia of the pancreas or islets in which reduction of the islet tissue is so marked as undoubtedly to act as a factor predisposing to the disease. The conclusion is that reduction of the islet tissue, while operating in rare cases, is still/

still generally unproven and therefore unacceptable as a factor of genuine aetiological significance.

These observations regarding the islets in diabetic subjects and laboratory experiments culminated in the isolation of insulin by Banting and Best (1921-22). The preparation of insulin confirmed the idea that damage to the pancreatic islets is frequently an important factor in the disease, but it failed to explain the mechanism of the damage or the remarkable variation in the types of damage or the fact that the pancreatic islets in 26 per cent. of diabetic subjects are histologically normal. The finding of apparently normal islets in so many cases suggests of itself that the cause of the disease lies primarily in some extrapancreatic disturbance and that it is this disturbance which is responsible for the islet damage. The subject consequently demands a less insular outlook and thus leads to a consideration of the part played in carbohydrate metabolism by the pituitary gland.

Pituitary Gland

The possible role of the pituitary gland in carbohydrate metabolism was originally suggested by clinical observation. This consisted in the recognition by Loeb (1884) of the frequency with which glycosuria occurs in cases of pituitary tumour, and many reports since then have led to the acceptance of a definite relationship between acromegaly and diabetes. In point of fact, Warren (1938) /

(1938) finds that 28 per cent. of the reported cases of acromegaly have shown glycosuria. Such clinical surmise, moreover, has recently been supported by much experimental evidence. Thus, Houssay and Magenta (1925) first found that absence of the pituitary gland induces an increased sensitivity to the hypoglycaemic action of insulin, and the same result was observed by Houssay and Potick (1929) to follow loss of the pars glandularis, which corresponds to the anterior lobe of mammals. Houssay and Biasotti (1930) subsequently showed that loss of the pituitary gland or of only the pars glandularis followed by pancreatectomy prevented or alleviated the diabetic condition which ordinarily results from absence of the pancreas and that such hypophysectomised-depancreatised subjects survived for much longer than purely depancreatised individuals. An important deduction from this experiment is the fact that the tissues are apparently able to metabolise sugar without the assistance of the pancreas and pituitary gland. In other words, they possess an inherent capacity to deal with sugar just as the heart beat is an inherent property of the cardiac musculature. Finally, three groups of workers - Evans et al. (1931-32), Baumann and Marine (1931-32) and Houssay et al. (1932-33) - proved that the administration of a suitable anterior pituitary extract to normal subjects resulted in the development of a diabetic condition.

The response of a susceptible subject to daily treatment/

treatment with diabetogenic anterior pituitary extract may be divided into four phases (Young, 1937, 1938a, 1939a and b) : (1) A latent phase which lasts three to five days. The blood sugar is not significantly raised and no glycosuria or ketonuria occurs, but a relative resistance develops to the hypoglycaemic action of insulin. (2) A phase of temporary diabetes which continues for three to seven days. Glycosuria, ketonuria and polyuria appear and increase to a maximum, subsequently to decline and disappear in spite of continued daily treatment with the same amount of extract. Other features are diminished sugar tolerance, relative insensitivity to the hypoglycaemic action of insulin, and sometimes raised liver glycogen. (3) A refractory phase which may be of long or indefinite duration. Glycosuria and ketonuria are absent, but relative insensitivity to the action of insulin remains for some time and the fasting liver glycogen may be high. Another spell of diabetes can be produced at this stage by increasing the daily dose of extract and such a recurrence may indeed be so achieved a number of times. (4) A phase of permanent diabetes which lasts indefinitely. This is brought about by increasing the daily dose of anterior pituitary extract every few days and continuing in this way for a period of one and a half to four weeks. The refractory phase is thus circumvented and replaced by a permanent diabetes which persists even after cessation of extract treatment. The metabolic features/

features of permanent pituitary diabetes differ in various ways from those of pancreatic diabetes. Thus, pituitary diabetic subjects are able to survive for long periods without insulin therapy provided they are given sufficient food. Nevertheless, despite the absence of any obvious insensitivity to the hypoglycaemic action of insulin, more insulin is apparently required for the control of their glycosuria. They also tend to gain weight and have a high liver glycogen.

