THE PANCREAS :

STUDIES IN ITS DEVELOPMENT, PATHOLOGY,

AND RELATIVE METABOLISM

A Thesis

presented by

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with

188 ILLUSTRATIONS.

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SECTION V./

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Preface.

This thesis is an account of my researches in the sphere of the pancreas. It was carried out at intervals over a period of about 18 years and represents the product of a little spare time and much over time during a life filled to capacity with routine hospital, teaching, literary, administrative and other duties. Strangely enough, the first case I was ever officially given to investigate as a medical student was a thirteen year old boy suffering from diabetes mellitus. I can well remember the morning when, to my consternation, Dr. A. Fergus Hewat asked the clinique to gather round and listen to me give a resumé of the history and condition of my young diabetic protégé. That was five years after the discovery of insulin by Banting and Best (1921 - 22) in Toronto. I sometimes wonder what became of that boy and whether with the help of insulin he is still alive or whether he has succumbed to ketosis or infection or some vascular complication.

The research, however, really originated in a casual meeting with Dr. John Eason at the west gate of the Royal Infirmary, Edinburgh, one morning in the year 1931. Dr. Eason was then a senior physician in the Infirmary and a specialist in the relatively new field of the internal secretions. He was interested among other endocrinological problems in the aetiology of obesity and enquired whether/

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whether I had ever examined the pancreatic islets in cases of this condition. I naturally had not, since such an idea had never occurred to me, but being then an assistant in the Pathological Department of the Infirmary, I did not have to wait long for material upon which to make trial of the suggestion. The pancreatic islets in the first obese subjects I examined were suspiciously enlarged and thereby encouraged me to proceed with the investigation on a properly controlled basis. An account of my findings is given in Section II of the thesis. This work, apart from any intrinsic value, had the dual effect of creating in me an interest in carbohydrate metabolism such as has grown increasingly greater with the passing years and incidentally of indicating new fields for exploration. One of these was naturally the functional condition of the enlarged pancreatic islets observed in a proportion of obese subjects. Thus I soon found myself with the kind permission of Professor D. Murray Lyon and the willing assistance of Sister Ruth Pybus carrying out sugar tolerance tests in obese individuals in the Dietetic Out-Patient Department of the Royal Infirmary. The results of the tests were correlated with the duration of the obese condition, the amount of overweight and ovarian function and in respect of both these correlations and the conclusions to be drawn therefrom are described in Section III. Reference to original articles à propos the investigation/

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investigation incidentally disclosed that sugar tolerance was distinctly greater in the infant than in the adult. I was much taken with this observation and thought that it might be explained by the presence of a relatively larger amount of islet tissue in the infant than in the adult. I therefore decided to put my idea to the test. A necessary step was the assessment of the quantity by weight of islet tissue in the individual pancreas and the means of doing this were fortunately already at hand in the projection technique outlined in Section II. Further consideration of the method, moreover, showed that its expansion along certain lines would render possible a determination not only of the weight of islet tissue, but also of the number and average weight of the islets in a pancreas. So the whole conception of the next investigation was broadened from a mere correlation of the sugar tolerance and pancreatic islet tissue in infancy and adult life to a comprehensive survey of the growth of the pancreatic islets numerically and dimensionally and also relative to the growth of the pancreatic acinar tissue and body as a whole during the period between birth and late middle age. Such work was timely in view of the ignorance and confusion extant in the literature regarding such simple questions as, for example, whether the islets increase numerically after birth and the average weight of islet tissue in the adult pancreas. The relative data are analysed and illustrated/

illustrated graphically in Section I. This piece of research, although in reality performed third as regards order, is placed first in the thesis since it deals with the normal development of the pancreas and ought accordingly to precede the other investigations inasmuch as these all have a distinctively pathological trend.

The years approaching 1940 saw me absorbed in the writing of a volume on " Pathological Histology" but during the making thereof I was fascinated, like all other interested people, by Young's (1937) production in the dog of permanent diabetes through giving large, increasing amounts of anterior pituitary extract. The mainly degenerative changes observed by Richardson (1939 - 40) in the pancreatic islets of those permanent pituitary diabetic dogs were so reasonably similar to the phenomena described by Warren (1938) in the islets of human diabetic subjects as to warrant their production and further study. I soon realised, however, that the limited supply of ox pituitary glands available at the Edinburgh Corporation abattoir and consequently of anterior pituitary extract which I was able to prepare therefrom would be quite insufficient to maintain such large animals as dogs and so I had perforce to choose smaller experimental subjects in the shape of English rabbits. The results obtained on treating 28 of these animals with the anterior pituitary extract of my own making are given with protocols and graphs in Section/

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Section IV. My experience here was akin to the accidental discovery by von Mering and Minkowski (1890) of how pancreatectomy produces severe diabetes in the dog. Thus my rabbits responded to anterior pituitary extract by showing not anticipated destruction, but converse growth of the islets as evidenced by enlargement and very occasionally a differentiation of new islets from the ducts as in the embryo.

During the investigation I further observed that some of the animals, while being given anterior pituitary extract, increased in weight on a diet which was previously just sufficient to maintain a more or less constant body weight. This phenomenon aroused my interest in the intimate and now well recognised relationship between anterior pituitary extract and growth. As the protocols show, I had enough data as regards the body weight, food consumption and pancreatic islet tissue of 15 of the animals to indicate certain conclusions, with particular reference to the increased amount of insular tissue as part of the mechanism whereby anterior pituitary extract encourages growth. The data and conclusions referred to are set forth in Section V.

I had just completed the foregoing research early in 1943, when the Honyman-Gillespie Trust invited me to give an open lecture in the Royal Infirmary, Edinburgh, on a subject of my own choice. I was at once alive to the honour and onus of such an/

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invitation and felt that I could not do greater justice to the occasion than by giving a review of the factors concerned in the syndrome of diabetes mellitus, incidentally incorporating my own experimental observations. The presentation of this intricate locus of the metabolic sphere necessitated the preliminary selection of a plan allowing treatment of all the facts in as lucid, logical and complete a manner as possible. Any worker in the field will readily admit that the conception of such a framework is by no means easy, but will probably agree with the plan adopted for " The Aetiology of Diabetes Mellitus " in Section VI inasmuch as it permits a reasonable lay out of many, if not all, of the relative historical, physiological, pathological and experimental data. Section VI, with the omission of the fourth part, has often been given and, I understand, appreciated as a postgraduate lecture. The explanation of this may lie in the first three parts representing a concrete, circumscribed attempt to elucidate and correlate some of the outstanding features of diabetes mellitus in terms of experimental findings and so to bring some sense and cohesion out of otherwise confusion and disharmony, while the last part introduces a subject of great and growing importance in the conception of the disease etiologically.

I communicated Section IV to the Pathological Society of Great Britain and Ireland at Manchester in/

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in 1942. At that meeting I was immediately preceded in the programme by the late Professor J. Shaw Dunn of Glasgow who described in characteristic manner his now universally famous discovery, again purely by accident, of how alloxan produces rapid, selective necrosis of the pancreatic islets in the rabbit. My contribution, on the other hand, consisted in an account of the way in which the pancreatic islets in the rabbit could be made to grow by means of anterior pituitary extract. Alloxan and anterior pituitary extract thus contrast in causing respectively destruction and growth of the pancreatic islets in the rabbit and these opposing actions accordingly occurred to me as being capable of combination in a single and seemingly worthwhile investigation. I therefore made a number of rabbits severely diabetic with alloxan and then treated them with anterior pituitary extract in the hope of alleviating and even, if possible, curing the established diabetic condition through the pancreotropic action of the extract. The results of this prolonged research are described, illustrated graphically and histologically, and supported with protocols in Section VII. The necessity of controlling my findings in the work just mentioned entailed the administration of alloxan to several pairs of litter-mate rabbits. The animals of one pair were both made permanently diabetic with the compound and are detailed in Section VII. The animals in another pair responded/

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responded to alloxan by showing only transitory diabetes and were thereupon used in one case for injection with anterior pituitary extract and in the other as a control. My findings and conclusions in this limited and yet reasonably controlled experiment were similar to those in Sections IV and V and are laid out in Section VIII.

Rich and Duff (1936) in a comprehensive paper on the aetiology of acute haemorrhagic pancreatitis drew attention to obstruction of the duct system of the pancreas as being in their opinion an important factor in the production of the condition. They cited as factors capable of causing duct obstruction and subsequent pancreatitis a gall stone impacted in the ampulla of Water, duodenal diverticulum, pancreatic calculus, carcinoma of the head of the pancreas, and particularly hyperplastic transitional metaplasia of the lining epithelium. During the following two or three years I encountered four cases of perivaterine duodenal diverticulum, of which one was associated with gross distension of the main pancreatic duct and fibrotic atrophy of the pancreas and three with acute haemorrhagic pancreatitis. The four cases were written up and used as a basis for reviewing the complications of duodenal diverticula with particular reference to acute pancreatic necrosis etiologically. The material with appropriate illustrations including two in colour constitutes Section IX.

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The above is a brief account of the origin and growth of the thesis. Its component sections at or about the time of their completion were communicated, by offer or invitation, to various medical bodies including the Pathological Society of Great Britain and Ireland, the Association of Physicians of Great Britain and Ireland, the Diabetic Association, the British Dietetic Association and the Edinburgh Pathological Club. As indicated on the title page of each section they have all, apart from Section VIII, been published in the Journal of Pathology and Bacteriology, Quarterly Journal of Medicine, British Journal of Surgery, Journal of Endocrinology, or Edinburgh Medical Journal. Section VIII is about to be submitted for publication to the Journal of Pathology and Bacteriology.

Particular attention is drawn to the fact that no attempt whatever has been made to modernise the conclusions or references in any of the earlier parts. Sections II and III, especially the former, may thus appear incomplete inasmuch as little or no reference is made during the discussion of their results to now well recognised facts such as, for example, the influence of anterior pituitary extract in producing nitrogen retention, increased growth, diabetes and enlargement of the pancreatic islets. Modernisation, however, was after due consideration regarded as impracticable and replaced by the simpler expedient of presenting the various sections more/

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more or less as they were originally published. This conservative plan serves two purposes. First, it reveals any progress in personal ability to approach, plan and prosecute a piece of medical research, and secondly, it epitomises the growth of knowledge in certain spheres of carbohydrate metabolism from the time when the pancreas was the main centre of thought through the years dominated by the anterior pituitary gland and adrenal cortex to the present day when alloxan diabetes is beginning to open up new correlations between carbohydrate and purine physiology. The hope is accordingly entertained that the nine sections of the thesis, although individual in their conception and prosecution, may be read and regarded as a composite whole, reflecting the progress of almost two decades.

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Section I.

A Quantitative Estimation of the Pancreatic Islet Tissue

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Section I.

A Quantitative Estimation of the Pancreatic Islet Tissue.

This investigation is a study of the pancreas between birth and late middle age as regards :-

(1) the weight of acinar tissue ;

(2) the weight of islet tissue ;

(3) the average weight of the islets ;

(4) the number of islets ;

(5) the amount of increase of 1, 2, 3 and 4 ;

(6) the rate of increase of 1, 2, 3 and 4 individually and relative to both each other and the rate of increase of the weight of the body ;

(7) the variation of 1, 2, 3 and 4 at any given age ; and

(8) the possibility of sugar tolerance being greater in the infant than in the adult by reason of a relatively greater amount of pancreatic islet tissue in the infant than in the adult.

Material and Methods.

The material consisted of 100 human pancreases. The 59 female and 41 male subjects from whom the pancreases were obtained varied between newly born infants and an adult of 64 years and in every instance appeared post mortem to be normally nourished. They had incidentally died from a great variety of causes, e.g. bronchopneumonia, cerebral haemorrhage, perforated/

perforated gastric ulcer, burns, etc.

(1) Estimation of weight of islet tissue. The method employed was the extension of a technique previously described by Ogilvie (1933). It was at first thought to be original, but was later discovered to have already been devised by Heiberg (1906). He used the method, however, to make only a single determination of the weight of the pancreatic islet tissue and no record of any other such estimation has been found in the literature.

Each pancreas was carefully dissected out, freed as much as possible from fat and weighed in grams. Blocks of tissue were taken from the head, body and tail of the organ, fixed in Helly's bichromate-sublimate-formalin solution and cut in paraffin. The sections were stained by the azan method and thereafter showed reasonably good differentiation between the islet and acinar tissues.

The stained section from the head of the pancreas was fixed into a microscope with the tube placed horizontally instead of vertically. A strong carbon-arc light at the objective end (Watson para 2/3) and a prism fitted to the eye piece (Watson 4) were used to case an image of the section with a magnification of 120 on a sheet of quarto notepaper. Fifteen unselected fields of the section were passed by means of the movable stage over the sheet and thereon were traced in pencil all the visible pancreatic islets. An estimate of the total area of islet/

islet tissue in those fifteen fields was obtained by first weighing the sheet in grams and then measuring its area in square centimetres : then all the islets were cut out of the sheet with scissors and weighed separately. The ratio

$$\frac{\text{area of islet tissue}}{\text{area of sheet}} : \frac{\text{weight of islet paper}}{\text{weight of sheet}}$$

facilitated a calculation of the area of islet tissue in fifteen fields of pancreas. The area of one field and so of fifteen fields was estimated from direct measurement of the radius. The known factors now allowed a determination of the percentage area of islet tissue in the head of the pancreas. The same measurement was likewise carried out in respect of the islet tissue in the body and tail and thereby permitted an estimate of the average percentage area of islet tissue in the whole pancreas. This figure was applied to the weight of the organ and so, on the supposition that islet and acinar tissues have the same specific gravity, an estimate was finally made of the weight of the islet tissue. The impossibility of finding fifteen fields in sections of small infant pancreases was overcome by examining as many fields as possible and calculating therefrom the figure for fifteen fields.

(2) Estimation of total number of islets. The average area of the islets in the section from the head of the pancreas was calculated from the total area of a known number of islets therein. A similar estimate was likewise made of the islets in the sections/

sections from the body and tail and so facilitated an assessment of the average area of the islets in the sections from the three regions of the pancreas. Now, if the average islet be regarded as a sphere, OABC (Fig.1), then all sections of the average islet must represent planes between the centre of the sphere, O, and its periphery B. Therefore, the average sectional area as calculated represents the area of a circle whose diameter, ADC, passes at right angles through the midpoint D, of OB, the radius of the average sphere. The known area of this circle allowed the calculation of its radius AD. OD being $\frac{1}{2}$ OA and $\angle$ ODA being 90°, $\angle$ OAD was 30°. From the equation $\tan \angle$ OAD $(30^{\circ}) = \frac{OD}{AD}$, the line OD was determined since it was the only unknown. 2 OD gave OB, the radius of the average sphere. The real size of OB was obtained on division by 120, the power of magnification. The real radius now permitted the assessment of the volume of the sphere OABC ($\frac{4}{3} \widetilde{\pi} r^3$). Then, separate evaluation of the specific gravity of pancreatic tissue at 1.05 and the assumption, as before, that islet and acinar tissue have the same specific gravity enabled the weight of an average islet to be estimated from the formula, mass = density x volume. Determination of the weight of an average islet and of the total weight of islet tissue thus allowed a calculation of the total number of islets.

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The method can be summarised thus :

Area of average islet on section = πr^2 = x.

$\therefore$ r = AD = $\sqrt{\left(\frac{x}{\pi}\right)}$.

$\therefore$ R = real radius of average islet (sphere OABC)

$$= \frac{AD \times 2 \tan 30^\circ}{120} = \frac{AD \times 2 \times .5774}{120} =$$

.0096 AD.

$\therefore$ Volume of average islet = $\frac{4}{3}\pi (AD \times .0096)^3$

$$= 4.1 (AD \times .0096)^3.$$

$\therefore$ Mass of average islet = Volume x Density

$$= 4.1 (AD \times .0096)^3 \times 1.05.$$

$\therefore$ Number of islets =

$$\frac{\text{Total weight of islet tissue}}{4.1 (AD \times .0096)^3 \times 1.05}.$$

The factors assessable in each case were thus : (1) weight of body ; (2) weight of pancreas ; (3) weight of acinar tissue ; (4) weight of islet tissue; (5) weight of acinar and islet tissue per kg. body weight ; (6) average weight of islets ; and (7) total number of islets. The calculation of a case is demonstrated in Table I.

The sources of possible error in the above method were four in number. (1) Infant pancreases sometimes raised the problem of necessarily distinguishing islets from ductules and acini. Such difficulty is reasonable in view, as described by Laguesse (1895, 1909-10), Pearce (1903) and Kuster (1904), of the common origin of acini and islets from ductules, but considerable accuracy in differentiation was/

Table I.

Calculation of a Case.

Sex and age.	Pancreas.	No. of fields.	Wt. of sheet in g.	Wt. of islets in g.	Area of sheet in sq. cm.	Area of islets in sq. cm.	Area of pancreas in 15 fields in sq. cm.	Percentage area of islet tissue in pancreas.		No. of islets in 15 fields.
Male	Head	15	4.60	1.68	516.64	188.7	4,996.8	3.77	Aver-	137
2 yrs.	Body	15	4.59	1.09	516.64	122.7	4,996.8	2.45	age	132
2 mths.	Tail	15	4.61	1.63	516.64	182.7	4,996.8	3.65	3.29	155

Sex and age.	Pancreas.	Av. area of one islet in sq. cm.		Wt. of pancreas in g.	Wt. of islet tissue in g.	Wt. of acinar tissue in g.	Body wt. in kg.	Wt. of islet tissue per kg. body wt. in g.	Wt. of acinar tissue per kg. body wt. in g.	Average wt. of one islet in γ	No. of islets.
Male	Head	1.38	Aver-								
2 yrs.	Body	0.93	age	19.3	0.64	18.7	12.7	0.050	1.5	0.840	755,952
2 mths.	Tail	1.18	1.16								

was nevertheless achieved with experience. (2) The investigation was limited to only forty five fields in each pancreas, but the examination of a greater area was precluded by the tediousness of the method. Regional differences incidentally were covered by the fields being equally distributed between head, body and tail. (3) Calculation of the weight of islet tissue from the percentage area took for granted that islet and acinar tissues have the same specific gravity. No way exists of proving this identity, but any difference is probably minimal. (4) The assumption of the average islet to be perfectly spherical was probably justified in some islets, but many islets undoubtedly departed in varying degrees from so regular a form.

Results

Examination of the above noted 100 cases yielded figures summarised in Table II.