Richardson (1939-40) and Lukens and Dohan (1942) found that the pancreatic islets of pituitary diabetic subjects show various degenerative and reparative changes, mainly the former. These changes are (1) degranulation of the beta cells, either partial or complete ; (2) hydropic degeneration of individual beta cells ; (3) atrophy of the islet tissue to groups of alpha cells with a few agranular or normal beta cells ; (4) hyalinisation which replaces the beta cells selectively or destroys the islets completely ; (5) fibrosis ; (6) lymphocytic infiltration ; (7) mitotic division in some islets. The beta cells apparently first lose their granules, then undergo hydropic degeneration and are finally absorbed, leaving atrophied islets made up mainly of alpha cells. Alternatively, the islets show one or more of the other three types of lesion. Lukens and Dohan (1942) also found that treatment of the diabetes in the early permanent phase or stage of hydropic degeneration by dieting or/

or insulin results in a morphological restoration of the islets and in a functional recovery of the subject which is maintained after cessation of the therapy. On the other hand, similar treatment of the diabetes in the late permanent phase or stage of islet atrophy is not followed by recovery. The pancreas at this stage, accerding to Campbell, Keenan and Best (1939), yields on extraction a definitely diminished amount of insulin.

Anterior pituitary extract in addition to its diabetogenic property shows a number of other actions. The glycotropic action first observed by Houssay and Potick (1929) induces a relative insensitivity to the hypoglycaemic effect of insulin. It occurs, as already noted, when the blood sugar is not significantly altered, e.g. in the latent period between the start of extract treatment and the development of diabetes, and may vary inversely as the amount of glycosuria. The responsible factor, in the opinion of Young (1938b), is the direct antagonist of insulin and may therefore be accredited with a threefold action in that it inhibits the oxidation of sugar by the peripheral tissues, promotes the formation of sugar from glycogen in the liver, and depresses the synthesis of glycogen from sugar in the liver and muscles. The glycostatic action resembles the glycotropic in that it depresses the oxidation of sugar in the muscles (Fisher et al., 1936 ; Russell and Bennett, 1936) and the adrenocorticotropic action, which takes place through/

through the adrenal cortex, stimulates the formation of glycogen from protein in the liver (Russell, 1938 ; Bennett, 1937-38 ; Long et al., 1940). The ketogenic action first noted by Burn and Ling (1930) manifests itself in an increased excretion of ketones. The appearance of ketones may definitely precede that of sugar and the amount of ketonuria characteristically shows a sudden rise just before the establishment of the permanent phase. Best and Campbell (1938) observed that ketogenic pituitary extract also brings about a rapid and substantial accumulation of fat in the liver, apparently at the expense of the fat stores. No agreement exists at the moment regarding the manner in which anterior pituitary extract promotes ketogenesis. Thus, Black et al. (1934) attribute the phenomenon to a specific ketogenic factor, while Shipley and Long (1938) believe it to be due to an increased breakdown of fat consequent upon interference with carbohydrate and protein catabolism. The pancreotropic action increases the amount of pancreatic islet tissue. The amount of this tissue has been doubled by Richardson and Young (1937-38) using crude anterior pituitary extract, and according to Ogilvie (1944) such increase is due to hypertrophy of the islets to twice their original size and occasionally also a formation of new islets from proliferated ducts (Figs. 11 and 12). Marks and Young (1939, 1940) also found that the administration of crude extract nearly doubles the insulin/

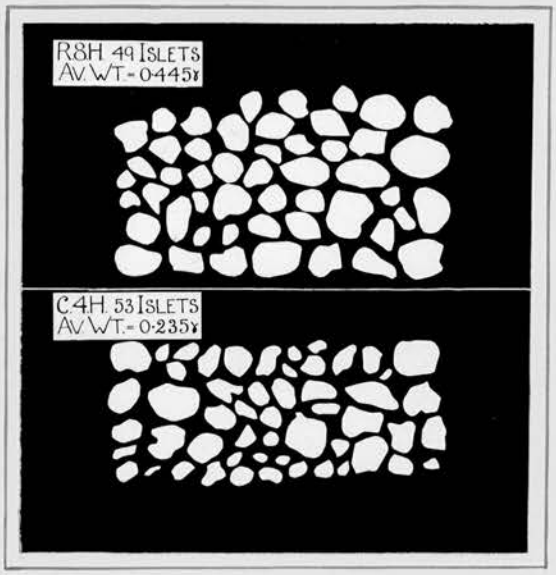


Fig. 11. The average weight (0.445 γ) of the upper group of 49 islets from the pancreas of a subject treated with crude anterior pituitary extract approximates closely to the average weight (0.451 γ) of the islets of 28 treated subjects, while the average weight (0.235 γ) of the lower group of 53 islets from the pancreas of a control subject approximates closely to the average weight (0.230 γ) of the islets of 10 control subjects. The upper group averages approximately double the size of the lower group.

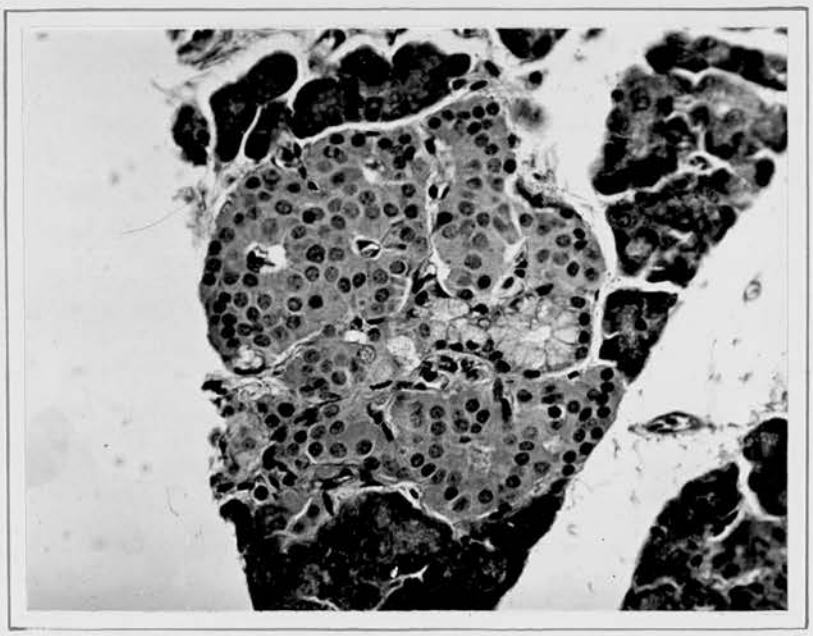


Fig. 12. Pancreas. The subject was treated with crude anterior pituitary extract. The vacuolated intralobular duct to right of centre has recently given origin to the immediately related islet. Haematoxylin and Eosin. x 340.

insulin content of the pancreas. They distinguish between the pancreotropic factor which increases the amount of islet tissue and the insulin-increasing factor which augments the amount of extractable insulin, but these two factors being so closely related in action may be assumed to be one and the same. The pancreotropic factor thus apparently stimulates (1) proliferation of the pancreatic ducts, (2) differentiation of new islets from those proliferated ducts, (3) division of the islet cells with hypertrophy of original islets, and (4) formation of insulin by the islet tissue.

These observations suggest that human diabetes mellitus may be due to hyperfunction of the anterior pituitary gland, and such hyperactivity may very well be the explanation in cases associated with an eosinophile or basophile adenoma of the anterior lobe. They also indicate that the diabetic syndrome is probably due not to a single factor, but to a complex made up of glycotropic, glycostatic, ketogenic and perhaps other principles. These various factors secreted in excess would combine so to depress the oxidation and storage of sugar on the one hand, and on the other so to stimulate the manufacture of sugar and ketones as finally to induce the diabetic syndrome. An oversecretion of the glycotropic factor is particularly interesting in that it would serve to explain those cases of diabetes requiring for their control hundreds or even thousands of units of insulin daily. Himsworth (1936/

(1936, 1940), indeed, believes that the young, thin, non-hypertensive diabetic is characteristically insulin-sensitive, whereas the middle-aged, obese, hypertensive diabetic is insulin-insensitive. This idea is supported by the fact that in the opinion of de Wesselow and Griffiths (1936) the plasma of middle-aged, obese, diabetic patients may show anti-insulin properties, while the plasma of young diabetic subjects is inactive in this respect. Finally, the diabetes of acromegaly and Cushing's syndrome, according to Himsworth (1940), is of the insulin-insensitive type and irradiation of the pituitary region in such cases has benefited both the diabetes and the insulin-insensitivity. All these observations suggest that the glycotropic factor may in some cases be aetiologically important, but it must in conclusion be stated that differentiation of diabetic subjects into clearly defined insulin-sensitive and insensitive types and the anti-insulin property of diabetic plasma have not been generally accepted as proven facts.