1. Weight of (a) body ; (b) acinar tissue ; and (c) islet tissue. Each of these factors follows a generally similar pattern of growth (Figs. 2 -5). The curve rises rapidly during the first two or three years and particularly the first year of life. It is then characterised by consecutive phases of relatively slow and rapid increase in childhood (4- 12 years) and of relatively rapid and slow increase in adolescence (13- 21 years). The curve eventually becomes temporarily or permanently stabilised about 21 years. The body weight increases between averages of/

Table II.

No.	Sex.	Age.	Wt. of body in kg.	Wt. of pancreas in g.	Wt. of acinar tissue in g.	Wt. of acinar tissue per kg. body wt. in g.	Wt. of islet tissue in g.	Wt. of islet tissue per kg. body wt. in g.	Av. wt. one islet in γ	No. of islets.
1	F	Still-born	3.0	2.42	2.30	0.77	0.12	0.052	1.476	105,014
2	F	Died at birth	4.3	4.08	3.97	0.90	0.11	0.026	0.421	263,658
3.	F	Still-born	3.2	2.40	2.35	0.73	0.05	0.015	0.344	139,535
4.	F	Still-born	3.6	2.30	2.11	0.60	0.19	0.053	0.447	425,056
5.	M	Still-born	3.3	1.92	1.83	0.56	0.09	0.027	0.185	486,486
6.	M	2 days	3.3	3.04	2.92	0.89	0.12	0.035	0.508	236,220
7.	M	6 days	2.9	1.47	1.41	0.49	0.06	0.021	0.508	118,110
8.	F	5 wks.	3.5	6.77	6.50	1.86	0.27	0.079	0.539	513,915
9.	F	9 wks.	3.5	2.75	2.66	0.76	0.09	0.026	0.237	379,747
10	F	3 mths.	3.3	3.61	3.54	1.07	0.07	0.021	0.366	185,792
11	F	4 mths.	4.3	5.10	4.86	1.13	0.24	0.056	0.275	876,364
12	M	5 mths.	10.2	4.77	4.53	0.44	0.24	0.024	0.344	709,302
13	F	6 mths.	5.0	4.99	4.88	0.98	0.11	0.022	0.421	263,658
14	M	6 mths.	5.9	5.94	5.72	0.97	0.18	0.031	0.237	772,152
15	F	6 mths.	5.5	9.04	8.83	1.61	0.21	0.039	0.715	296,503
16	F	7 mths.	7.3	12.60	11.93	1.73	0.67	0.092	1.296	513,846
17	F	7 mths.	5.1	6.20	6.00	1.18	0.20	0.039	0.220	900,000
18	F	7 mths.	5.0	3.65	3.55	0.71	0.10	0.021	0.254	405,512
19	F	8 mths.	5.5	4.42	4.22	0.77	0.20	0.038	0.508	393,701
20	M	8 mths.	6.5	12.78	12.31	1.89	0.47	0.073	0.203	2,325,123
21	F	9 mths.	9.5	13.23	12.77	1.34	0.46	0.049	0.680	679,412
22	M	9 mths.	7.7	7.33	7.14	0.95	0.19	0.024	0.169	1,100,592
23	F	10 mths.	6.7	11.90	11.45	1.70	0.55	0.082	0.607	909,390

No.	Sex	Age.	Wt. of body in kg.	Wt. of pancreas in g.	Wt. of acinar tissue in g.	Wt. of acinar tissue per kg. body wt. in g.	Wt. of islet tissue in g.	Wt. of islet tissue per kg. body wt. in g.	Av. wt. one islet in γ	No. of islets.
24	M	10 mths.	9.6	10.32	9.90	1.03	0.42	0.044	0.572	739,510
25	F	1 yr.	6.9	9.02	8.84	1.28	0.18	0.026	0.392	454,082
26	F	1 yr.	7.4	7.42	7.21	0.97	0.21	0.029	1.817	117,226
27	M	1 yr.	9.1	9.96	9.63	1.06	0.33	0.037	0.392	841,837
28	F	1 yr.1mth.	7.7	12.80	12.37	1.60	0.43	0.056	0.607	708,402
29	F	1 yr.1 m.	9.1	9.83	9.49	1.04	0.34	0.037	0.642	529,595
30	F	1 yr.2 m.	6.6	8.70	8.29	1.26	0.41	0.062	0.275	1,483,638
31	M	1 yr.3 m.	7.8	8.10	7.83	1.00	0.27	0.034	0.447	597,315
32	F	1 yr.3 m.	8.2	13.15	12.53	1.53	0.62	0.075	0.644	959,627
33	F	1 yr.5 m.	10.3	17.60	16.98	1.65	0.62	0.061	0.508	1,220,472
34	F	1 yr.5 m.	8.9	11.89	11.18	1.26	0.71	0.080	1.240	572,581
35	M	1 yr.6 m.	9.4	8.45	8.23	0.88	0.22	0.023	0.254	854,331
36	M	1 yr.9 m.	10.8	14.49	14.07	1.30	0.42	0.039	0.237	1,763,713
37	F	2 yr.1 m.	10.6	13.64	13.52	1.28	0.12	0.011	0.680	176,471
38	M	2 yr.2 m.	12.7	19.30	18.66	1.47	0.64	0.050	0.840	755,952
39	M	2 yr.3 m.	9.9	21.56	20.78	2.10	0.78	0.080	0.715	1,090,909
40	M	2 yr.6 m.	12.2	15.60	14.84	1.22	0.76	0.062	0.642	1,185,358
41	M	3 yrs.	10.6	12.76	12.54	1.19	0.22	0.021	0.476	457,983
42	F	5 yrs.	16.0	28.60	28.17	1.76	0.43	0.027	0.447	961,969
43	M	5 yrs.	15.5	19.60	19.21	1.24	0.39	0.025	0.421	926,366
44	M	5 yrs.	16.0	24.30	23.7	1.48	0.60	0.038	0.607	988,468
45	M	6 yrs.	14.0	23.00	22.4	1.60	0.60	0.043	0.758	791,557
46	M	6 yrs.	20.5	20.60	20.2	0.99	0.40	0.020	0.254	1,574,803
47	F	6 yrs.	15.5	22.70	21.87	1.41	0.83	0.054	0.478	1,736,402
48	M	7 yrs.	17.0	42.10	41.65	2.45	0.45	0.026	0.421	1,068,884
49	M	10 yrs.	25.5	21.40	21.05	0.81	0.35	0.014	0.344	1,017,442
50	F	13 yrs.	25.0	28.60	27.90	1.12	0.70	0.028	1.025	679,612

No.	Sex.	Age.	Wt. of body in kg.	Wt. of pancreas in g.	Wt. of acinar tissue in g.	Wt. of acinar tissue per kg. body wt. in g.	Wt. of islet tissue in g.	Wt. of islet tissue per kg. body wt. in g.	Av. wt. one islet in γ	No. of islets
51.	M	13 yrs.	33.0	58.80	58.25	1.76	0.55	0.017	0.715	783,217
52	M	13 yrs.	52.5	44.60	43.54	0.83	1.06	0.020	0.644	1,645,963
53	F	14 yrs.	34.0	55.50	54.91	1.62	0.59	0.017	0.643	917,574
54	M	14 yrs.	46.5	56.60	55.87	1.20	0.73	0.016	1.184	618,644
55	F	15 yrs.	37.0	40.50	39.28	1.06	1.22	0.033	1.240	983,871
56	M	15 yrs.	40.5	35.10	34.49	0.85	0.61	0.015	0.930	655,914
57	F	15 yrs.	48.0	46.20	45.35	0.94	0.85	0.017	0.715	1,188,951
58	F	15 yrs.	40.5	51.80	51.18	1.26	0.62	0.015	0.644	962,733
59	F	15 yrs.	43.5	78.30	76.87	1.77	1.43	0.033	1.240	1,153,226
60	F	16 yrs.	42.0	50.20	49.58	1.18	0.62	0.015	0.572	1,083,916
61.	M	18 yrs.	33.0	59.90	59.12	1.79	0.77	0.023	1.076	712,963
62	F	18 yrs.	50.0	79.80	78.49	1.57	1.31	0.026	1.240	1,056,532
63	F	18 yrs.	50.0	49.00	48.56	0.97	0.44	0.009	0.680	647,059
64	F	19 yrs.	49.5	44.70	44.13	0.89	0.57	0.011	0.840	678,571
65	M	19 yrs.	64.5	90.40	90.36	1.39	1.04	0.016	0.447	232,662
66	F	19 yrs.	48.0	52.00	51.08	1.06	0.92	0.019	0.978	940,695
67	F	20 yrs.	57.5	77.50	77.15	1.32	1.35	0.023	0.715	1,888,112
68	F	21 yrs.	50.0	61.60	59.79	1.20	1.81	0.036	1.416	1,274,648
69	F	22 yrs.	50.5	88.00	85,94	1.70	2.06	0.041	1.476	1,391,892
70	F	23 yrs.	43.0	52.90	52.41	1.22	0.49	0.011	0.680	720,588
71	M	24 yrs.	48.0	100.50	97.18	2.05	2.32	0.048	2.738	846,715
72	M	24 yrs.	38.0	63.00	61.90	1.63	1.10	0.029	0.478	2,301,255
73	F	24 yrs.	37.0	45.00	44.28	1.20	0.72	0.019	1.476	486,486
74	F	25 yrs.	44.0	49.50	48.66	1.11	0.84	0.019	1.128	743,363
75	F	25 yrs.	46.0	88.00	87.45	1.90	0.55	0.012	0.758	725,594
76	M	28 yrs.	56.0	61.20	60.63	1.08	0.57	0.010	0.715	797,203
77	M	28 yrs.	55.0	79.10	77.81	1.42	1.29	0.023	1.351	955,555

No.	Sex.	Age.	Wt. of body in kg.	Wt. of pancreas in g.	Wt. of acinar tissue in g.	Wt. of acinar tissue per kg. body wt. in g.	Wt. of islet tissue in g.	Wt. of islet tissue per kg. body wt. in g.	Av. wt. one islet in γ	No. of islets
78	F	28 yrs.	53.0	67.00	65.74	1.24	1.26	0.024	2.122	594,340
79	M	33 yrs.	52.0	79.50	77.67	1.49	1.83	0.035	1.744	1,051,149
80	F	35 yrs.	60.0	67.60	66.98	1.12	0.62	0.010	0.392	1,581,633
81	F	39 yrs.	48.5	76.10	75.28	1.55	0.82	0.017	0.758	1,018,794
82	F	39 yrs.	37.0	88.00	86.62	2.34	1.38	0.037	1.817	758,242
83	M	40 yrs.	46.0	79.80	78.69	1.71	1.11	0.024	0.840	1,321,429
84	F	40 yrs.	51.0	66.00	64.79	1.27	1.21	0.024	1.817	664,835
85	F	40 yrs.	40.5	41.80	40.64	1.00	1.16	0.029	1.416	816,901
86	F	41 yrs.	43.0	58.60	58.28	1.35	0.32	0.007	0.930	344,086
87	F	41 yrs.	53.0	50.30	49.15	0.93	1.15	0.022	1.351	851,852
88	F	42 yrs.	36.0	58.60	58.22	1.62	0.38	0.010	1.184	322,034
89	M	44 yrs.	48.0	70.00	69.55	1.45	0.45	0.009	0.883	509,627
90	F	47 yrs.	48.0	61.90	60.62	1.26	1.28	0.027	1.918	666,666
91	M	49 yrs.	49.0	56.50	55.49	1.13	1.01	0.021	1.476	684,282
92	M	50 yrs.	54.0	74.50	73.54	1.36	0.96	0.018	0.978	981,595
93	F	50 yrs.	51.0	74.70	73.32	1.44	1.38	0.027	0.978	1,411,043
94	F	50 yrs.	53.0	67.20	66.39	1.25	0 .81	0.015	1.076	750,000
95	F	52 yrs.	46.0	46.30	45.05	0.98	1.25	0.027	1.240	1,008,065
96	M	56 yrs.	57.0	61.30	60.21	1.06	1.09	0.019	0.715	1,524,477
97	M	57 yrs.	52.5	94.20	93.06	1.77	1.14	0.022	0.840	1,357,142
98	M	57 yrs.	64.5	95.20	93.35	1.45	1.85	0.029	0.978	1,891,616
99	F	61 yrs.	53.5	71.80	70.94	1.33	0.86	0.016	0.978	879,346
100	M	64 yrs.	49.5	63.60	62.44	1.26	1.16	0.023	0.930	1,247,312

of 3.5 kg. and 48 kg., the acinar tissue between averages of 2.6 g. and 66 g., and the islet tissue between averages of 0.12 g. and 1.07 g. at birth and 21 years respectively. The curve of the body weight remains constant between 21 years and 45 years and thereafter rises slowly to reach an average of about 55 kg. at 64 years. On the other hand, the curves of the weights of the acinar and islet tissues maintain a persistently constant level between 21 years and 64 years. The weight of the acinar tissue incidentally varies within wider limits than the weight of the body and the weight of the islet tissue within wider limits than the weight of both the body and acinar tissue at any particular age.

The relative rates of increase of the body, acinar tissue and islet tissue in respect of weight are shown in Table III and Fig. 12. The periods considered in this analysis are the first, second and third years of life, childhood (4 - 12 years), adolescence (13 - 21 years), and adult life (22 - 64 years). The data tabulated were obtained from the curves in Figs. 2, 3, 4, 9 and 10 and also by carefully considering the ratios of the weights of the acinar and islet tissues to the weight of the body and of the weight of the islet to the weight of the acinar tissue during the specified periods.

In the first year, the acinar and islet tissues grow rapidly and equally (x 3.5), while the body as a whole increases less quickly (x 2.2). During the second year, much slower growth characterises all three/

Table III.

To show relative increase in weight of body, acinar and islet tissue, and in the number of islets and average weight of one islet.

Years.	1st.	2nd.	3rd.	4-12	13-21	22-64
Body weight	2.2	1.3	1.2	2.3	1.7	1.(2)
Weight of acinar tissue.	3.5	1.4	1.2	2.3	1.7	1.0
Weight of islet tissue	3.5	1.4	1.06	1.2	1.7	1.0
No. of islets	2.5	1.3	1.03	1.0	1.0	1.0
Average weight of one islet	1.4	1.1	1.02	1.2	1.7	1.0

three factors, but the acinar and islet tissues still grow equally (x 1.4) and exceed the growth of the body (x 1.3). In the third year, the three factors show even less rapid growth than during the previous year and also a change in their relative rates of growth in the direction of equality between the body and acinar tissue (x 1.2) and a lag on the part of the islet tissue (x 1.06). During childhood, the body and acinar tissue continue continue to grow equally (x 2.3), while the islet tissue maintains its slower growth (x 1.2). In adolescence, the islet tissue grows more rapidly than during childhood and equals the growth of the body and acinar tissue (x 1.7). After 21 years, the three factors are stable except for the already noted increase in body weight during the period after 45 years.

The associated changes in the relations of the acinar and islet tissues in respect of weight to the weight of the body and to age are detailed in Figs. 6, 7 and 8. Both the acinar tissue and the islet tissue per kg. body weight increase rapidly during the first year and much more slowly during the second year. The acinar tissue per kg. body weight thereupon becomes stabilised, while the islet tissue per kg. body weight declines more or less rapidly to reach stabilisation at 12 years. The acinar tissue per kg. body weight increases between averages of 0.74 g. and 1.33 g. at birth and end of two years respectively. The islet tissue per kg. body weight averages 32 mg., 53 mg. and 22 mg. at birth, end

of/

of two years and 12 years respectively.

2. Number and average weight of islets. The islets can be evaluated numerically in Table II and Figs. 10, 11 and 12. They vary between 105,014 and 486,486 and average 284,000 at birth. The count increases during the first three years, but does so more rapidly during the first year (x 2.5) than the second year (x 1.5) and especially the third year (x 1.03). It becomes stabilised at 960,000 by the end of the third year. The islets vary numerically within very wide limits at all ages. Thus, two subjects of eight months (19 and 20) have counts of respectively 393,701 and 2,325,123, while two cases of 24 years (73 and 72) have counts of respectively 486,486 and 2,301,255.

The average weight of the islets can be evaluated in Table II and Figs. 9, 11 and 12. It varies (excluding case 1 which is apparently exceptional) between 0.185 γ and 0.447 γ and averages 0.350 γ at birth. It increases rapidly during the first year (x1.4) and progressively more slowly in the second year (x 1.1) and third year (x 1.02). The average weight rises slowly during childhood (x 1.2) and more rapidly again in adolescence (x 1.7). It slows down quickly in its increase towards the end of the adolescent period and becomes stabilised about 1.2 γ at 21 years. The average weight of the islets varies within wide limits at all ages. Thus, two subjects of one year (25 and 26) have islets averaging respectively 0.392 γ /

0.392 and 1.817 γ , while two cases of 24 years (72 and 71) have islets averaging respectively 0.478 γ and 2.738 γ .

The relative parts played in the increase of the islet tissue by the increase in the number and in the average weight of the islets are illustrated in Table III and Fig. 12. The increase of the islet tissue during the first three years is due more to an increase in the number than in the average weight of the islets. The rôle enacted by the increase in number of the islets as compared with that due to increase in the average weight of the islets, moreover, is greatest in the first year (x 2.5 and 1.4 respectively) and progressively less marked in the second year (x 1.3 and 1.1 respectively) and third year (x 1.03 and 1.02 respectively). The increase of the islet tissue during childhood and adolescence is effected wholly by simple hypertrophy without any accompanying hyperplasia of the islets. Cessation of such insular enlargement finally entails stabilisation of the islet tissue as a whole at 21 years.

The relationship between the number and average weight of the islets was investigated by the construction of a special graph (not illustrated). This shows that a small number is usually accompanied by a low average weight, that an intermediate number may go with either a low or high average weight, and that a large number tends to be paralleled by a low/

low average weight.

Discussion.

Several investigators including Opie (1900), Sauerbeck (1902), Heiberg (1906) and Cecil (1912) have made counts of the islets in specified sectional areas of human pancreas. The total number of islets in the human pancreas, however, has been computed by only Clark (1913) using the method of Bensley (1911-12) for estimating the total islets in the pancreas of the guinea pig. This technique involves transfusing the organ immediately after death with neutral red or janus green in order selectively to stain the islets, under a low power of the microscope counting the islets in several teased slices from the head, body and tail, weighing these pieces and calculating the total number of islets according to the weight of the whole pancreas. Clark (1913) in seven subjects varying in age from six months to 45 years obtained total counts between 120,000 and 1,760,000. He entertained hopes of using the method in autopsy subjects, but met with such discouraging results on transfusing four recently dead individuals as ultimately to consider the technique valueless except in subjects killed by violence. On the other hand, the mathematical method herein described is readily applicable to ordinary post mortem material and has thereby made possible estimates of the total islets in a reasonably large series of cases. The total count

in/

in the adult individual according to this investigation averages 960,000, but is incidentally remarkable for its wide variation at any particular age.

The fact of the present series covering the first 64 years of life further affords an opportunity of determining whether the pancreatic islets actually increase in number after birth. This question is variously answered in the literature. Thus, the islets in the opinion of Laguesse (1893) are more numerous during foetal life than at birth and thereafter diminish further in number. Again, Opie (1900) considers that after birth the islets remain constant numerically and merely become separated by a growth of acinar tissue. Finally, a continued new formation of islets from ducts after birth is postulated by Weichselbaum and Kyrle (1909) on the grounds of islets in the adult organ being found contiguous with ducts showing evidence of cellular division. Now, the islets according to this investigation clearly continue to increase numerically during the first three years of life and in this time actually multiply between averages of 284,000 and 960,000. In other words, the islets increase as much as 3.4 times during the first three years of life. The opinion of Weichselbaum and Kyrle (1909) favouring an increase in the number of islets postnatally is thus, on the basis of the present observations, much to be preferred to that of Laguesse (1893) and Opie (1900).

The/

The islet tissue increases on the average nine times in weight between birth and 21 years. During the first three years the increase is due to associated hypertrophy and hyperplasia of the islets, but the amount of hyperplasia is always greater than the degree of hypertrophy, albeit in decreasing measure. Hyperplasia of the islets ceases at the end of the third year and thereafter the sole means by which the islet tissue reaches its full quota at 21 years is through hypertrophy of the already formed islets. Hypertrophy entails a total average increase of the islets from 0.35 ɣ to 1.20 ɣ . That is to say, the first 21 years are characterised by the islets growing on the average 3.4 times in weight and thus exactly duplicating the measure of their average increase numerically during the first three years. The wide variation of the islets in number is further paralleled by their corresponding variability as regards weight at all ages. No relation, however, exists between the number and average weight of the islets in the individual pancreas.

The islet and acinar tissues increase equivalently during the first two years, but much more rapidly in the first than the second year. The third year is characterised by lesser growth on the part of the islet than the acinar tissue. This relationship is maintained during childhood, but is replaced throughout adolescence by further equivalent increase of the two parts of the pancreatic structure. These/

These observations point to an equal differentiation of the small pancreatic ducts into islets and acini during the first two years. The rapid decline in the formation of islets from the ducts in the third year, however, is apparently not compensated by correspondingly increased hypertrophy of the already formed islets with the result that at this time the islet tissue shows relatively less growth than the acinar fraction. The acinar increase continues to exceed islet hypertrophy during childhood, but in adolescence is overtaken by an equivalent enlargement of the islets.

The acinar tissue grows more rapidly than the body as a whole during the first two years and especially the first year. This observation might be interpreted on the grounds of the milk diet of the infant, through its demands for digestive juices, acting as a greater stimulus to the growth of the acinar tissue than of the body as a whole. If this be so, the preferential dietetic stimulus is maintained by the changes, quantitative and qualitative, occurring in the diet after weaning, but must disappear about the end of the second year since the acinar tissue and body increase equivalently from the beginning of the third year onwards.

The relatively high amount of islet tissue in the body during infancy and childhood is interesting in regard to the sugar tolerance of these periods, especially infancy. Thus, Mogwitz (1913-14) estimating/

estimating sugar tolerance in six children between four and thirteen months fed five with milk providing about 2 g. of sugar per kg. body weight. Four responded with a rise in their blood sugar of at most 17 mg. per cent, while the curve peaks of the other cases were 124 and 134 mg. per cent. Bergmark (1914) investigated the response of the blood sugar of infants to the ingestion of various kinds of sugar. Lactose, maltose and saccharose in his opinion produce increasingly high responses, but all the resultant curves are much lower than in adults. Spence (1920-1) after estimating blood-sugar curves in a series of infants and adults makes the statement that children under three years of age normally have a low sugar-tolerance curve. Brown (1924-5) arrived at a similar conclusion after an investigation of ten healthy infants under thirteen months. Now, the period of high sugar tolerance, i.e. the first three years according to Spence (1920-1), is characterised by a relatively very high content of islet tissue in the body. The unusual activity of the carbohydrate-storage mechanism in young children may thus reasonably be due to the outpouring from a relatively large quota of islet tissue of a correspondingly large amount of insulin whereby the rising blood sugar is prevented from reaching the higher adult level.

Sugar tolerance according to the above reasoning should increase during the first two years and decrease during childhood to reach the adult standard/

standard at puberty. No increase of sugar tolerance during the first two years is apparent in the data of either Spence (1920-1) or Brown (1924-5) and Spence (1920-1) also states that sugar tolerance after the age of three years is of the adult type. Both of these investigators, however, deal with relatively few cases and the four children between four and seven years upon whom Spence (1920-1) bases his conclusion regarding sugar tolerance after the age of three years might inadvertently have had a low quota of islet tissue. The present observations certainly suggest on the basis of the accompanying increase and decrease in the relative amount of islet tissue in the body that the first two years and childhood might well be proved, by the investigation of a reasonably large series of suitable subjects, to be characterised by gradations of sugar tolerance in the direction during the first period of increase and during the second period of decline from the higher to the lower level of the infant and adult respectively.

Sugar tolerance according to Marshall (1930-1), Hale-White and Payne (1925-6) and Ogilvie (1935) diminishes progressively with advancing years. The period after the age of fifty, however, has been found in this work, despite the accompanying increase in body weight, to be characterised by no significant change in the relative amount of islet tissue in the body. The deterioration of sugar tolerance with increasing/

increasing age would thus appear to be due to a gradual failure in the secretion of insulin such as in exaggerated form sometimes causes the elderly subject to become mildly diabetic. The explanation of this late deterioration in sugar tolerance, of course, may lie primarily, not in the islet tissue, but in the anterior hypophysis which has lately been shown by Houssay and Biasotti (1930) to play an important part in carbohydrate metabolism.

Summary

Methods are described whereby, given the weights of the body and pancreas, estimates can be made of the pancreas as regards (1) weight of acinar tissue ; (2) weight of islet tissue ; (3) weight of acinar and islet tissue per kg. body weight ; (4) average weight of islets ; and (5) total number of islets.

These factors have been determined for the pancreases of 59 females and 41 males varying between newly born infants and an adult of 64 years and on the basis thereof have been further assessed, so far as the period specified is concerned, in respect of the amount of their increase and also the rate of their increase individually and relative to both each other and the rate of increase of the weight of the body.

The infant has been shown to have a relatively greater amount of islet tissue than the adult and this finding is suggested as the reason for sugar tolerance being higher in the infant than in the adult.

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Protocols.

Sex.	Age.	Part of pan-creas.	No. fields.	No. islets.	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
F	Still-born	H	7	102	4.83	1.92	516.64	205.4
		B	8	69	4.80	1.10	516.64	118.4
		T	9	136	4.82	1.67	516.64	179.0
F	Died at birth	H	15	180	4.74	1.27	516.64	138.4
		B	10	120	4.94	0.75	516.64	78.4
		T	12	162	4.72	1.12	516.64	122.6
F	Still-born	H	15	137	4.94	1.15	516.64	120.3
		B	15	178	4.85	0.77	516.64	87.8
		T	15	164	4.92	0.85	516.64	89.3
F	Still-born	H	8	186	4.54	1.13	516.64	128.6
		B	5	183	4.57	1.48	516.64	167.4
		T	5	271	4.55	1.51	516.64	171.5
M	Still-born	H	3	95	4.59	0.32	516.64	36.2
		B	8	139	4.60	0.44	516.64	49.4
		T	3	175	4.59	0.73	516.64	82.7
M	2 days	H	12	163	4.55	1.29	516.64	146.5
		B	9	162	4.58	1.08	516.64	121.8
		T	8	125	4.59	0.91	516.64	102.4
M	6 days	H	14	281	4.56	1.65	516.64	186.9
		B	11	154	4.66	1.37	516.64	151.9
		T	-	-	-	-	-	-
F	5 wks.	H	12	191	4.77	1.30	516.64	140.8
		B	13	158	4.93	1.40	516.64	146.7
		T	9	178	4.72	1.47	516.64	160.9

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
439.5	4996.8	8.79	Av.	229.5	Av.	2.00	Av.	
2812.0	4996.8	4.44	6.40	129.5	195.2	1.71	1.68	2.42
2 98.5	4996.8	5.97		226.5		1.32		
138.4	4996.8	2.77		180.0		0.77		
117.6	4996.8	2.35	2.73	180.0	187.5	0.65	0.73	4.08
153.0	4996.8	3.06		202.5		0.76		
120.3	4996.8	2.41		137.0		0.88		
87.8	4996.8	1.76	1.99	178.0	159.7	0.49	0.64	2.40
89.3	4996.8	1.79		164.0		0.54		
241.5	4996.8	4.83		349.5		0.69		
502.5	4996.8	10.05	8.38	549.0	570.5	0.92	0.75	2.3
513.5	4996.8	10.27		813.0		0.63		
181.5	4996.8	3.63		475.0		0.38		
92.7	4996.8	1.85	4.58	261.0	537.0	0.36	0.40	1.92
413.5	4996.8	8.27		875.0		0.47		
183.0	4996.8	3.66		204.0		0.90		
202.5	4996.8	4.05	3.85	270.0	236.0	0.75	0.82	3.04
192.0	4996.8	3.84		234.0		0.82		
200.3	4996.8	4.00		301.5		0.66		
207.2	4996.8	4.14	4.07	210.0	255.8	0.99	0.83	1.47
-		-		-		-		
175.5	4996.8	3.51		238.5		0.74		
169.5	4996.8	3.39	4.09	183.0	239.5	0.93	0.86	6.77
268.5	4996.8	5.37		297.0		0.90		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.12	2.30	3.0	0.052	0.77	1.406	1.476	105,014
0.111	4.0	4.3	0.026	0.923	0.401	0.421	263,658
0.048	2.35	3.2	0.015	0.74	0.328	0.344	139,535
0.19	2.11	3.6	0.053	0.60	0.426	0.447	425,056
0.09	1.8	3.3	0.027	0.56	0.176	0.185	486,486
0.12	2.9	3.3	0.035	0.89	0.484	0.508	236,220
0.060	1.41	2.9	0.021	0.49	0.484	0.508	118,110
0.277	6.5	3.5	0.079	1.86	0.513	0.539	513,915

No.	Sex.	Age.	Part of pan-creas.	No. fields.	No. islets.	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
9	F	9 wks.	H	6	164	4.62	0.66	516.64	73.8
			B	14	160	4.63	1.11	516.64	123.9
			T	6	136	4.66	0.67	516.64	74.3
10	F	3 mths.	H	15	158	4.84	0.92	516.64	98.2
			B	10	91	4.72	0.53	516.64	58.0
			T	8	102	4.69	0.62	516.64	68.3
11	F	4 mths.	H	8	253	4.93	1.48	516.64	155.4
			B	10	220	4.85	1.05	516.64	111.8
			T	9	308	4.91	1.42	516.64	149.4
12	M	5 mths.	H	8	237	4.83	1.28	516.64	136.9
			B	7	169	4.72	0.94	516.64	102.9
			T	8	230	4.82	1.47	516.64	157.8
13	F	6 mths.	H	15	135	4.95	0.84	516.64	87.7
			B	10	96	4.76	0.75	516.64	81.4
			T	13	154	4.97	1.02	516.64	106.0
14	M	6 mths.	H	12	242	4.67	1.21	516.64	133.9
			B	12	249	4.97	1.15	516.64	118.9
			T	12	266	4.70	1.06	516.64	116.5
15	F	6 mths.	H	15	148	4.81	1.12	516.64	120.3
			B	15	103	4.92	1.28	516.64	134.4
			T	15	106	4.84	0.92	516.64	98.2
16	F	7 mths.	H	10	141	4.68	1.86	516.64	205.3
			B	15	86	4.55	1.22	516.64	138.5
			T	10	164	4.63	2.08	516.64	232.1

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
184.5	4996.8	3.69	Av.	409.5	Av.	0.45	Av.	
132.8	4996.8	2.66	3.36	171.0	306.5	0.46	0.49	2.75
186.0	4996.8	3.72		339.0		0.55		
98.2	4996.8	1.96		158.0		0.68		
58.0	4996.8	1.16	1.89	136.5	162.2	0.64	0.66	3.61
128.1	4996.8	2.56		192.0		0.67		
291.0	4996.8	5.82		474.0		0.61		
168.0	4996.8	3.36	4.72	330.0	438.5	0.51	0.54	5.1
249.0	4996.8	4.98		511.5		0.49		
256.6	4996.8	5.13		444.0		0.58		
220.5	4996.8	4.41	5.12	361.5	412.5	0.61	0.63	4.77
295.5	4996.8	5.81		432.0		0.69		
87.7	4996.8	1.75		135.0		0.65		
122.1	4996.8	2.44	2.22	144.0	152.0	0.85	0.73	4.99
123.0	4996.8	2.46		177.0		0.69		
167.4	4996.8	3.35		303.0		0.59		
148.7	4996.8	2.97	3.08	311.3	315.6	0.48	0.50	5.94
145.7	4996.8	2.91		332.6		0.44		
120.3	4996.8	2.41		148.0		0.83		
134.4	4996.8	2.69	2.35	103.0	119.0	1.30	1.02	9.04
98.2	4996.8	1.96		106.0		0.93		
308.0	4996.8	6.16		211.5		1.46		
138.5	4996.8	2.77	5.30	86.0	181.2	1.61	1.50	12.6
348.2	4996.8	6.96		246.0		1.42		

;. ;let issue g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.09	2.7	3.5	0.026	0.76	0.226	0.237	379,747
0.068	3.5	3.3	0.021	1.07	0.349	0.366	185,792
0.241	4.9	4.25	0.056	1.13	0.262	0.275	876,364
0.244	4.5	10.2	0.024	0.444	0.328	0.344	709,302
0.111	4.9	5.0	0.022	0.98	0.401	0.421	263,658
0.183	5.7	5.9	0.031	0.97	0.226	0.237	772,152
0.212	8.8	5.5	0.039	1.61	0.681	0.715	296,503
0.668	11.9	7.3	0.092	1.73	1.234	1.296	513,846

No.	Sex.	Age.	Part of pan-creas.	No. fields.	No. islets.	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
17	F	7 mths.	H	15	275	4.49	1.12	516.64	128.9
			B	15	308	4.49	1.32	516.64	151.8
			T	8	234	4.50	0.93	516.64	106.8
18	F	7 mths.	H	11	179	4.62	0.80	516.64	89.5
			B	13	230	4.87	1.28	516.64	135.8
			T	8	154	4.60	0.69	516.64	77.5
19	F	8 mths.	H	13	233	4.57	2.04	516.64	230.6
			B	12	211	4.47	1.42	516.64	164.1
			T	13	246	4.47	1.56	516.64	180.3
20	M	8 mths.	H	10	227	4.54	1.57	516.64	178.7
			B	15	217	4.56	1.08	516.64	122.4
			T	15	272	4.55	1.44	516.64	163.5
21	F	9 mths.	H	15	210	4.79	1.70	516.64	183.4
			B	15	230	4.79	2.06	516.64	222.2
			T	15	109	4.53	1.04	516.64	118.6
22	M	9 mths.	H	15	331	4.74	1.22	516.64	133.0
			B	16	282	4.89	0.99	516.64	104.6
			T	12	291	4.92	1.13	516.64	118.7
23	F	10 mths.	H	13	225	4.57	1.87	516.64	211.4
			B	15	251	4.63	1.84	516.64	205.3
			T	10	164	4.63	1.47	516.64	164.0
24	M	10 mths.	H	12	189	4.71	1.14	516.64	125.0
			B	10	153	4.80	1.35	516.64	145.3
			T	10	154	4.73	1.47	516.64	160.6

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
128.9	4996.8	2.58		275.0		0.47		
151.8	4996.8	3.04	3.20	308.0	340.6	0.49	0.47	6.2
199.5	4996.8	3.99		438.8		0.46		
121.5	4996.8	2.43		244.5		0.50		
156.0	4996.8	3.12	2.82	265.5	266.5	0.59	0.53	3.65
145.5	4996.8	2.91		289.5		0.50		
265.5	4996.8	5.31		268.5		0.99		
205.2	4996.8	4.10	4.53	263.8	272.4	0.78	0.83	4.42
208.5	4996.8	4.17		285.0		0.73		
268.1	4996.8	5.36		340.5		0.79		
122.4	4996.8	2.45	3.69	217.0	276.5	0.56	0.45	12.78
163.5	4996.8	3.27		272.0		0.60		
183.4	4996.8	3.67		210.0		0.87		
222.2	4996.8	4.44	3.49	230.0	183.0	0.97	0.98	13.23
118.6	4996.8	2.37		109.0		1.09		
133.0	4996.8	2.66		331.0		0.40		
98.0	4996.8	1.96	2.53	264.0	320.0	0.37	0.39	7.33
148.5	4996.8	2.97		364.0		0.41		
244.5	4996.8	4.89		259.5		0.94		
205.3	4996.8	4.12	4.64	251.0	252.2	0.82	0.92	11.9
246.0	4996.8	4.92		246.0		1.00		
156.0	4996.8	3.12		236.3		0.66		
217.5	4996.8	4.35	4.10	229.5	232.3	0.95	0.88	10.32
241.5	4996.8	4.83		231.0		1.04		

t. slet issue n g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.198	6.0	5.1	0.039	1.18	0.209	0.220	900,000
0.103	3.6	5.0	0.021	0.71	0.242	0.254	405,512
0.200	4.2	5.5	0.038	0.76	0.484	0.508	393,701
0.472	12.3	6.5	0.073	1.87	0.193	0.203	2,325,123
0.462	12.8	9.5	0.049	1.34	0.648	0.680	679,412
0.186	7.14	7.7	0.024	0.95	0.161	0.169	1,100,592
0.552	11.45	6.7	0.082	1.7	0.578	0.607	909,390
0.423	9.9	9.6	0.044	1.03	0.545	0.572	739,510