The postulation of a ketogenic secretion by the anterior hypophysis throws doubt on the established idea that the ketonaemia of human diabetes is secondary to disturbed carbohydrate oxidation. Again, the appearance of ketonuria in pituitary diabetes before glycosuria and the lapse of pituitary diabetic subjects into coma just before the permanent phase are interesting relative to diabetes in childhood. The disease at this age sometimes shows/

shows itself first in coma, and such an occurrence might conceivably be explained by a sudden, marked oversecretion of the ketogenic factor. The pancreotropic factor is intriguing from a therapeutic angle. Many cases of diabetes undoubtedly involve destruction of the pancreatic islet tissue and a growth of new islet tissue as an additional source of insulin would naturally be an important advance in such cases. The pancreotropic factor, however, yet remains to be isolated from the other anterior pituitary secretions and to be proved functionally active in the human being.

The similarity between the types of pancreatic islet damage in pituitary and human diabetes affords reason for believing that the islet damage in the human disease results from oversecretion of the pituitary diabetogenic factor or factors. Data regarding menstruation, acromegaly and other conditions indicate that the secretory activity of the pituitary gland varies considerably at different times. Over-secretion of the diabetogenic factor may therefore only be temporary, but nevertheless of such intensity as permanently to exhaust and damage many of the pancreatic islets. Viewed from this angle, diabetes mellitus is initiated by transitory hyperfunction of the anterior pituitary gland and subsequently maintained through pancreatic islet degeneration and insulin deficiency. No explanation, however, can be given for the initial pituitary hyperfunction and the anterior lobe histologically also/

also fails to reveal any abnormality. At the same time, Davis et al. (1935) have drawn attention to the possible rôle of the nervous system in the genesis of the condition through showing that the hypothalamus apparently influences the control exerted on carbohydrate metabolism by the anterior hypophysis. Finally, the islet hypertrophy commonly observed in human diabetic subjects is no doubt a compensatory mechanism and the experimental findings indicate that it may also be mediated through excessive secretion of the pancreotropic factor operating in the period of islet exhaustion or degeneration.

Balance between Pancreas and Pituitary Gland

Reference must now be made to two important clinical facts. The first which has been emphasised by White (see Joslin, 1940b, and Coggeshall and Root, 1940) is that the children who develop diabetes are often abnormally tall and show precocious bone , dental and sex development. The second is that the majority of adult diabetic subjects, according to Joslin (1940a), are or have been obese: obesity, indeed,is the commonest antecedent factor in diabetes. The disease is thus commonly preceded by abnormal growth vertically in the child and laterally in the adult. Its frequency, moreover, indicates that this association is not fortuitous, but that the two types of growth are probably related both to each other and to the genesis of the diabetes./

diabetes.

The obese subject, as Dunlop and Murray-Lyon (1931) have shown, does not put on weight continuously. The amount of overweight instead is largely determined during the first five years or less and thereafter an equilibrium is maintained for many years. Loss of weight finally occurs with the onset of diabetes. The obese diabetic subject as regards weight thus passes through phases of increase, equilibrium, and decrease. Ogilvie (1935), in an investigation of 65 overweight subjects, found also that as the duration of the obese state increases a progressive diminution occurs in sugar tolerance. Moreover, one-third of these cases with a history of obesity up to 5 years showed an increased sugar tolerance, while the remainder in this period had normal tolerance. Subjects who had been obese for between 6 and 11 years also had normal sugar tolerance. Examples of lowered sugar tolerance thereafter made their appearance and every case with a history of obesity for 18 years or more finally exhibited a slightly or definitely decreased tolerance. Diabetes supervened after periods of 12 to 38 years' obesity. These results, assuming sugar tolerance to be an index of pancreatic islet activity, indicate that the islets pass through phases of increased, normal, and decreased function in one-third of obese diabetic subjects, while in the remainder they merely show stages of normal and decreased activity. The fact that according to Ogilvie/

Ogilvie (1933, 1935) the islets in a high proportion of obese subjects are hypertrophied (Fig. 13) during the phase of diminished sugar tolerance also suggests that these structures are overactive at first and later depressed. The initial increase and ultimate decrease in weight of the obese diabetic subject are thus respectively accompanied by phases of increased (proportion of cases only) and markedly decreased pancreatic islet activity, while normal or moderately decreased islet function is associated with the intermediate stage of equilibrium. Finally, Rabinowitch (1938) having found that diabetic subjects on caloric values definitely below theoretical requirements either maintain their weight or lose very much less weight than the anticipated amount has thereby shown that the diabetic state is characterised by reduced catabolism or increased anabolism or both.