No	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
25	F	1 yr.	H	15	149	4.92	1.03	516.64	108.2
			B	15	119	4.68	0.59	516.64	65.1
			T	15	146	4.74	1.12	516.64	122.6
26	F	1 yr.	H	-	-	-	-	-	-
			B	15	141	4.89	1.34	516.64	141.6
			T	15	183	4.65	1.31	516.64	145.5
27	M	1 yr.	H	15	214	4.57	0.90	516.64	101.7
			B	12	217	4.55	1.52	516.64	172.6
			T	5	82	4.56	0.55	516.64	62.3
28	F	1 yr. 1 mth.	H	-	-	-	-	-	-
			B	10	154	4.54	1.33	516.64	149.8
			T	15	131	4.58	1.03	516.64	113.7
29	F	1 yr. 1 mth.	H	15	175	4.58	1.52	516.64	171.5
			B	15	178	4.61	1.31	516.64	146.8
			T	12	154	4.60	1.39	516.64	156.1
30	F	1 yr. 2 mths.	H	15	232	4.81	1.03	516.64	110.6
			B	7	230	4.91	1.42	516.64	149.4
			T	8	273	4.84	1.36	516.64	145.4
31	M	1 yr. 3 mths.	H	15	236	4.49	1.28	516.64	147.3
			B	15	199	4.44	1.22	516.64	142.0
			T	14	200	4.49	1.65	516.64	189.9
32	F	1 yr. 3 mths.	H	15	212	4.71	1.39	516.64	152.5
			B	15	155	4.64	1.25	516.64	139.2
			T	6	185	4.84	1.55	516.64	165.5

rea slets 5 fields n sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
168.2	4996.8	2.16		149.0		0.69		
65.1	4996.8	1.30	1.97	119.0	138.0	0.55	0.69	9.02
122.6	4996.8	2.45		146.0		0.84		
-	-	-		-		-		-
141.6	4996.8	2.83	2.87	141.0	162.0	1.00	1.90	7.42
145.5	4996.8	2.91		183.0		0.80		
101.7	4996.8	2.03		214.0		0.48		
216.0	4996.8	4.32	3.36	270.0	243.3	0.80	0.68	9.96
186.9	4996.8	3.74		246.0		0.76		
-	-	-		-		-		
225.0	4996.8	4.50	3.39	231.0	181.0	0.97	0.92	12.8
113.7	4996.8	2.27		131.0		0.87		
171.5	4996.8	3.43		175.0		0.98		
146.8	4996.8	2.94	3.42	178.0	181.7	0.84	0.94	9.83
195.0	4996.8	3.90		192.0		0.01		
110.6	4996.8	2.21		232.0		0.48		
319.5	4996.8	6.39	4.69	495.0	412.8	0.65	0.55	8.70
273.0	4996.8	5.46		511.5		0.53		
147.3	4996.8	2.95		236.0		0.62		
142.0	4996.8	2.84	3.29	199.0	216.4	0.71	0.76	8.1
204.0	4996.8	4.08		214.3		0.95		
152.5	4996.8	3.05		212.0		0.72		
139.2	4996.8	2.78	4.70	155.0	277.3	0.90	0.84	13.15
414.0	4996.8	8.28		465.0		0.90		

.et sue g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
.178	8.8	6.9	0.026	1.28	0.373	0.392	454,082
0.213	7.2	7.4	0.029	0.97	1.730	1.817	117,226
0.33	9.6	9.1	0.037	1.06	0.373	0.392	841,837
0.43	12.4	7.7	0.056	1.6	0.578	0.607	708,402
0.34	9.5	9.1	0.037	1.04	0.611	0.642	529,595
0.408	8.3	6.6	0.062	1.26	0.262	0.275	1,483,638
0.267	7.8	7.8	0.034	1.0	0.426	0.447	597,315
0.618	12.5	8.2	0.075	1.52	0.613	0.644	959,627

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
33	F	1 yr. 5 mths.	H	15	220	4.56	1.65	516.64	186.0
			B	15	180	4.57	1.21	516.64	139.5
			T	12	209	4.55	1.44	516.64	165.3
34	F	1 yr. 5 mths.	H	10	116	4.59	1.66	516.64	186.8
			B	10	121	4.63	1.69	516.64	188.6
			T	9	161	4.64	1.83	516.64	203.8
35	M	1 yr. 6 mths.	H	15	207	4.64	0.86	516.64	95.8
			B	15	163	4.64	0.64	516.64	71.3
			T	12	235	4.66	1.42	516.64	174.3
36	M	1 yr. 9 mths.	H	8	236	4.69	1.30	516.64	143.2
			B	15	146	4.99	0.58	516.64	60.1
			T	15	229	4.70	0.94	516.64	103.3
37	F	2 yrs. 1 mth.	H	15	48	4.82	0.41	516.64	43.9
			B	15	43	4.82	0.43	516.64	46.1
			T	15	46	4.80	0.39	516.64	42.0
38	M	2 yrs. 2 mths.	H	15	137	4.60	1.68	516.64	188.7
			B	15	132	4.59	1.09	516.64	122.7
			T	15	155	4.61	1.63	516.64	182.7
39	M	2 yrs. 3 mths.	H	12	181	4.57	1.36	516.64	149.8
			B	15	156	4.57	1.43	516.64	160.2
			T	13	152	4.53	1.53	516.64	174.5
40	M	2 yrs. 6 mths.	H	8	211	4.52	1.93	516.64	220.6
			B	15	101	4.50	0.87	516.64	99.9
			T	15	275	4.49	1.90	516.64	218.6

ea lets fields sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
186.0	4996.8	3.72		220.0		0.85		
139.5	4996.8	2.79	3.55	180.0	220.3	0.78	0.81	17.6
207.0	4996.8	4.14		261.0		0.79		
280.2	4996.8	5.60		174.0		1.61		
282.9	4996.8	5.66	6.02	181.5	214.5	1.56	1.48	11.89
339.5	4996.8	6.79		268.0		1.27		
95.8	4996.8	1.92		207.0		0.46		
71.3	4996.8	1.43	2.57	163.0	221.3	0.43	0.54	8.45
217.9	4996.8	4.36		293.8		0.74		
268.5	4996.8	5.37		442.5		0.61		
60.1	4996.8	1.20	2.88	146.0	272.5	0.41	0.49	14.49
103.3	4996.8	2.06		229.0		0.45		
43.9	4996.8	0.88		48.0		0.91		
46.1	4996.8	0.92	0.88	43.0	45.7	1.07	0.96	13.64
42.0	4996.8	0.84		46.0		0.91		
188.7	4996.8	3.77		137		1.38		
122.7	4996.8	2.45	3.29	132	141.3	0.93	1.16	19.3
182.7	4996.8	3.65		155		1.18		
187.5	4996.8	3.75		226.5		0.83		
160.2	4996.8	3.20	3.66	156.0	186.0	1.03	1.00	21.56
201.0	4996.8	4.02		175.5		1.15		
414.0	4996.8	8.28		395.6		1.05		
99.9	4996.8	2.00	4.88	101.0	257.2	0.99	0.94	15.6
218.6	4996.8	4.37		275.0		0.79		

t. slet issue n g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.62	17.0	10.3	0.061	1.65	0.484	0.508	1,220,472
0.71	11.2	8.9	0.080	1.26	1.181	1.240	572,581
0.217	8.23	9.4	0.023	0.88	0.242	0.254	854,331
0.418	14.1	10.8	0.039	1.30	0.226	0.237	1,763,713
0.120	13.5	10.6	0.011	1.28	0.648	0.680	176,471
0.635	18.7	12.7	0.050	1.47	0.800	0.840	755,952
0.78	20.8	9.9	0.080	2.10	0.681	0.715	1,090,909
0.761	14.8	12.2	0.062	1.22	0.611	0.642	1,185,358

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
41	M	3 yrs.	H	15	130	4.69	1.08	516.64	119.0
			B	15	54	4.67	1.32	516.64	35.3
			T	15	125	4.67	0.92	516.64	101.8
42	F	5 yrs.	H	15	94	4.78	0.76	516.64	82.1
			B	15	73	4.80	0.44	516.64	47.4
			T	15	111	4.76	0.86	516.64	93.3
43	M	5 yrs.	H	16	185	4.72	1.04	516.64	113.8
			B	15	159	4.74	0.98	516.64	106.8
			T	15	104	4.72	0.75	516.64	82.1
44	M	5 yrs.	H	15	132	4.68	0.87	516.64	96.3
			B	15	124	4.69	1.13	516.64	124.5
			T	15	144	4.71	1.36	516.64	149.2
45	M	6 yrs.	H	15	171	4.68	1.08	516.64	119.9
			B	15	79	4.64	0.77	516.64	85.7
			T	15	93	4.63	1.22	516.64	136.1
46	M	6 yrs.	H	15	220	4.68	1.17	516.64	129.2
			B	15	137	4.68	0.57	516.64	62.9
			T	15	195	4.69	0.90	516.64	99.1
47	F	6 yrs.	H	10	292	4.71	1.25	516.64	137.1
			B	15	182	4.66	1.41	516.64	156.3
			T	15	172	4.67	1.66	516.64	183.6
48	M	7 yrs.	H	15	72	4.79	0.46	516.64	49.6
			B	15	68	4.77	0.39	516.64	42.2
			T	15	78	4.78	0.63	516.64	68.1

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
119.0	4996.8	2.38		130		0.92		
35.3	4996.8	0.71	1.71	54	103.0	0.65	0.79	12.76
101.8	4996.8	2.04		125		0.81		
82.1	4996.8	1.64		94		0.87		
47.4	4996.8	0.95	1.49	73	92.7	0.65	0.75	28.6
93.3	4996.8	1.87		111		0.84		
106.7	4996.8	2.13		173.4		0.66		
106.8	4996.8	2.14	1.97	159.0	145.5	0.67	0.71	19.6
82.1	4996.8	1.64		104.0		0.79		
96.3	4996.8	1.93		132		0.73		
124.5	4996.8	2.49	2.47	124	133.3	1.00	0.92	24.3
149.2	4996.8	2.98		144		1.04		
119.9	4996.8	2.40		171		0.70		
85.7	4996.8	1.71	2.61	79	114.3	1.08	1.08	23.0
136.1	4996.8	3.72		93		1.46		
129.2	4996.8	2.58		220		0.59		
62.9	4996.8	1.26	1.94	137	150.7	0.46	0.52	20.6
99.1	4996.8	1.98		195		0.51		
205.5	4996.8	4.11		438		0.47		
156.3	4996.8	3.13	3.64	182	264.0	0.86	0.80	22.7
183.6	4996.8	3.67		172		1.07		
49.6	4996.8	0.99		72		0.69		
42.2	4996.8	0.84	1.06	68	72.7	0.62	0.73	42.1
68.1	4996.8	1.36		78		0.87		

Wt. Islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.218	12.54	10.6	0.021	1.19	0.453	0.476	457,983
0.43	28.2	16	0.027	1.76	0.426	0.447	961,969
0.39	19.2	15.5	0.025	1.24	0.401	0.421	926,366
0.60	23.7	16	0.038	1.48	0.578	0.607	988,468
0.60	22.4	14	0.043	1.60	0.722	0.758	791,557
0.40	20.2	20.5	0.020	0.99	0.242	0.254	1,574,803
0.83	21.9	15.5	0.054	1.41	0.451	0.478	1,736,402
0.45	41.75	17.0	0.026	2.45	0.401	0.421	1,068,884

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
49	M	10 yrs.	H	15	156	4.64	0.80	516.64	89.1
			B	15	89	4.66	0.70	516.64	77.6
			T	15	118	4.64	0.68	516.64	75.7
50	F	13 yrs.	H	15	129	4.92	1.15	516.64	120.8
			B	15	74	4.92	0.92	516.64	96.6
			T	15	81	4.95	1.43	516.64	149.3
51	M	13 yrs.	H	15	34	4.55	0.18	516.64	20.4
			B	15	47	4.57	0.43	516.64	48.6
			T	15	47	4.56	0.62	516.64	70.2
52	M	13 yrs.	H	15	138	4.68	0.83	516.64	91.6
			B	15	123	4.74	0.87	516.64	94.8
			T	15	153	4.66	1.54	516.64	170.7
53	F	14 yrs.	H	15	81	4.81	0.74	516.64	79.5
			B	15	46	4.76	0.43	516.64	46.7
			T	15	38	4.79	0.30	516.64	32.4
54	M	14 yrs.	H	15	52	4.69	0.47	516.64	51.8
			B	-	-	-	-	-	-
			T	15	40	4.67	0.69	516.64	76.3
55	F	15 yrs.	H	15	117	4.94	1.43	516.64	149.6
			B	15	86	4.70	1.13	516.64	120.0
			T	15	100	4.95	1.75	516.64	182.6
56	M	15 yrs.	H	15	66	4.76	0.82	516.64	89.0
			B	15	63	4.74	0.65	516.64	70.8
			T	15	84	4.74	0.92	516.64	100.3

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
89.1	4996.8	1.78		156		0.57		
77.6	4996.8	1.55	1.61	89	121.0	0.87	0.69	21.4
75.7	4996.8	1.51		118		0.64		
120.8	4996.8	2.42		129		0.94		
96.6	4996.8	1.93	2.45	74	94.7	1.31	1.33	28.6
149.3	4996.8	2.99		81		1.84		
20.4	4996.8	0.41		34		0.60		
48.6	4996.8	0.97	0.93	47	32.0	1.03	1.03	58.8
70.2	4996.8	1.40		47		1.49		
91.6	4996.8	1.83		138		0.66		
94.8	4996.8	1.90	2.38	123	138.0	0.77	0.85	44.6
170.7	4996.8	3.41		153		1.12		
79.5	4996.8	1.59		81		0.98		
46.7	4996.8	0.93	1.06	46	53.0	1.01	0.95	55.5
32.4	4996.8	0.65		38		0.85		
51.8	4996.8	1.04		52		1.00		
-	-	-	1.29	-	46.0	-	1.46	56.6
76.3	4996.8	1.53		40		1.91		
149.6	4996.8	2.99		117		1.28		
120.0	4996.8	2.40	3.01	86	101.0	1.40	1.50	40.5
182.6	4996.8	3.65		100		1.83		
89.0	4996.8	1.78		66		1.35		
70.8	4996.8	1.42	1.74	63	71.0	1.12	1.22	35.1
100.3	4996.8	2.01		84		1.19		

Wt. Islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.μ.	Wt. of one islet in γ	Total No. of islets
0.35	21.0	25.5	0.014	0.81	0.328	0.344	1,017,442
0.70	27.9	25	0.028	1.12	0.976	1.025	679,612
0.55	58.2	33	0.017	1.76	0.681	0.715	783,217
1.06	43.5	52.5	0.020	0.83	0.613	0.644	1,645,963
0.59	54.9	34.0	0.017	1.62	0.610	0.643	917,574
0.73	55.9	46.5	0.016	1.20	1.128	1.184	618,644
1.22	39.3	37.0	0.033	1.06	1.181	1.240	983,871
0.61	34.5	40.5	0.015	0.85	0.886	0.930	655,914

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
57	F	15 yrs.	H	15	87	4.79	0.69	516.64	74.4
			B	15	74	4.72	0.76	516.64	83.2
			T	15	112	4.75	1.09	516.64	118.6
58	F	15 yrs.	H	15	58	4.79	0.31	516.64	33.5
			B	15	46	4.77	0.52	516.64	56.3
			T	15	113	4.78	0.83	516.64	89.8
59	F	15 yrs.	H	15	68	4.74	0.90	516.64	98.1
			B	15	49	4.71	0.65	516.64	71.3
			T	15	68	4.68	0.96	516.64	106.0
60	F	16 yrs.	H	15	64	4.72	0.37	516.64	40.5
			B	15	63	4.76	0.59	516.64	64.0
			T	15	80	4.73	0.73	516.64	79.7
61	M	18 yrs.	H	15	47	4.63	0.47	516.64	52.4
			B	15	35	4.68	0.45	516.64	49.7
			T	15	59	4.61	0.82	516.64	91.9
62	F	18 yrs.	H	15	44	4.73	0.74	516.64	80.8
			B	15	53	4.77	0.52	516.64	56.3
			T	15	72	4.70	0.99	516.64	108.8
63	F	18 yrs.	H	15	52	4.77	0.42	516.64	45.5
			B	15	54	4.75	0.41	516.64	44.6
			T	15	37	4.54	0.40	516.64	45.5
64	F	19 yrs.	H	15	33	4.98	0.32	516.64	33.2
			B	15	51	4.98	0.59	516.64	61.2
			T	15	80	4.97	0.94	516.64	97.7

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
74.4	4996.8	1.49		87		0.86		
83.2	4996.8	1.66	1.84	74	91.0	1.12	1.01	46.2
118.6	4996.8	2.37		112		1.06		
33.5	4996.8	0.67		58		0.58		
56.3	4996.8	1.13	1.20	46	72.3	1.22	0.86	51.8
89.8	4996.8	1.80		113		0.79		
98.1	4996.8	1.96		68		1.44		
71.3	4996.8	1.43	1.83	49	61.7	1.46	1.49	78.3
106.0	4996.8	2.12		68		1.56		
40.5	4996.8	0.81		64		0.63		
64.0	4996.8	1.28	1.23	63	69.0	1.02	0.88	50.2
79.7	4996.8	1.59		80		1.00		
52.4	4996.8	1.05		47		1.11		
49.7	4996.8	0.99	1.29	35	47.0	1.42	1.36	59.9
91.9	4996.8	1.84		59		1.56		
80.8	4996.8	1.62		44		1.84		
56.3	4996.8	1.13	1.64	53	56.3	1.06	1.47	79.8
108.8	4996.8	2.81		72		1.51		
45.5	4996.8	0.91		52		0.88		
44.6	4996.8	0.89	0.90	54	47.7	0.83	0.98	49.0
45.5	4996.8	0.91		37		1.23		
33.2	4996.8	0.66		33		1.01		
61.2	4996.8	1.22	1.28	51	54.7	1.20	1.14	44.7
97.7	4996.8	1.95		80		1.22		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.μ.	Wt. of one islet in γ	Total No. of islets
0.85	45.3	48.0	0.017	0.94	0.681	0.715	1,188,951
0.62	51.2	40.5	0.015	1.26	0.613	0.644	962,733
1.43	76.9	43.5	0.033	1.77	1.181	1.240	1,153,226
0.62	49.6	42.0	0.015	1.18	0.545	0.572	1,083,916
0.77	59.1	33.0	0.023	1.79	1.025	1.076	712,963
1.31	78.5	50.0	0.026	1.57	1.181	1.240	1,056,532
0.44	48.6	50.0	0.009	0.97	0.648	0.680	647,059
0.57	44.1	49.5	0.011	0.89	0.800	0.840	678,571

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheeting.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
65	M	19 yrs.	H	15	84	4.78	0.50	516.64	54.0
			B	15	75	4.78	0.46	516.64	49.7
			T	15	76	4.76	0.64	516.64	69.5
66	F	19 yrs.	H	15	78	4.69	0.83	516.64	91.4
			B	15	54	4.79	0.82	516.64	88.4
			T	15	90	4.81	0.80	516.64	85.9
67	F	20 yrs.	H	15	71	4.54	0.57	516.64	64.8
			B	15	67	4.54	0.67	516.64	76.2
			T	15	109	4.55	1.06	516.64	120.4
68	F	21 yrs.	H	15	81	4.68	1.10	516.64	121.4
			B	15	78	4.71	1.16	516.64	127.2
			T	15	111	4.71	1.74	516.64	190.9
69	F	22 yrs.	H	15	61	4.72	1.05	516.64	114.0
			B	15	61	4.75	0.98	516.64	106.6
			T	15	95	4.76	1.23	516.64	133.3
70	F	23 yrs.	H	15	64	4.87	0.54	516.64	57.3
			B	15	35	4.83	0.34	516.64	36.4
			T	15	45	4.84	0.42	516.64	44.8
71	M	24 yrs.	H	15	50	4.64	1.03	516.64	112.5
			B	15	55	4.67	0.61	516.64	67.5
			T	15	41	4.61	1.49	516.64	167.0
72	M	24 yrs.	H	15	138	4.69	0.80	516.64	88.1
			B	15	100	4.86	0.78	516.64	82.9
			T	15	109	4.71	0.83	516.64	91.0

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
54.0	4996.8	1.08		84		0.64		
49.7	4996.8	0.99	1.15	75	78.3	0.66	0.74	90.4
69.5	4996.8	1.39		76		0.91		
91.4	4996.8	1.83		78		1.17		
88.4	4996.8	1.77	1.77	54	74.0	1.64	1.25	52.0
85.9	4996.8	1.72		90		0.95		
64.8	4996.8	1.30		71		0.91		
76.2	4996.8	1.52	1.74	67	82.3	1.14	1.05	77.5
120.4	4996.8	2.41		109		1.10		
121.4	4996.8	2.43		81		1.50		
127.2	4996.8	2.54	2.93	78	90.0	1.63	1.62	61.6
190.9	4996.8	3.82		111		1.72		
114.9	4996.8	2.30		61.0		1.88		
106.9	4996.8	2.13	2.34	61.0	72.3	1.75	1.68	88.0
133.3	4996.8	2.60		95.0		1.40		
57.3	4996.8	1.15		64		0.90		
36.4	4996.8	0.73	0.93	35	48.0	1.04	0.98	52.9
44.8	4996.8	0.90		45		1.00		
112.5	4996.8	2.25		50		2.25		
67.5	4996.8	1.35	2.31	55	48.6	1.23	2.52	100.5
167.0	4996.8	3.34		41		4.07		
88.1	4996.8	1.76		138		0.64		
82.9	4996.8	1.66	1.75	100	115.6	0.83	0.77	63.0
91.0	4996.8	1.82		109		0.83		

t. slet issue n g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
1.04	89.4	64.5	0.016	1.39	0.426	0.447	232,662
0.92	51.1	48.0	0.019	1.06	0.931	0.978	940,695
1.35	76.1	57.5	0.023	1.32	0.681	0.715	1,888,112
1.81	59.8	50.0	0.036	1.20	1.349	1.416	1,274,648
2.06	85.9	50.5	0.041	1.70	1.406	1.476	1,391,892
0.49	52.4	43.0	0.011	1.22	0.648	0.680	720,588
2.32	98.2	48.0	0.048	2.05	2.608	2.738	846,715
1.10	61.9	38.0	0.029	1.63	0.455	0.478	2,301,255

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets.	Wt. sheet in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
73	F	24 yrs.	H	15	45	4.92	0.80	516.64	84.0
			B	15	47	4.69	0.57	516.64	62.8
			T	15	54	4.93	0.89	516.64	93.3
74	F	25 yrs.	H	15	58	4.68	0.56	516.64	61.8
			B	15	46	4.68	0.61	516.64	67.3
			T	15	75	4.72	1.14	516.64	124.8
75	F	25 yrs.	H	15	17	4.77	0.17	516.64	18.4
			B	15	35	4.89	0.41	516.64	43.3
			T	15	37	4.73	0.32	516.64	32.8
76	M	28 yrs.	H	15	73	4.70	0.57	516.64	62.6
			B	15	56	4.63	0.27	516.64	30.1
			T	15	30	4.64	0.42	516.64	46.8
77	M	28 yrs.	H	15	29	4.65	0.30	516.64	33.3
			B	15	54	4.64	1.04	516.64	115.8
			T	15	62	4.71	0.87	516.64	95.4
78	F	28 yrs.	H	15	21	4.89	0.42	516.64	44.4
			B	15	39	4.62	0.65	516.64	72.7
			T	15	69	4.92	1.59	516.64	167.0
79	M	33 yrs.	H	15	55	4.61	0.68	516.64	76.3
			B	15	65	4.65	1.10	516.64	122.2
			T	15	65	4.64	1.31	516.64	145.9
80	F	35 yrs.	H	15	65	4.76	0.29	516.64	31.5
			B	15	76	4.75	0.50	516.64	54.4
			T	15	64	4.72	0.48	516.64	52.5

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
84.0	4996.8	1.68		45		1.87		
62.8	4996.8	1.26	1.60	47	38.7	1.34	1.65	45.0
93.3	4996.8	1.87		54		1.73		
61.8	4996.8	1.24		58		1.07		
67.3	4996.8	1.35	1.70	46	59.7	1.46	1.40	49.5
124.8	4996.8	2.50		75		1.67		
18.4	4996.8	0.37		17		1.08		
43.3	4996.8	0.87	0.63	35	29.7	1.24	1.07	88.0
32.8	4996.8	0.66		37		0.89		
62.6	4996.8	1.25		73		0.86		
30.1	4996.8	0.60	0.93	56	53.0	0.54	0.99	61.2
46.8	4996.8	0.94		30		1.56		
33.3	4996.8	0.67		29		1.15		
115.8	4996.8	2.32	1.63	54	48.3	2.14	1.61	79.1
95.4	4996.8	1.91		62		1.54		
44.4	4996.8	0.84		21		2.11		
72.7	4996.8	1.45	1.88	39	43.0	1.86	2.13	67.0
167.0	4996.8	3.34		69		2.42		
76.3	4996.8	1.53		55		1.39		
122.2	4996.8	2.44	2.30	65	61.6	1.88	1.84	79.5
145.9	4996.8	2.92		65		2.25		
31.5	4996.8	0.63		65		0.49		
54.4	4996.8	1.09	0.92	76	68.3	0.72	0.68	67.6
52.5	4996.8	1.05		64		0.82		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. in g.	Volume of one islet in c.u.	Wt. of one islet in	Total No. of islets
0.72	44.3	37.0	0.019	1.20	1.406	1.476	486,486
0.84	48.7	44.0	0.019	1.11	1.074	1.128	743,363
0.55	87.4	46.0	0.012	1.90	0.722	0.758	725,594
0.57	60.6	56.0	0.010	1.08	0.681	0.715	797,203
1.29	77.8	55.0	0.023	1.42	1.287	1.351	955,555
1.26	65.7	53.0	0.024	1.24	2.021	2.122	594,340
1.829	77.7	52.0	0.035	1.49	1,661	1.744	1,0[illegible]1,149
0.62	67.0	60.0	0.010	1.12	0.373	0.392	1,581,633

No.	Sex.	Age.	Part of pan-creas	No. fields	No. islets	Wt. sheets in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
81	F	39yrs.	H	15	47	4.95	0.60	516.64	62.6
			B	15	29	4.95	0.25	516.64	26.1
			T	15	70	4.94	0.65	516.64	68.0
82	F	39 yrs.	H	15	45	4.63	0.66	516.64	73.6
			B	15	37	4.65	0.60	516.64	66.7
			T	15	41	4.62	0.86	516.64	96.2
83	M	40 yrs.	H	15	59	4.76	0.69	516.64	74.9
			B	15	61	4.76	0.75	516.64	81.4
			T	15	60	4.76	0.48	516.64	52.1
84	F	40 yrs.	H	15	43	4.88	0.55	516.64	58.2
			B	15	56	4.65	0.64	516.64	71.1
			T	15	71	4.90	1.40	516.64	147.6
85	F	40 yrs.	H	15	88	4.98	1.22	516.64	126.6
			B	15	81	4.99	1.25	516.64	129.4
			T	15	87	5.04	1.55	516.64	158.9
86	F	41 yrs.	H	15	17	4.81	0.14	516.64	15.0
			B	15	13	4.85	0.16	516.64	17.0
			T	15	34	4.79	0.46	516.64	49.6
87	F	41 yrs.	H	15	62	4.75	0.68	516.64	74.0
			B	15	51	4.76	1.06	516.64	115.1
			T	15	108	4.79	1.42	516.64	153.2
88	F	42 yrs.	H	15	24	4.78	0.29	516.64	31.3
			B	15	18	4.95	0.34	516.64	35.5
			T	15	29	4.95	0.28	516.64	29.2

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
62.6	4996.8	1.35		47		1.33		
26.1	4996.8	0.52	1.08	29	48.7	0.90	1.07	76.1
68.0	4996.8	1.36		70		0.97		
73.6	4996.8	1.47		45		1.64		
66.7	4996.8	1.33	1.57	37	31.0	1.80	1.93	88.0
96.2	4996.8	1.92		41		2.35		
74.9	4996.8	1.50		59		1.24		
81.4	4996.8	1.63	1.39	61	60.0	1.34	1.15	79.8
52.1	4996.8	1.04		60		0.87		
58.2	4996.8	1.16		43		1.35		
71.1	4996.8	1.42	1.84	56	56.7	1.27	1.90	66.0
147.6	4996.8	2.95		71		2.68		
126.6	4996.8	2.53		88		1.43		
129.4	4996.8	2.59	2.77	81	85.3	1.60	1.62	41.8
158.9	4996.8	3.18		87		1.83		
15.0	4996.8	0.30		17		0.82		
17.0	4996.8	0.34	0.54	13	21.3	1.31	1.20	58.6
49.6	4996.8	0.99		34		1.46		
74.0	4996.8	1.48		62		1.03		
115.1	4996.8	2.30	2.28	51	73.7	2.26	1.57	50.3
153.2	4996.8	3.06		108		1.42		
31.3	4996.8	0.63		24		1.30		
35.5	4996.8	0.71	0.64	18	23.7	1.97	1.43	58.6
29.2	4996.8	0.58		29		1.01		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.μ.	Wt. of one islet in γ	Total No. of islets
0.82	75.3	48.5	0.017	1.55	0.722	0.758	1,081,794
1.38	86.6	37.0	0.037	2.34	1.730	1.817	758,242
1.11	78.7	46.0	0.024	1.71	0.800	0.840	1,321,429
1.21	64.8	51.0	0.024	1.27	1.730	1.817	664,835
1.16	40.6	40.5	0.029	1.00	1.349	1.416	816,901
0.32	58.3	43.0	0.007	1.35	0.886	0.930	344,086
1.15	49.1	53.0	0.022	0.93	1.287	1.351	851,852
0.38	58.2	36.0	0.010	1.62	1.128	1.184	322,034

No	Sex	Age	Part of pan-creas	No. fields	No. islets	Wt. sheets in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
89	M	44 yrs.	H	15	31	4.96	0.31	516.64	32.3
			B	15	38	4.72	0.46	516.64	50.4
			T	15	11	4.94	0.12	516.64	12.5
90	F	47 yrs.	H	15	61	4.67	1.24	516.64	137.2
			B	15	34	4.66	0.60	516.64	66.5
			T	15	60	4.64	0.96	516.64	106.9
91	M	49 yrs.	H	15	62	4.83	0.98	516.64	104.8
			B	15	51	4.83	0.87	516.64	93.1
			T	15	47	4.88	0.67	516.64	70.9
92	M	50 yrs.	H	15	50	4.56	0.56	516.64	63.4
			B	15	38	4.55	0.43	516.64	48.8
			T	15	60	4.52	0.71	516.64	81.2
93	F	50 yrs.	H	15	80	4.97	0.77	516.64	79.7
			B	15	68	4.95	0.73	516.64	76.2
			T	15	76	4.70	1.13	516.64	124.2
94	F	50 yrs.	H	15	46	4.69	0.40	516.64	44.1
			B	15	36	4.68	0.50	516.64	55.2
			T	15	48	4.73	0.74	516.64	80.8
95	F	52 yrs.	H	15	106	4.95	1.34	516.64	139.9
			B	15	69	4.96	1.02	516.64	106.2
			T	15	95	5.01	1.55	516.64	159.8
96	M	56 yrs.	H	15	68	4.95	0.60	516.64	62.6
			B	15	78	4.98	0.56	516.64	58.1
			T	15	102	4.95	1.39	516.64	145.1

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av. area one islet in sq.cm.		Wt. pancreas in g.
32.3	4996.8	0.65		31		1.04		
50.4	4996.8	1.01	0.64	38	26.7	1.33	1.17	70.0
12.5	4996.8	0.25		11		1.14		
137.2	4996.8	2.74		61		2.25		
66.5	4996.8	1.33	2.07	34	51.7	1.96	2.00	61.9
106.9	4996.8	2.14		60		1.78		
104.8	4996.8	2.10		62		1.68		
93.1	4996.8	1.86	1.79	51	53.3	1.83	1.68	56.5
70.9	4996.8	1.42		47		1.51		
63.4	4996.8	1.27		50		1.27		
48.8	4996.8	0.98	1.29	38	49.3	1.28	1.27	74.5
81.2	4996.8	1.62		60		1.35		
79.7	4996.8	1.59		80		1.00		
76.2	4996.8	1.52	1.86	68	74.7	1.12	1.25	74.7
124.2	4996.8	2.48		76		1.63		
44.1	4996.8	0.88		46		0.96		
55.2	4996.8	1.10	1.20	36	43.3	1.53	1.39	67.2
80.8	4996.8	1.62		48		1.68		
139.9	4996.8	2.80		106		1.32		
106.2	4996.8	2.12	2.71	69	90.0	1.54	1.51	46.3
159.8	4996.8	3.20		95		1.68		
62.6	4996.8	1.25		68		0.92		
58.1	4996.8	1.16	1.77	78	82.7	0.74	1.03	61.3
145.1	4996.8	2.90		102		1.42		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.μ.	Wt.of one islet in γ	Total No. of islets
0.45	69.5	48.0	0.009	1.45	0.841	0.883	509,627
1.28	60.6	48.0	0.027	1.26	1.874	1.918	666,666
1.01	55.5	49.0	0.021	1.13	1.406	1.476	684,282
0.96	73.5	54.0	0.018	1.36	0.931	0.978	981,595
1.38	73.3	51.0	0.027	1.44	0.931	0.978	1,411,043
0.81	66.4	53.0	0.015	1.25	1.025	1.076	750,000
1.25	45.0	46.0	0.027	0.98	1.181	1.240	1,008,065
1.09	60.2	57.0	0.019	1.06	0.681	0.715	1,524,477

No.	Sex	Age	Part of pan-creas	No. fields	No. islets	Wt. sheets in g.	Wt. islets in g.	Area sheet in sq.cm.	Area islets in sq.cm.
97	M	57 yrs.	H	15	51	4.99	0.51	516.64	52.8
			B	15	48	4.99	0.37	516.64	38.3
			T	15	57	5.00	0.87	516.64	89.9
98	M	57 yrs.	H	15	90	4.72	1.00	516.64	109.5
			B	15	57	4.76	0.75	516.64	81.4
			T	15	89	4.78	0.93	516.64	100.5
99	F	61 yrs.	H	15	72	4.79	0.68	516.64	73.3
			B	15	54	4.76	0.58	516.64	63.0
			T	15	59	4.78	0.40	516.64	43.2
100	M	64 yrs.	H	15	42	4.76	0.47	516.64	51.0
			B	15	73	4.76	0.71	516.64	77.1
			T	15	110	4.75	1.34	516.64	145.7

Area islets 15 fields in sq.cm.	Area pancreas 15 fields in sq.cm.	% area islet tissue in pancreas		No. islets in 15 fields		Av.area one islet in sq.cm.		Wt. pancreas in g.
52.8	4996.8	1.06		51		1.03		
38.3	4996.8	0.77	1.21	48	52.0	0.80	1.14	94.2
89.9	4996.8	1.80		57		1.58		
109.5	4996.8	2.19		90		1.22		
81.4	4996.8	1.63	1.94	57	78.7	1.43	1.26	95.2
100.5	4996.8	2.01		89		1.13		
73.3	4996.8	1.47		72		1.02		
63.0	4996.8	1. 26	1.20	54	61.7	1.16	1.30	71.8
43.2	4996.8	0.86		59		0.73		
51.0	4996.8	1.02		42		1.21		
77.1	4996.8	1.54	1.82	73	75.0	1.06	1.20	63.6
145.7	4996.8	2.91		110		1.33		

Wt. islet tissue in g.	Wt. acinar tissue in g.	Body wt. in kg.	Islet tissue per kg. B.W. in g.	Acinar tissue per kg. B.W. in g.	Volume of one islet in c.μ.	Wt. of one islet in γ	Total No. of islets
1.14	93.1	52.5	0.022	1.77	0.800	0.840	1,357,142
1.85	93.3	64.5	0.029	1.45	0.931	0.978	1,891,616
0.86	70.9	53.5	0.016	1.33	0.930	0.978	879,346
1.16	62.4	49.5	0.023	1.26	0.886	0.930	1,247,312

SECTION II

The Pancreatic Islets in Obese Subjects.

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SECTION II

The Pancreatic Islets in Obese Subjects.

This paper describes an investigation into the condition of the pancreatic islets in obese as compared with control subjects. The obese cases were ordinary overweight individuals with an obvious excess of fat in the subcutaneous, mesenteric and omental regions, while the control subjects were naturally lean people with limited amounts of fat in these areas. Both obese and control cases had an individually sugar-free urine during their residence in hospital and died from an assortment of causes including lobar pneumonia, cerebral abscess and chronic valvular disease. These lethal factors being equally varied in the two groups and of no significance in relation to the present observations are accordingly not considered worthy of further comment. Finally, the investigation, it should be mentioned, was limited to the pancreatic islets and not extended to any of the other endocrine glands.