The significance of these clinical observations in relation to the genesis of diabetes is enlightened by recent work on the part of Young (1941a, 1941-42, 1942), Marx et al. (1941-42), and Ogilvie (1945). Thus, anterior pituitary extracts have been observed to be growth-promoting both in growing and fully-grown subjects. The growing subject, indeed, usually responds with accelerated growth only and rarely becomes diabetic, whereas increased growth and diabetes are usually concomitant results in the fully-grown subject. This increased growth, moreover, takes place on a diet equal to or even less than/

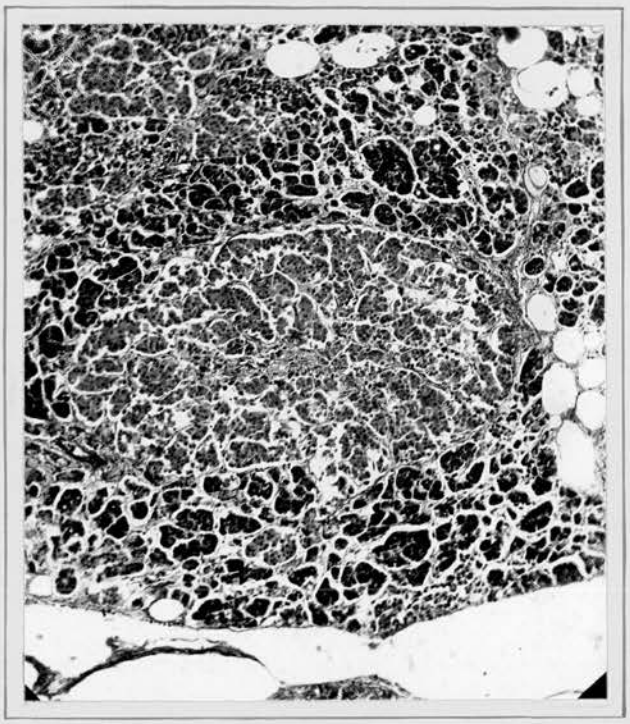
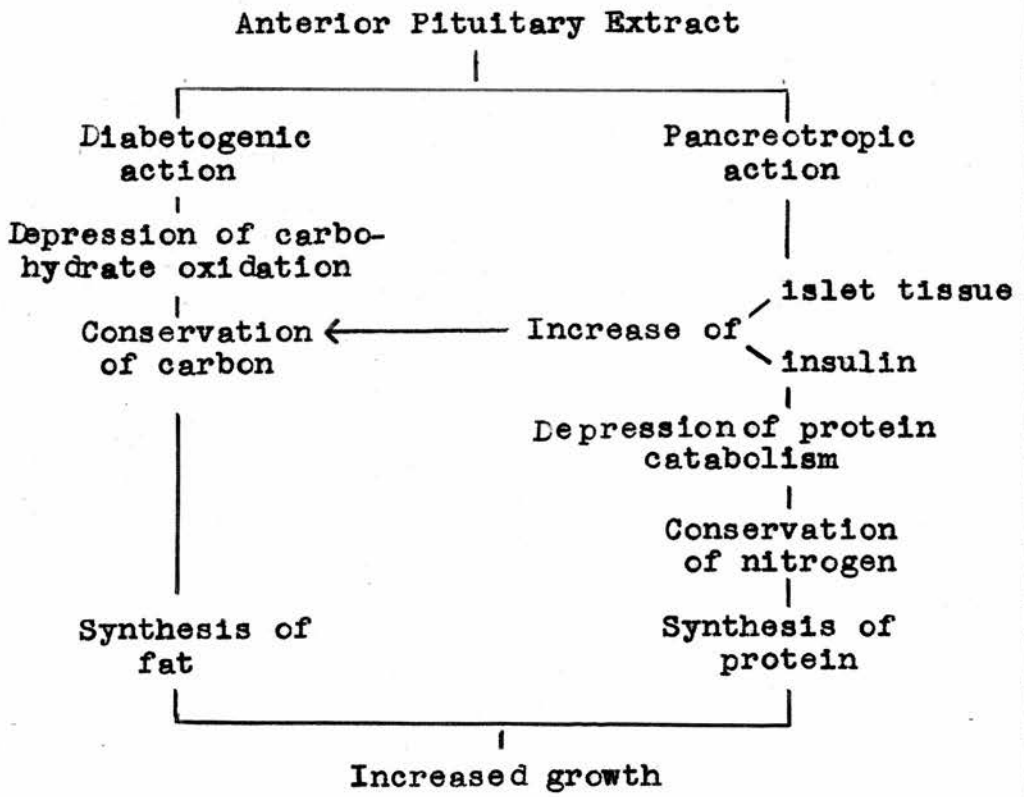