Materials and Methods

The pancreases investigated were obtained from 19 obese and 19 lean subjects. The obese cases consisted of 17 females and 2 males ranging from 27 to 67 years, while the lean subjects comprised 11 females and 8 males varying between 19 and 67 years. Three blocks of tissue representative of the head, body and tail were taken from each pancreas. These were fixed in Helly's bichromate-sublimate-formalin/

formalin solution and cut in paraffin. The sections were then stained by the azan method.

The percentage area of islet tissue in each pancreas was estimated as follows. The stained section from the head of the organ was fixed into a microscope with the tube placed horizontally instead of vertically. A strong carbon-arc light at the objective end (Watson para $\frac{2}{3}$) and a prism fitted to the eye piece (Watson 4) were then used to cast an image of the section with a magnification of 120 on a sheet of quarto notepaper. Fifteen different unselected fields of the section were, with the help of the movable stage, passed over the sheet and thereon were traced in pencil all the visible pancreatic islets. An estimate of the total area of the islets was made by first weighing the sheet in grams and measuring it in square centimetres : then all the islets were cut out of the sheet with scissors and weighed separately. The ratio

$$\frac{\text{Weight of islet paper}}{\text{Weight of sheet}} : \frac{\text{Area of islet paper}}{\text{Area of sheet}}$$

enabled a calculation of the total area of the islets, being the only unknown. This gave the area of islet tissue in 15 fields of the section. Direct measurement of the radius led to an estimate of the area of one field and so of 15 fields. The data now permitted an easy calculation of the percentage area of islet tissue. The same measurement was similarly carried out in the body and tail of the organ/

organ and so facilitated the determination of an average for the whole pancreas. Other factors obtained were the number of islets in 15 fields and the average area of the islets, of which the latter was determined by dividing the total area by the total number of the islets in 15 fields of the head, body and tail. The calculation of a case is illustrated in Table I.

All the pancreases in the control group and most of those in the obese series showed varying amounts of adiposity. This was sometimes extreme, particularly in the obese group, and caused corresponding separation of the parenchymatous lobules. Now, the included fat was not considered in the above method. It was regarded as parenchyma and so favoured abnormally low estimates of the percentage area of islet tissue and the number of islets in 15 fields. Some adjustment was therefore attempted by determining the percentage area of pure adipose tissue in the head, body and tail of each pancreas in exactly the same way as the percentage area of islet tissue except that the calculation was based on 5 instead of 15 fields. The amounts of fat in the head, body and tail of the pancreas used as an illustration in Table I were thus found to be 32.5, 14 and 12 per cent respectively with the result that 67.5, 86 and 88 per cent respectively were the proportions of pure parenchyma in the corresponding regions of the same organ. The original figures giving the percentage/

Table I.

Calculation of a Case uncorrected for Fat.

Sex and age.	Pancreas	No. of fields	Wt. of sheet in g.	Wt. of islets in g.	Area of sheet in sq. cm.	Area of islets in sq.cm	Area of pancreas in 15 fields in sq. cm.	% area of islet tissue in pancreas.	No. of islets in 15 fields.	Av. area of one islet in sq. cm.
F. 46	Head	15	4.48	0.41	516.64	47.3	333.12 x 15 = 4996.8	0.95	31	1.52
	Body	15	4.48	0.70	516.64	80.7	333.12 x 15 = 4996.8	1.61 Av. 1.35	50 Av. 45.7	1.61 Av. 1.49
	Tail	15	4.51	0.65	516.64	74.5	333.12 x 15 = 4996.8	1.49	56	1.33

percentage area of islet tissus per whole pancreas (parenchyma + fat) and the number of islets in 15 fields of whole pancreas were then corrected to obtain estimates of the percentage area of islet tissue per pure parenchyma and the number of islets in 15 fields of pure parenchyma. The corrected figures for the case detailed in Table I are shown in Table II. The average area of the islets, being unaffected by the amount of fat in the pancreas, naturally remains unchanged. Incidentally, the true average are of the islets could, if required, be obtained by dividing the given figures by the square of the megnification (120^2).

The above technique also fails to consider the weight of the pancreas. The organ unfortunately was not usually weighed, but was so in 6 control and 4 obese cases. These pancreases, after being corrected for their content of adipose tissue on the supposition that fat and parenchyma.have the same specific gravity, weighed as follows : (1) control cases = 39.7 g., 73.8 g., 67.5 g., 69.1 g., 51.4 g. and 69.1 g. ; and (2) obese cases = 83.5 g., 69.1 g., 71.1 g. and 63.1 g. These figures with the exception of the first, unusually small, control organ show a close similarity in the weight of the pancreas in the two groups.

Results

The findings in 19 control (lean) subjects are given/

Table II.

Calculation of same Case as in Table 1 corrected for Fat.

Sex and age.	Pancreas	% area of adipose tissue.		% area of islet tissue per parenchyma.		No. of islets in 15 fields of parenchyma		Av. area of one islet in sq. cm.	
Female, 46 yrs.	Head	32.5	Av.	1.41	Av.	44.9	Av.	1.52	Av.
	Body	14.0	19.5	1.87	1.66	58.1	55.9	1.61	1.49
	Tail	12.0		1.69		63.6		1.33	

given in Table III. While naturally showing some variation, the average area of the islets is remarkably constant, being usually near the grand average of 1.57 sq.cm. The average number of islets in 15 fields of parenchyma, on the other hand, varies considerably and is therein naturally accompanied by an equivalent variation in the average percentage area of islet tissue per parenchyma. A percentage area of islet tissue above 2.58 obtains in cases 3, 5 and 12, but each of these is characterised by an exceptionally large number of islets. An amount of 2.58 may thus be regarded, given an average quota of islets, as the highest normal percentage area of islet tissue per parenchyma.

The findings in 19 obese subjects are summarised in Table IV. The grand average area of the islets in the obese series is 2.59 sq.cm. or 65 per cent greater than the grand average area of the islets in the control group. Thirteen or 68.4 per cent of the obese subjects, moreover, have islets with an average area of more than 2.22 sq.cm., the upper limit of the control series. The insular enlargment is very distinct in 7 cases and may be termed striking in 4 subjects (8, 15, 17 and 18). It is further emphasised by grouping the cases of both obese and control series according to the average area of their islets as in Table V. The average area of the islets in the entire control group with two exceptions and in most of the obese series/

Table III.

Control Subjects.

Controls	Sex and age.	Av. % area of adipose tissue in pancreas	Av. % area of islet tissue per parenchyma.	Av. number of islets in 15 fields of parenchyma	Av. area of one islet in sq. cm.
1	F 19	5.9	2.22 14	72.1	1.55 8
2	F 22	3.2	2.54 15	80.7	1.55 9
3	M 22	5.0	3.84 19	91.1	1.84 14
4	M 32	6.5	2.58 16	73.5	1.79 16
5	F 38	20.4	2.83 17	90.4	1.62 11
6	F 40	10.8	0.80 1	25.0	1.59 10
7	M 45	23.6	1.97 10	55.5	1.70 14
8	F 46	19.5	1.66 5	55.9	1.49 5
9	M 53	3.3	1.38 4	40.7	1.66 12
10	M 54	9.5	2.20 13	52.2	2.22 19
11	F 57	12.0	1.91 9	75.3	1.27 4
12	F 57	11.8	3.54 19	101.0	1.69 13
13	M 58	3.9	1.97 11	63.5	1.75 15
14	F 59	7.7	1.68 6	79.7	1.04 3
15	F 60	10.1	1.68 7	53.6	1.54 6
16	F 62	5.4	1.80 8	58.0	1.54 7
17	F 65	9.8	2.07 12	53.0	2 .00 18
18	M 66	2.5	1.28 3	59.5	1.03 2
19	M 67	5.4	1.11 2	55.4	0.99 1
		Aver.= 9.3	Aver.= 2.05	Aver.= 65.0	Aver.= 1.57
Lower Limit		2.5	0.80	25	0.99
Upper Limit		23.6	3.84	101	2.22

Table IV.

Obese Subjects.

Obese	Sex and age.	Av. % area of adipose tissue in pancreas	Av. % area of islet tissue per parenchyma	Av. number of islets in 15 fields of parenchyma	Av. area of one islet in sq. cm.
1	F 27	12.4	1.80 4	30.0	2.99 15
2	F 35	13.9	0.74 1	20.9	1.83 3
3	F 37	0	2.93 10	62.5	2.27 7
4	F 41	9.5	3.07 11	70.9	2.18 6
5	F 42	13.2	2.16 7	56.9	1.90 4
6	F 49	48.5	3.64 13	64.3	2.86 14
7	F 50	24.1	1.57 2	33.3	2.36 9
8	F 52	16.5	5.26 17	68.8	3.21 18
9	F 53	35.7	1.92 6	57.4	1.61 2
10	F 53	2.6	1.80 5	61.5	1.46 1
11	M 54	19.1	1.60 3	35.3	2.32 8
12	F 57	32.3	2.84 9	59.4	2.04 5
13	F 58	3.3	3.69 14	74.1	2.72 13
14	F 60	15.8	2.24 8	45.7	2.41 10
15	M 63	15.4	4.82 16	70.0	3.19 17
16	F 63	22.9	4.05 15	80.9	2.53 12
17	F 63	11.6	3.21 12	50.3	3.19 16
18	F 64	13.2	5.57 18	49.4	5.78 19
19	F 67	14.4	5.71 19	93.6	2.48 11
		Aver. = 17.1	Aver. = 3.19	Aver. = 57.2	Aver. = 2.59
Lower Limit		0	0.74	20.9	1.46
Upper Limit		48.5	5.71	93.6	5.78

155%.

Table V.

Islet Area in Control and Obese Subjects.

Area of islets in sq.cm.	0.5 to 1	1 to 1.5	1.5 to 2	2 to 2.5	2.5 to 3	3 to 3.5	5.5 to 6
Controls	1 5%	4 21%	68% 13	1 5%	0	0	0
Obese	0	1 5%	16% 3	7 37%	4 21%	3 16%	1 5%

series then lies between 1 sq. cm. and 2 sq.cm. and between 2 sq.cm. and 3.5 sq.cm. respectively (Figs. 1-8). Case 18 of the obese group has islets with the extraordinarily high average area of 5.78 sq.cm. The number of islets per 15 fields of parenchyma, on the other hand, shows more or less the same range and average in the obese as in the control series.

Enlargement of the islets in obese cases with an average number of islets has effected an obvious increase in the percentage area of islet tissue per parenchyma. Thus, 9 of the 13 obese subjects showing insular hypertrophy have a percentage area of islet tissue above 2.58, the upper limit of the control group in association with an average number of islets. The remaining 4 subjects (1, 7, 11 and 14), while possessing enlarged islets, have a percentage area of islet tissue less than 2.58. These subjects, however, have a relatively low quota of islets and ought to be separately contrasted with corresponding controls. Respective quotas of 30 and 25 islets per 15 fields suggest a reasonable comparison in obese case 1 and control case 6 and these subjects are then found to have a very different percentage area of islet tissue in 1.08 and 0.8 respectively. In other words, even the above mentioned, four obese subjects may also justifiably be regarded as having an abnormally large percentage area of islet tissue per parenchyma. Finally, a very/

very high percentage area of islet tissue may be produced, it will be noted, by the association of either moderate hypertrophy and a very large number of the islets or marked hypertrophy and an average number of the islets as in obese cases 19 and 18 respectively.

The pancreatic islets in the obese subjects, apart from central fibrosis in one much enlarged specimen in obese case 18, were histologically normal.

Discussion

The pancreatic islets in 68 per cent of the present obese subjects showed varying and occasionally striking hypertrophy. The enlargement of the islets, as with hypertrophy of any other tissue such as the myocardium in association with valvular or hypertensive disease, naturally infers a phase of overactivity. This deduction is further supported by the obese state, according to the literature, being sometimes characterised by an abnormally low blood sugar with or without obvious hypoglycaemic manifestations. Thus, Harris (1924) records the case of an obese female who, on reducing herself by dieting from 210 lbs. to 160 lbs., experienced " spells of weakness and nervousness " between 1 a.m. and 2 a.m. She had discovered that eating would relieve her condition and so kept an orange or glass of milk within reach. Her fasting blood sugar was 47 mg. per cent. She was treated by/

by frequent feeding with a low carbohydrate diet and was thereby rapidly restored to normal. Harris (1932) describes how another obese individual had a blood sugar of 45 mg. per cent and marked lipaemia, but did not experience any symptoms of hypoglycaemia. Winans (1930) cites two further cases of obese females with a low blood sugar. The first had been dieting to reduce and complained of weakness, trembling and inability to keep from crying. The second was liable to spells of weakness, dizziness, " pain in the pit of the stomach," and extreme hunger before lunch and in the middle of the afternoon. Her blood sugar in the late afternoon was 67 mg. per cent. Both subjects had lived on a high carbohydrate diet. Phillips (1931) also reports the case of a well nourished negro who was admitted to hospital in a semiconscious condition. Investigation revealed a blood urea of 133 mg. per cent and blood sugar of 45 mg. per cent, while autopsy disclosed a subacute glomerulonephritis and a distinct enlargement of the pancreatic islets. Accordingly, both general principles and the clinical data justify the conclusion that the pancreatic islets in the 68 per cent of the present obese subjects showing enlargement thereof were or had been overactive.

The increase of the pancreatic islets in size and function naturally invites explanation. Clinical investigation gave no information about the diets of the present obese subjects, but such over-weight individuals are nevertheless known to have certain/

certain dietetic idiosyncracies. Thus, according to Lyon (1931) and Dunlop and Lyon (1931), gross overeating is sometimes the distinctive abnormality, but a much commoner finding is a wrongly balanced diet with a preponderance of starchy food. Carbohydrate acts as a stimulus to the secretion of insulin and, in excess, would ultimately lead to hypertrophy of the pancreatic islets. Now, an enlarged condition of the islets is also found in the offspring of diabetic mothers. Dubreuil and Anderodias (1920) and Gray and Feemster (1926), for example, describe how the islets in two such infants, born prematurely at the beginning of the ninth and eighth months respectively, were in the first case markedly hypertrophied but normal numerically, and were in the second instance increased three and eight times in number and average size respectively. The infants incidentally weighed 5,000 g. and 3,300 g. respectively : in other words, both were much heavier than the normal. Their increased weight is attributed by Dubreuil and Anderodias and the enlarged condition of their islets by both them and Gray and Feemster to the maternal hyperglycaemia and the consequently large supply of sugar at the disposal of the infants. These observations accordingly support the above suggestion that the hypertrophy of the pancreatic islets noted in 68 per cent of the present obese subjects may have been due to a prolonged, excessive consumption of carbohydrate.

The/

The insular enlargement, on the other hand, may be regarded as a primary phenomenon of unknown etiology. The resultant increased supply of insulin, perhaps through the hypoglycaemic state such as has been shown to exist in some obese subjects, might then explain the excessiveness of the appetite for carbohydrate and thereby of the deposition of fat, both of which are so prominently associated with the insular enlargement. The present type of obesity would thus be justifiably aligned with giantism, Cushing's syndrome, osteitis fibrosa and other conditions due to a primary, inexplicable increase of the endocrine elements, while the dietetic idiosyncracies of the obese state would also be placed on a rational, physiological basis.

No final decision is possible between the acquisition of the carbohydrate habit of diet and the enlarged condition of the pancreatic islets as regards their respective claim to be the primary phenomenon. Albeit, the development of one would probably, on the logic of the above arguments, soon lead to the appearance of the other and so to a cycle in which excessive carbohydrate would require more insulin and insular hypertrophy would demand more carbohydrate. The effect of either genesis, following the conversion of carbohydrate to fat, would be a progressive development of the obese state.

Such reasoning infers sustained hyperfunction of the islets, but prolonged overactivity is apt, irrespective/

irrespective of the tissue, to be followed by deterioration and exhaustion. The function of the pancreatic islets in the present obese subjects may thus, in the period before death, have still been increased or, on the other hand, normal or decreased. Exhaustion of the islets further means an upset in the mechanism whereby carbohydrate is converted into and stored as fat with the consequent excretion of some of the ingested carbohydrate as sugar in the urine. In other words, the purely obese ultimately becomes, as is well known, a mixed obese diabetic condition. The diabetic phase was envisaged as possibly being, in its approach or inception, diagnosable through the recognition of early changes in the pancreatic islets. The only significant finding, however, was well marked central fibrosis in a very large islet in obese case 18. Otherwise, the islets in this case and also in all the other obese subjects were without any distinctive pathology. Such a negative observation was, of course, in keeping with the sugar-free character of the urine of all the obese subjects, at least during their residence in hospital.

Summary

(1) A method is described whereby in a section of pancreas estimates can be made of (i) the percentage area of islet tissue ; (ii) the number of islets in a specified area ; and (iii) the average/

average area of the islets.

(2) The method was used to compare the pancreatic islets in 19 obese and 19 lean subjects, and thirteen or 68 per cent of the obese group were thereby found to have (i) an unusually high percentage area of islet tissue ; (ii) an average number of islets ; and (iii) abnormally large islets.

(3) The pancreatic islets in the obese subjects, apart from central fibrosis in one enlarged specimen, were histologically normal.

(4) The enlargement of the pancreatic islets found in a proportion of the obese subjects is discussed in relation to the obese state.

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SECTION III.

Sugar Tolerance in Obese Subjects.

A Review of Sixty Five Cases.

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Section III.

Sugar Tolerance in Obese Subjects.
A Review of Sixty Five Cases.

The sugar tolerance of the obese subject according to Labbé and Boulin (1925), Allison (1927), and John (1927, 1934) may be normal or reduced. The reduction of tolerance varies in degree and ultimately expresses itself clinically as diabetes. These observations agree with the recognised association between obesity and diabetes. Thus, Joslin (1921) in an analysis of 1,063 cases of diabetes noted antecedent obesity in 40 per cent, although Root and Miles (1922) place the figure at only 20 per cent. On the other hand, some obese subjects periodically experience symptoms which might have been produced by an overdose of insulin and are incidentally accompanied by an unmistakable hypoglycaemia. Such cases have been recorded by Harris (1924) and Winans (1930). Harris (1932) also reports the case of an obese subject who had a blood sugar of 45 mg. per cent without any hypoglycaemic manifestations.

The above observations suggest the possibility of the pancreatic islets of the overweight individual being functionally overactive for a time, probably during the early years of the obese state, and thereafter consecutively normal and deficient in their capacity to secrete insulin. The possible detection of such a transition on the part of the secretory capacity of the insular tissue in the obese subject/

subject with corresponding changes in sugar tolerance accordingly formed the main object of enquiry in the present investigation. Proof of the phenomena at issue naturally necessitated particular attention being given to subjects with a short history of overweight. The progress of the research also led in time to the investigation of the relation of sugar tolerance in the obese individual to other factors, viz. duration of the obese condition, percentage overweight, age, and ovarian function. The hypertrophied state of the pancreatic islets described by Ogilvie (1933) in a proportion of obese subjects also presented a problem for consideration.

Material and Methods.

The 65 subjects investigated comprised 63 women and 2 men. Each patient having fasted since 9 p.m. the previous evening reported at the Dietetic Out-Patient Department at 8 a.m. and was put to rest in bed. At 9 a.m. ½ c.c. of blood was taken by venepuncture at the elbow, and 0.2 c.c. of this was used for estimation of the blood sugar. At the same time the patient was asked to empty the bladder and a sample of urine was tested for sugar and acetone. Thereupon 50 g. of glucose were given in a tumblerful of water flavoured with lemon juice. Further samples of blood were taken at half-hour intervals up to two hours, at the end of which time a second specimen of urine was tested for sugar and acetone. The blood sugar was estimated/

estimated by the method of Hagedorn and Jensen 1923.

The patient's history was carefully investigated as regards the duration of the obese state, the relation of its onset to any particular event in the patient's life, the possible existence of a menstrual upset and the date of the menopause. Height and weight were taken, and the percentage overweight was then calculated with the help of tables* of standardized weights.

Results.

The facts accumulated from an examination of the 65 obese subjects are arranged in Table 1 and may be analysed as follows :-

1. Relation of sugar tolerance to duration of obesity. Fig. 1 shows all the cases plotted according to the duration of the obese condition in each instance. No account is here taken of age. The method adopted has merely been to chart the peak of the sugar-tolerance curve of the individual subjects. Thus, the confusion of plotting a large series of curves together has been avoided without obscuring any of the inferences. The cases are numbered individually and in the event of being diabetic (5,39,47,48 and 56) are additionally marked with a D.

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* Published by the Association of Life Insurance Directors and Acturial Society of America. New York, 1912. p. 38.

Details of 65 Obese Subjects.

No.	Sex.	Age.	%age over-weight	Duration of obesity in years	Blood sugar in mg. %. Fasting	After 50 g. glucose. ½ hr.	1 hr.	1½ hrs.	2 hrs.	Glycosuria. Before test.	After test.	Menstruation.
1	F	35	106	17	130	171	155	148	130	-	-	Regular.
2	F	39	66	14	110	140	110	98	94	-	-	Regular.
3	F	29	82	4	93	121	150	128	114	-	-	Regular.
4	F	46	40	12	94	172	156	102	90	-	-	Regular.
5	F	35	40	13	111	195	180	150	134	-	+	Regular.
6	F	31	98	5	101	125	126	126	93	-	-	Regular.
7	F	49	40	4	95	152	127	118	114	-	-	Menopause occurring.
8	F	32	34	7	96	135	126	126	126	-	-	Regular.
9	F	32	49	2½	94	132	125	109	96	-	-	Regular.
10	F	34	31	1	76	89	129	112	107	-	-	Regular.
11	F	26	82	4	75	120	82	91	77	-	-	Regular.
12	F	42	53	2	92	125	93	90	92	-	-	Regular.
13	F	29	31	¾	84	118	94	94	98	-	-	Regular.
14	F	60	25	18	114	186	159	96	70	-	-	Menopause at 45 years.
15	F	35	42	1	85	118	118	116	88	-	-	Regular.
16	F	35	30	6	111	153	98	82	101	-	-	Regular.
17	F	48	31	18	120	183	151	149	119	-	-	Regular.
18	F	30	44	9	89	167	170	150	127 *	-	-	Regular.

* Since it has obviously been missed, the peak of each of these cases has been plotted in the graphs at a slightly higher level than the figures given.

No.	Sex.	Age.	% age over-weight	Duration of obesity in years	Blood sugar in mg. %. Fasting	After 50 g. glucose. ½ hr.	1 hr.	1½ hrs.	2 hrs.	Glycosuria Before test.	After test.	Menstruation
19	F	66	67	43	100	199	136	100	93	-	-	Menopause at 45 yrs.
20	M	49	71	10	89	137	152	126	98	-	-	
21	F	58	80	18	89	129	152	130	119	-	-	Menopause at 52 yrs.
22	F	24	57	4	107	150	119	116	116	-	-	Regular.
23	F	54	58	10	78	125	168	154	158	-	-	Menopause occurring.
24	F	48	31	9	104	146	126	107	99	-	-	Menopause at 37 yrs.
25	F	46	47	5	100	126	144	153	95	-	-	Menopause occurring.
26	F	47	37	20	129	203	180	160	124	-	-	Menopause at 45 yrs.
27	F	52	38	17	103	156	138	108	99	-	-	Menopause at 49 yrs.
28	F	23	34	4	83	138	120	87	-	-	-	Regular.
29	F	38	37	13	106	174	152	127	99	-	-	Regular.
30	F	24	40	1½	98	137	151	133	113	-	-	Before unilateral oophorectomy 7/28 : after, 3/28 and loss scanty.
31	F	41	32	8	107	170	143	120	110	-	-	Regular.
32	F	33	75	13	80	139	126	105	86	-	-	Regular.
33	F	58	57	25	114	190	95	100	100	-	-	Menopause at 47 yrs.
34	F	25	42	¾	126	175	220	155	119	-	-	1 spot - 7-12 weeks.
35	F	48	38	12	102	160	160	131	115 *	-	-	Menopause occurring.
36	F	44	46	2⅔	101	185	163	134	125	-	-	Sterilized by radium.

* Since it has obviously been missed, the peak of each of these cases has been plotted in the graphs at a slightly higher level than the figures given.

No.	Sex.	Age.	% age over-weight	Duration of obesity in years	Blood sugar in mg. %. Fasting	After 50 g. glucose ½ hr.	1 hr.	1½ hrs.	2 hrs.	Glycosuria Before test.	After test.	Menstruation.
37	F	42	43	7	85	143	104	90	81	-	-	Regular.
38	F	43	22	5	110	155	141	119	110	-	-	Menopause occurring.
39	F	59	45	34	107	209	261	194	179	-	+	Menopause at 49 yrs.
40	F	34	30	2/3	87	164	162	130	87	-	-	Sterilized by deep X-rays.
41	F	49	63	25	137	157	210	190	170	-	-	Regular.
42	F	36	34	7	75	146	119	87	70	-	-	Regular.
43	F	29	67	2 5/6	100	134	118	107	96	-	-	Regular.
44	F	34	28	9	118	175	141	123	111	-	-	Regular.
45	F	36	29	10	107	175	157	134	118	-	-	Regular.
46	F	29	32	2 5/6	120	189	155	135	115	-	-	Amenorrhoea for 2 yrs. 10 mths. since birth of last child.
47	F	39	80	12	130	220	260	210	145	-	++	Regular.
48	F	57	14	27	170	250	295	350	280	++	++	Menopause at 54 yrs.
49	F	53	67	12	112	155	155	145	98*	-	-	Menopause at 47 yrs.
50	F	65	25	25	107	194	146	123	107	-	-	Menopause at 50 yrs.
51	F	28	44	4	93	153	126	109	93	-	-	Regular.
52	F	35	37	7	100	143	169	134	109	-	-	Regular.
53	F	60	17	4	89	150	106	86	80	-	-	Menopause at 38 yrs.

* Since it has obviously been missed, the peak of each of these cases has been plotted in the graphs at a slightly higher level than the figures given.

No.	Sex.	Age.	%age over-weight.	Duration of obesity in years	Blood sugar in mg. %. Fasting	After 50 g. glucose. ½ hr.	1 hr.	1½ hrs.	2 hrs.	Glycosuria. Before test.	After test.	Menstruation
54	F	29	40	4	104	143	170	139	109	-	-	Scanty : 1-2 days. / 2-12 months.
55	F	45	85	19	91	163	164	139	119*	-	-	Menopause occurring.
56	F	60	74	38	111	199	239	234	168*	-	++	Menopause at 52 yrs.
57	F	34	33	3	92	117	92	94	94	-	-	Regular.
58	F	27	38	3¾	109	141	86	102	119	-	-	Regular.
59	M	36	32	8	99	163	105	72	79	-	-	-
60	F	25	49	5	102	121	157	127	102	-	-	Regular.
61	F	50	137	28	103	168	187	155	128	-	-	Menopause occurring.
62	F	60	82	24	122	165	187	154	110	-	-	Menopause at 48 yrs.
63	F	54	36	17	115	190	176	140	125	-	-	Menopause at 37 yrs.
64	F	50	57	14½	110	154	139	112	110	-	-	Menopause at 47 yrs.
65	F	62	46	13	100	146	123	121	117	-	-	Menopause at 49 yrs.

* Since it has obviously been missed, the peak of each of these cases has been plotted in the graphs at a slightly higher level than the figures given.

The chart is advisably interpreted without considering two groups of cases, viz. the obese diabetics already mentioned and also cases 30, 34, 36, 40, 46 and 54, all of which have a sugar tolerance much below that of the other cases with a corresponding history of obesity and incidentally admit to a common gynecological abnormality hereafter described. The average trend of the sugar tolerance with the omission of these groups is represented by the line AB. This line indicates that the sugar tolerance of the cases diminishes progressively with increase in duration of the obese condition. Their tolerance would also appear to decline more rapidly during the earlier than the later years of the obese state, but this conclusion is uncertain owing to the paucity of cases with a history of more than twenty years' overweight.

Fig. 1 , however, takes no account of the influence of age on sugar tolerance. Tolerance for sugar, as shown by Spence (1920-1) and corroborated later in this series of cases, declines progressively throughout life. The sugar curve of a patient in the third decade cannot thus be legitimately compared with that of one in the sixth decade. Accordingly, the cases were grouped in decades in order to eliminate the influence of age as much as possible and recharted according to the duration of the obesity. The groupings are illustrated in Figs. 2-6. These charts are again advisably interpreted without cases 30, 34, 46 and 54 in Fig. 2, case 40 in/

in Fig. 3, and case 36 in Fig. 4, since these form, as already mentioned, a distinctly separate group. The curves of obese diabetic subjects, moreover, are specified by evenly broken lines.

The interpretation of Figs. 2 -6 necessitates the preliminary definition of the limits of the normal sugar tolerance curve in people between 20 and 70 years of age. The fasting blood sugar, according to investigators such as Kjer (1924-5) who have employed the Hagedorn-Jensen method, is generally considered to lie between 80-100 mg. per cent. After 50 g. of glucose the blood sugar rises in about three-quarters of an hour to between 140 - 160 mg. per cent. Thereafter it falls and reaches normal in one and a half to two hours. As already mentioned, Spence (1920-1) has put forward evidence to show that sugar tolerance declines with advancing years, but a rise above 180 mg. per cent is generally taken as representing an abnormally low sugar tolerance [Hansen (1923), Petrén (1923)] . Finally, most investigators would agree, although figures in support of the statement are scarce, that a rise of less than 35 mg. per cent above the original fasting level represents an abnormally good sugar tolerance.

A consideration of Fig. 2 in which are plotted all cases in their third decade reveals a steady fall in tolerance between case 13 and case 60 with a history of obesity for respectively eight months and five years. This progressive decline in tolerance is/

is also demonstrated by cases in the fourth decade and particularly in the fifth decade where the duration of the obesity increases to 17 - 22 years. The sixth and seventh decades include only a limited number of subjects, but such cases as have been obtained are so arranged as to favour the same conclusion during these periods. Figs. 2 -6 from which the influence of age has been largely eliminated thus corroborate the relationship observed in Fig. 1 between degree of sugar tolerance and duration of obesity.

The various curves may now be examined in more detail. The third decade (Fig.2) is characterised by cases 13 and 43 with each a total rise of 34 mg. per cent. In the fourth decade (Fig. 3) case 15 has a rise of 33 mg. per cent, case 57 a rise of 25 mg. per cent, and case 6 a rise of 24 mg. per cent. The fifth decade (Fig. 4) includes case 12 with a rise of 33 mg. per cent. Each of these cases has thus a curve with total rise of less than 35 mg. per cent and such a low type of response, as already noted, is generally accepted as indicating an increased tolerance for sugar. The members of this group, moreover, are also related inasmuch as each gives a history of a short period of obesity, the longest being 5 years in case 6. Case 2 in the fourth decade with a rise of only 29 mg. per cent at first sight falls into this group, but paradoxically enough gives a history of having been over weight for fourteen years. This

individual, however, is very difficult to assess accurately owing to the obvious discrepancy between the fasting and terminal points of its curve and so has been omitted from consideration.

Cases with a history of obesity up to eleven years excluding the above mentioned group have normal sugar-tolerance curves.

Cases with a history of obesity for more than eleven years may continue to fall within normal limits or show evidence of slightly, moderately or markedly diminished sugar tolerance. Thus, slightly reduced tolerance is seen e.g., in cases 17 and 55 (fifth decade) with curve peaks of 183 mg. per cent. case 61 (sixth decade) with a peak of 187 mg. per cent, and cases 14 and 62 (seventh decade) with peaks of 186 and 187 mg. per cent respectively. Definitely reduced sugar tolerance is evident e.g., in cases 26 and 41 (fifth decade) with peaks of 203 and 210 mg. per cent respectively, and cases 50 and 19 (seventh decade) with peaks of 194 and 199 mg. per cent respectively. Finally, markedly diminished tolerance is seen in cases 5 and 47 (fourth decade), cases 39 and 48 (sixth decade), and case 56 (seventh decade). These subjects show an abnormally great rise and a delayed fall and are characterised in each instance by a positive Fehling's test for sugar in the second specimen of urine. They have clearly passed into the phase of diabetes. The onset of diabetes in these cases, it will/

will be noted, was preceded by a period of overweight ranging from twelve years in case 47 to thirty eight years in case 56.

In summation, one third of the cases with a history of obesity for five years or less have an increased sugar tolerance, while the remainder in this group have normal tolerance. Thereafter, the sugar tolerance of all obese subjects lies within normal limits up to a duration of eleven years' obesity. Some exhibit normal tolerance even after having been overweight for eighteen years. The period after eleven years, nevertheless, is characterised by a progressive decline in sugar tolerance so that after eleven years examples of abnormally low tolerance make their appearance and after eighteen years every case without exception in the series has a more or less subnormal tolerance. Tolerance ultimately becomes so deficient as to provoke the symptoms and signs of diabetes. Diabetes among the cases under review supervened after periods of obesity ranging between twelve and thirty eight years.

2. Relation of sugar tolerance to percentage overweight. This relationship was investigated by grouping the cases in decades so as again to eliminate as much as possible the influence of age and plotting them according to their percentage overweight. Figs. 7 -11 were constructed in this way and show that the average tolerance in each decade is represented by a horizontal line. The

sugar tolerance of the obese subject, in other words, is in no way related to the amount of overweight. In the fourth decade, for example, case 32 with 75 per cent overweight has a slightly better tolerance than case 42 with 34 per cent overweight, and in the sixth decade case 61 with 137 per cent overweight has as good a tolerance as case 63 with only 36 per cent overweight. The amount of overweight is thus no index of the obese subject's sugar tolerance.

3. Relation of sugar tolerance to age. This association is illustrated in Fig. 12 where for the sake of clarity only the peaks of the tolerance curves have been plotted according to the patient's age. The line AB represents the average height of the peaks (omitting the two groups of cases mentioned in section I) and signifies a progressive decline of sugar tolerance with advancing years.

4. Relation of sugar tolerance to ovarian function. Such a relationship is suggested by a study of cases 30, 34, 36, 40, 46 and 54, and also of case 48. Each of the first group of six cases, as seen in Figs. 1-4, has a much lower tolerance for sugar than the others with a correspondingly short history of obesity. The cases in this group, moreover, are further remarkable for their common admission to a history of dominished ovarian function. Thus, case 30 is a married woman, aged 24, who had a unilateral oophorectomy performed two years ago. Prior to the operation her menses were of the 7/28 type and the loss was average. Since the/

the operation her menses have been half of their former duration, now 3/28, and the loss has been scanty. Her obesity dates from the operation also. Case 34 is a married woman, aged 25, with markedly irregular and scanty periods, her loss amounting to one or two spots every 7-12 weeks. Case 46 is a married woman, aged 29, who has had no menstrual period since the birth of her sixth and last child three years ago. Her menarche occurred at the age of 17 years and her pierods were regular, 3-4/28, until they ceased in 1931. Case 54 is a married woman (nullipara), aged 29, whose menstruation has consisted of a scanty period lasting one or two days every 2-12 months. Case 40, the only one in the fourth decade, is a married woman, aged 34, with six children. She had a severe haemorrhage eight months ago just before the birth of the sixth child and was accordingly sterilised by deep X-ray therapy. Lastly, case 36, the only one in the fifth decade, is a married woman, aged 44, who by reason of severe uterine haemorrhage two years ago was artificially sterilised by the insertion of radium.

Case 48, an obese female diabetic of the sixth decade, is best considered in relation to the trend of sugar tolerance at the menopause as seen in Fig. 12. In this graph, cases whose menopause is occurring or has occurred are indicated respectively by △ and ⊙ . The first of the group, i.e. case 38 (marked by arrow) is 43 years of age. In only five instances to the right of this case has no sign/

sign of the menopause yet appeared. The line AB thus continues to rise at the same rate during the years after as before the climacteric. In other words, the natural cessation of ovarian function at the menopause is not usually associated with any accelerated falling off in sugar tolerance. Now, case 48 gives a history of having been overweight for twenty seven years. She experienced her menopause three years ago and since then has been losing weight. In the year after her menopause she had an attack of pruritus and a second attack occurred a year later. When she came under observation this year she complained of thirst and polyuria and her sugar-tolerance curve, associated as it was with glycosuria, proves her to be frankly diabetic. From what has already been said, this elderly subject after being obese for twenty seven years may legitimately be regarded as having had a much reduced sugar tolerance. Her history, moreover, suggests that she became diabetic during her menopause. In other words, cessation of ovarian function at that time appears to have been associated with such an additional decline in tolerance as to make her grossly incapable of dealing with sugar. This case is thus an exception to the usual accomplishment of the menopause without any evident disturbance of sugar metabolism.

Discussion.