Fig. 13. Pancreas. Female aged 64 years. Obese non-diabetic subject. The selected islet shows marked hypertrophy. Haematoxylin and Eosin x 80.

than that was previously just sufficient to maintain a constant body weight and is accompanied by retention of nitrogen, deposition of fat, and hypertrophy of the pancreatic islets. Such observations suggest that anterior pituitary extract brings about a state of reduced catabolism or increased anabolism or more probably both and may be correlated as shown in the accompanying scheme.



The diabetogenic action of the extract by depressing oxidation leads to a conservation of carbon, while its pancreotropic influence produces pancreatic islet hypertrophy and more insulin. This insulin, through inhibiting protein catabolism, effects a sparing of nitrogen and also synthesises the conserved carbon and nitrogen into fat and protein respectively./

respectively. The resultant increase in body weight may consequently be interpreted as due to excessive diabetogenic action balanced by increased pancreatic islet function induced through the pancreotropic action of the extract.

These experimental observations suggest that a similar hypophysial-pancreatic balance operating at a higher level of activity than usual is responsible for the pre-diabetic increase of height in children and of weight in adults. Such growth accordingly represents a protective mechanism whereby the nitrogen and carbon retained in consequence of excessive anterior pituitary activity are stored as extra tissues under the influence of the pancreatic islets, increased function of which is effected through the pancreotropic action of the gland. The prediabetic increase vertically in the child and laterally in the adult, moreover, is maintained so long as the exaggerated activity of the pituitary gland is neutralised by corresponding hyperfunction of the pancreatic islets, but sustained overaction of the islets ultimately gives way to their exhaustion and even permanent degeneration. The outcome is that the nitrogen originally conserved in excess is no longer so retained, the carbon which remained unoxidised as a result of excessive diabetogenic action is excreted in the urine as sugar, and the body weight falls. Failure of the elevated hypophysial-pancreatic balance, in other words, expresses itself in diabetes mellitus.

Other/

Other Endocrine Glands

The thyroid gland plays a definite part in carbohydrate metabolism. This is seen in that hyperthyroidism is characterised by lowered sugar tolerance and sometimes glycosuria, while increased sugar tolerance is a feature of myxoedema. True diabetes mellitus may coexist with both of these conditions. In such combination, hyperthyroidism definitely intensifies the diabetic state, and the latter, on the other hand, improves on treatment of the hyperthyroidism with iodine or thyroidectomy. Similarly, the administration of thyroid extract in myxoedema aggravates diabetes, and diabetes in contrast may apparently disappear in advanced myxoedema. This influence of thyroid secretion on sugar metabolism is probably mediated through the sympathetic nervous system and the output of adrenalin. The thyroid gland and pancreatic islets thus function antagonistically, but in an indirect way. Further, the islets in cases of diabetes associated with hyperthyroidism show no characteristic changes. This is in agreement with the general belief that the concurrence of diabetes mellitus with hyperthyroidism and myxoedema is fortuitous and that the pancreatic and thyroid conditions bear no aetiological relationship.

The adrenal glands are intimately related to carbohydrate metabolism through the secretions of both their medulla and cortex. Adrenalin acts by liberating sugar rapidly into the circulation from the liver/

liver and muscles in emotional states. The adrenal medulla, in other words, functions essentially in emergencies and thus contrasts with the anterior hypophysis and adrenal cortex, the diabetogenic influences of which are definitely sustained. The antagonism between adrenalin and insulin is well seen in insulin hypoglycaemia when the body in an endeavour to raise the blood sugar pours adrenalin into the circulation as a protective mechanism and so produces the tremor, sweating and blanching characteristic of the hypoglycaemic state. The glycosuria of hyperthyroidism, as already mentioned, is also probably mediated through the adrenal medulla. The fact that the adrenal cortex plays an important part in sugar metabolism is manifest in those diseases involving destruction or increase of the cortex. Addison's disease, for example, is characterised by increased sugar tolerance, low fasting blood sugar and hypersensitivity to insulin. Concurrent Addison's disease and diabetes mellitus has been described on rare occasions and Bloomfield (1939) has observed that in these circumstances the diabetes with the development of the adrenal condition requires less insulin for its control. On the other hand, patients, with hyperplasia, adenoma or carcinoma of the adrenal cortex, according to Lukens et al. (1937), frequently show decreased sugar tolerance and glycosuria. Long (1935-36), moreover, has shown that bilateral removal of the adrenal cortex alleviates the diabetes produced by pancreatectomy in the same

way as hypophysectomy. Clinical and experimental observations thus both indicate that so far as the control of carbohydrate metabolism is concerned the adrenal cortex closely rivals the anterior hypophysis.

The ovary also influences carbohydrate metabolism. Since sugar tolerance continues to fall at the same rate after as before the menopause (Ogilvie, 1935), the natural cessation of ovarian function at that time obviously does not influence sugar tolerance. This is, of course, only to be expected for the reason that cessation of ovarian function at the menopause being usually a gradual process the tissues have time to adjust themselves to the altering conditions. In contrast, cases with a history of spontaneously occurring or artificially produced amenorrhoea may show both rapidly increasing obesity and definitely decreased sugar tolerance (Ogilvie, 1935). The time of maximum susceptibility to the development of diabetes, moreover, is the early postmenopausal period. These observations suggest that the ovary controls the anterior pituitary gland and that on removal of the ovarian restraint the hypophysis exerts an undue diabetogenic influence on metabolism. On this basis, postmenopausal diabetes has been treated with oestrogens which have the additional recommendation that they stimulate the pancreatic islets to grow and secrete insulin (see Young, 1941b). Both natural and synthetic oestrogens have been used, but the results so far reported have been conflicting. Thus, while definite/

definite amelioration of the disease was noted by earlier investigators, later observations have been of a more or less negative nature.

Alloxan Diabetes

Alloxan, the ureide of mesoxalic acid, has recently been shown by Dunn and his colleagues (1943a and b) to have the property of producing selective necrosis of the pancreatic islets and consequently a state of permanent diabetes. The blood sugar following the administration of alloxan first rises and then falls to a subnormal level, probably owing, as Hughes et al. (1944) have suggested, to liberation of preformed insulin from the necrotic islet tissue. This hypoglycaemia, indeed, may be so severe as to result in death or, on the other hand, be succeeded by hyperglycaemia, glycosuria, and often the cardinal signs of severe, persistent diabetes. This discovery is important inasmuch as alloxan is known to be related to certain agents and functions in the body. Thus, it is derivable from uric acid and other purins and could conceivably be an intermediate product in the elaboration of these substances. Riboflavin is another allied compound. Lang (1866) and Liebig (1862) have also identified alloxan respectively in the urine of an oedematous patient and in the mucus of a case of intestinal catarrh. The significance of alloxan in these various circumstances will no doubt be extended before long, but such facts are sufficient to suggest that alloxan/

alloxan might in conditions of altered metabolism be liberated excessively into the circulation and so damage the pancreatic islets as to result in diabetes mellitus. One observation against this theory is the fact that pancreatic islet necrosis which is the characteristic effect of alloxan is by no means so typical of human diabetes. Necrosis, nevertheless, has been described on rare occasions in the human subject and the islet lesions more commonly found in human diabetes might well be produced as a result of further experimentation with alloxan.

The fact that the diabetic problem was originally described as complex has certainly been borne out by this review. At the same time, an attempt has been made to marshal some of the known facts by first considering the pancreas and the pituitary gland and then trying to strike a balance between these organs. The influence of the other endocrine glands on carbohydrate metabolism was mentioned and emphasis laid on the adrenal cortex as probably being more potently concerned than is at present imagined. Finally, alloxan diabetes has been considered and classed as a discovery such as may soon shed new light on the aetiology of diabetes mellitus.

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