Joslin (1921) believes that percentage over-

weight has an important bearing on the sugar tolerance of the obese subject in that the tendency to the development of diabetes increases in proportion to the amount of overweight. The present cases, however, sometimes show the association of small and large amounts of overweight with respectively low and high grades of sugar tolerance. In contrast, the ability of these subjects to deal with sugar deteriorates pregressively as the length of time during which they have been obese increases and ultimately after periods of overweight ranging between twelve and thirty eight years assumes a diabetic type. The duration of the obesity according to this investigation is thus of much more significance in relation to the sugar tolerance of the overweight subject than the degree of obesity. The same conclusion is favoured by Labbé and Boulin (1925) and Allison (1927). Spence (1920-1) has further drawn attention to the importance of advancing years in bringing about a lowering of the individual capacity to deal with sugar and such a relationship is again evident in this series of cases. Finally, several subjects in the present investigation are characterised by rapidly increasing overweight, a very low sugar tolerance for the duration of the obese condition, and signs of ovarian dysfunction. The factors influencing the sugar tolerance of the obese individual are thus varied in nature and include the duration of the overweight condition, the age of the patient, and ovarian/

ovarian dysfunction. All of these conditions, moreover, have the common effect of reducing the capacity of the obese person to deal with sugar.

According to this investigation the sugar tolerance of one third of obese subjects is consecutively increased, normal and decreased, whereas the ability of the other two thirds to deal with sugar is normal at first and later decreased. The assumption of a correlation between sugar tolerance and secretion of insulin enables these trends to be interpreted as indicating that the pancreatic islets in one third of obese subjects pass through phases of increased, normal and decreased function, while the insular tissue in the remainder merely shows stages of normal and decreased activity. Now, Ogilvie (1933) observed varying degrees of enlargement, of the pancreatic islets in thirteen out of nineteen unselected obese subjects. Most of the cases with hypertrophied islets, moreover, were 49 years of age or upwards and the present series after 47 years of age includes eleven examples of normal tolerance, ten of subnormal tolerance (peak above 180 mg. per cent), and three of frankly diabetic character. The hypertrophy of the pancreatic islets obtaining in a considerable proportion of obese people, in the light of such a declining sugar tolerance, may consequently be regarded as indicating transition of the insular tissue in these individuals from a hyperactive to a hypoactive condition. According to the foregoing/

going clinical and histological data, a proportion of obese subjects (probably about one third) thus apparently pass from a preliminary phase of increased pancreatic islet function and sugar.tolerance to a final condition of decreased pancreatic islet function and sugar tolerance, while the remainder of the cases merely show normal and decreased phases of these phenomena.

Such trends on the part of the pancreatic islets and sugar tolerance in the obese subject invite enquiry in respect of their causation. The observations of Dunlop and Murray Lyon (1931) as regards the dietary habits of 523 obese subjects are interesting in this connection. A few of their cases admitted to having grossly overeaten for many years. A much commoner finding (45 per cent of their cases), however, was a wrongly balanced diet with a preponderance of starchy foods. Some had a high fat intake, but this was not nearly so characteristic. Excessive quantities of carbohydrate naturally act as a stimulus to the secretion of insulin and the same effect, in view of the evidence indicating the necessity of insulin in the metabolism of fat, might be brought about by an excess of this material also. Accordingly, the trends of pancreatic islet activity and sugar tolerance regarded as obtaining in this series of obese subjects might be acceptably reasoned out on a dietetic basis. Such an approach, however, fails to explain the occurrence of a preliminary phase/

phase of increased pancreatic islet function and sugar tolerance in only a proportion of the present cases. Moreover, the period of increased pancreatic islet activity is apparently maintained for only about five years and thereafter passes into a stage of normal secretory function. In due time, the islets in all cases by reason of the sustained dietetic strain subside into a state of depressed activity and ultimately more or less exhaustion. The sugar tolerance of the obese subject is consequently normal for a time and later characterised by increasingly deficient qualities.

Much interest centres around the observed relation in the present investigation between carbohydrate metabolism and ovarian function. Physiological removal of the ovarian influence at the menopause is in most women a gradual process so that the tissues have time to adjust themselves to the altering metabolic conditions. Thus, no manifest upset in carbohydrate metabolism, as in the present series of cases, is usually to be found or expected during or after the climacteric. In contrast, cases 30, 34, 36, 40, 46 and 54 with a history of deficient function, premature exhaustion or artificial destruction of the ovaries show an obvious disturbance of their ability to deal with sugar and the same has been true of case 48 since the cessation of ovarian function at the menopause. The upset in sugar metabolism brought about by removal of the ovarian influence in all of these cases/

cases consists in a much reduced sugar tolerance. Whether this effect, when brought about by ovarian dysfunction during the active menstrual life of the female, occurs only in the subsequently obese or also in the subsequently thin remains to be decided by future investigation. Albeit, the reduction of tolerance in case 48 was such as to cause her sugar metabolism, already depleted in association with long standing obesity, to assume manifestly diabetic qualities. Now, Raab (1930-1) has found that normal women give much lower sugar tolerance curves after as compared with before the injection of follicular and luteal extracts. Again, ovariectomy in guinea pigs, according to Yuuki (1934) causes an increased glycosuria after the intravenous injection of glucose. Finally, Gulick et al (1934) conclude that in ovariectomised rats the liver glycogen is constantly higher than in normal females and that a reduction in hepatic glycogen is effected by theelin. The findings in both man and animals thus point to the importance of the ovary in the regulation of carbohydrate metabolism. The sugar tolerance of the individual may undoubtedly be, according to this investigation, adversely affected by removal of the ovarian stimulus so that the ovary must be accredited with the function of enhancing the ability of the individual to deal with sugar.

Conclusions.

Sugar tolerance tests carried out in 65 obese subjects/

subjects varying in age between 23 years and 65 years and in percentage overweight between 14 per cent and 137 per cent indicate the following conclusions :-

(1) sugar tolerance diminishes with increase in duration of the obese condition ;

(2) sugar tolerance is increased in about one third of the cases with a history of obesity for five years or less, whereas the remaining cases in this group have a normal sugar tolerance ;

(3) the declining sugar tolerance characteristic of the obese state ultimately expresses itself in diabetes ;

(4) sugar tolerance in the obese subject is not related to the amount of overweight ;

(5) the hypertrophy of the pancreatic islets obtaining in a proportion of obese subjects, considered in conjunction with the trends of the sugar tolerance, is interpreted as indicating transition of the insular tissue from a hyperactive to a hypoactive state ;

(6) sugar tolerance declines with advancing years ; and

(7) sugar tolerance in the obese subject is controlled by the ovary inasmuch as loss of the ovarian influence may induce an appreciably reduced capacity to deal with sugar.

18.

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SECTION IV.

Diabetogenic and Pancreotropic Actions of Ox Anterior Pituitary Extract in Rabbits.

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SECTION IV.

Diabetogenic and Pancreotropic Actions of Ox Anterior Pituitary Extract in Rabbits.

Following the production of temporary diabetes by Evans, Meyer, Simpson and Reichert (1932), Baumann and Marine (1932) and Houssay, Biasotti and Rietti (1932), Young (1937) induced permanent diabetes in adult dogs by an intensive course of crude anterior pituitary extract. This discovery was confirmed by Campbell and Best (1938) and Dohan and Lukens (1939). Richardson and Young (1938) and Richardson (1940) examined the pancreases of dogs so rendered temporarily or permanently diabetic and found that the beta cells of the islets of Langerhans showed variable degrees of degranulation, hydrops or hyalinisation. Lukens and Dohan (1942) observed similar changes in the islet tissue of cats made diabetic by partial pancreatectomy and subsequent treatment with pituitary extract. The production of such lesions experimentally is important inasmuch as corresponding phenomena have been described in human diabetic cases by Opie (1901), Cecil (1908), Weichselbaum (1911) and Warren (1938). The present investigation accordingly aimed at reproducing and evaluating the above mentioned changes, but in these objectives was frustrated by the choice of the rabbit as the experimental animal. The research, nevertheless/

nevertheless, realised certain positive and interesting conclusions.

METHODS.

Extract. This material was a crude saline product of ox anterior pituitary glands prepared after the method of Young (1938 A). The fresh whole glands were brought on ice to the laboratory and the anterior lobes were separated by careful dissection. The extract was made up so that 2 c.c. were equivalent to 1 g. gland. It was stored at a low temperature without freezing and used within five or at most six days of preparation. The method of administration was by injection intraperitoneally in three animals and subcutaneously in twenty five animals. The injections were given daily and consisted either in a constant amount of 1.5 g. gland per kg. body weight or in a quantity which was increased by 0.5 g. gland per kg. at intervals of five or six days from an initial 1 g. gland per kg. to a final 2.5 g. gland per kg. body weight. Aseptic precautions were observed during both preparation and administration of the extract.

Animals. The 28 rabbits used in this investigation comprised 27 English (Nos. 2 - 32 in Table 1) and 1 Dutch (No. 1 in Table 1) and included 13 males and 15 females. Their weight varied between 1502 g. and 2352 g., the average being 1899 g. They were kept in metabolism cages and given a daily allowance/

allowance of 100 g. of mixed bran, corn and maize, 300 g. of cabbage and water ad lib. Daily measurements included food consumption, body weight, urine volume and, when present, urine sugar and urine ketones. The 10 control rabbits used to estimate the pancreatic islet tissue were also English and consisted of 7 males and 3 females. They weighed between 1530 g. and 2380 g. and averaged 1947 g. so that they proportionately covered the range of weights of the 28 injected animals.

Estimations. Urine sugar was estimated by Cole's method, urine ketones by the Van Slyke-Denigès method and blood sugar by the Hagedorn-Jensen method. Allowance was made in determining ketone excretion for the normal ketone content of rabbit urine. Sugar tolerance and insulin sensitivity tests were performed after a fast of 15 hours. Sugar tolerance was determined by two methods. The single method consisted in one intravenous injection of 5 c.c. of a 20 per cent glucose solution and determination of the blood sugar before and at 5 min. or 10 min. intervals after injection for 50 min. The consecutive method recommended by Himsworth (1934) comprised four intravenous injections of 5 c.c. of a 20 per cent glucose solution at half-hour intervals and estimation of the blood sugar before the first injection and at intervals of 5 min. and 23 min. after each injection. Insulin sensitivity was tested/

tested after the manner of the single sugar tolerance method with the difference that the glucose injection was replaced by 0.5 unit of insulin.

The pancreas of each animal was arbitrarily divided into head, body and tail, fixed in Helly-Zenker solution and embedded in paraffin. Sections were stained by (1) alcoholic eosin and haematoxylin and (2) Heidenhain's iron haematoxylin as recommended by Richardson (1940). The first technique served routine histological purposes, while both methods specifically demonstrated the A- and B-cells of the islet tissue. The weight of islet tissue and the number of islets in each pancreas were calculated after the method described by Ogilvie (1937). The frond-like character of the rabbit pancreas, however, created difficulty in determining its weight. The pancreas and the sheet of mesentery in which it lay were, therefore, carefully dissected out and weighed. The area of the mesentery was measured by laying it upon graph paper and its weight was calculated from that of a known area of mesentery detached from the small intestine. The weight of the pancreas was then obtained by deducting the weight of the mesentery from the combined weights of pancreas and mesentery. A section from head, body and tail of each pancreas was used to determine the percentage area of islet tissue and the number of islets and averages of these quantities were struck for the whole pancreas. An endeavour was thus made to take account of regional variations in the distribution and size of the islets./

islets. Estimation of the area of whole pancreas was rendered difficult by the fact that the fronds of the organ usually occupied only a fraction of each projected field. The fronds had, therefore, to be traced, cut out and weighed so as to obtain an estimate of their combined area. The rabbit pancreas thus involved the tracing of both whole tissue and islets compared with islets alone in the human organ. The microscopical fields used for the estimations were selected according to the size of the paraffin section. Each consecutive field was investigated in a small section, but in a larger piece of tissue the examination was restricted to every second, third, fourth or fifth field. Finally, the conversion of islet volume to islet weight by multiplication of islet volume by 1.05, the density of whole human pancreas, involved the assumption that the islet tissue of rabbit pancreas had the same density as human pancreas. This assumption naturally could not be proved, but the error, if any, was probably small and certainly constant throughout the investigation.

RESULTS.

(1) Glycosuria. This phenomenon was observed in 23 of the 28 injected rabbits (Table 1 and Figs. 3, 5, 7-17, 19-28). It developed as early as the second day of treatment in Rabbit 26, but was delayed until the ninth day in Rabbits 7 and 9 and

TABLE I

Rabbit *	Sex	Anterior Pituitary Gland		Glycosuria			Ketonuria		
		Total	Daily **	Appearance	Duration	Peak	Appearance	Duration	Peak
1	M	44.7 g.	Increasing	-	-	-	-	-	-
2	F	29.0 g.	Increasing	-	-	-	-	-	-
3 ‡‡	F	10.2 g.	Constant	Sixth day	1 day	0.07 g. per 24 hr.	-	-	-
4	M	49.9 g.	Increasing	-	-	-	Tenth day	1 day	Not estimated
5	F	51.5 g.	Increasing	Sixth day	15days	5.8 g. per 24 hr.	-	-	-
6	F	61.6 g.	Increasing	-	-	-	Sixth day	†3 days	Not estimated
7	M	45.1 g.	Increasing	Ninth day	7 days	7.3 g. per 24 hr.	Eighth day	4 days	205 mg. per 24 hr.
8 ‡‡	M	10.7 g.	Constant	Fourth day	3 days	0.05 g. per 24 hr.	Third day	4 days	68 mg. per 24 hr.
9	M	60.7 g.	Increasing	Ninth day	11 days†	15.3 g. per 24 hr.	-	-	-
10	F	67.8 g.	Increasing	Sixth day	10 days	4.3 g. per 24 hr.	Fourth day	† 8 days	544 mg. per 24 hr.
11	F.	60.0 g.	Increasing	Seventh day	14 days	14.8 g. per 24 hr.	Fifth day	† 8 days	609 mg. per 24 hr.
12	F	55.1 g.	Increasing	Fifth day	8 days	4.0 g. per 24 hr.	Sixth day	8 days	1047 mg. per 24 hr.
13	M	52.9 g.	Constant	Sixth day	7 days†	13.6 g. per 24 hr.	Third day	† 8 days	1257 mg. per 24 hr.
14	M	47.5 g.	Constant	Third day	9 days†	10.0 g. per 24 hr.	Sixth day	2 days	61. gm. per 24 hr.
15	M	35.0 g.	Constant	Sixth day	6 days	2.3 g. per 24 hr.	Fourth day	7 days	212. mg. per 24 hr.
17 ‡‡	F	13.1 g.	Constant	Fourth day	1 day	0.1 g. per 24 hr.	Fourth day	3 days	63 mg. per 24 hr.
18	F	41.0 g.	Constant	Eighth day	7 days†	12.3 g. per 24 hr.	Fifth day	1 day	207 mg. per 24 hr.

(Table I. cont.)

20	M	24.2 g.	Constant	-	-	-	-	-	-
21	F	47.2 g.	Constant	Eighth day	8 days	7.9 g. per 24 hr.	-	-	-
22	F	57.6 g.	Constant	Sixth day	12 days	22.6 g. per 24 hr.	Tenth day	4 days	250 gm. per 24 hr.
24	M	57.1 g.	Constant	Fifth day	23 days†	5.5 g. per 24 hr.	Fifth day	5 days †	233 mg. per 24 hr.
25	M	40.9 g.	Constant	Seventh day	7 days †	1.1 g. per 24 hr.	Fifth day	6 days	391 mg. per 24 hr.
26	M	33.2 g.	Constant	Second day	10 days	4.4 g. per 24 hr.	Sixth day	3 days †	695 mg. per 24 hr.
28‡‡	F	23.9 g.	Constant	Sixth day	3 days	1.8 g. per 24 hr.	Fifth day	4 days †	268 mg. per 24 hr.
29	F	35.4 g.	Constant	Seventh day	3 days	2.0 g. per 24 hr.	Eleventh day	2 days	213 mg. per 24 hr.
30	F	28.7 g.	Constant	Sixth day	7 days	4.0 g. per 24 hr.	Eighth day	2 days	15 mg. per 24 hr.
31	F	32.0 g.	Constant	Third day	10 days	32.7 g. per 24 hr.	Eighth day	4 days	1706 mg. per 24 hr.
32	M	35.3 g.	Constant	Third day	9 days	27.5 g. per 24 hr.	-	-	-

* Rabbits 1 - 3 were injected intraperitoneally and Rabbits 4 - 32 subcutaneously.

** The terms <u>constant</u> and <u>increasing</u> have the significance defined above under Methods (Extract).

† These periods included occasional days during which no sugar or ketones were present in the urine.

‡‡ These rabbits died before complete sugar and ketone curves were obtained.

on the average manifested itself on the sixth day. After it appeared, the glycosuria rose to a peak and subsequently fell to zero and this type of response was observed both in animals which received a constant daily amount of extract and in those injected with extract which was increased at short intervals to an equivalent of as much as 2.5 g. gland per kg. body weight. The ingravescent stage was rapid throughout in most animals, but in almost as many cases an initial slow phase preceded a rapid rise to the peak. The peak was characteristically followed by a rapid disappearance of sugar from the urine, while in the remaining cases the sugar subsided less rapidly or even slowly or rapidly at first and later slowly. The peak lay between the sixth and twenty-second day of treatment in the case of Rabbits 12 and 24 respectively and on the average occurred on the eleventh day. The height of the peak varied within wide limits. Thus, considering merely those animals which gave a complete sugar curve Rabbit 25 excreted at most only 1.1 g. sugar per 24 hr., while Rabbit 31 passed as much as 32.7 g. sugar per 24 hr. The animals which received constant extract passed an average maximum of 11.2 g. sugar per 24 hr. against 8.6 g. per 24 hr. as an average maximum for those injected with increasing extract and the average sugar excretion for the entire series was 10.4 g. per 24 hr. Sugar was excreted over a period of between three days for Rabbit 29 and twenty-three days for Rabbit 24.

The/

The excretion of sugar by Rabbit 24, however, was relatively slight for more than a fortnight and punctuated by occasional sugar-free days. The longest period of continuous glycosuria was fifteen days in the case of Rabbit 5. The animals receiving constant extract excreted sugar on the average for nine days against eleven days on the average for the animals injected with increasing extract and the average duration of sugar excretion for the series was 9.6 days. The average glycosuric curve thus began on the sixth day of treatment, reached a peak of 10.4 g. sugar per 24 hr. on the eleventh day and returned to zero on the sixteenth day. Eighteen rabbits which showed glycosuria also excreted ketones. The excretion of sugar anticipated the appearance of ketones by a period of one to five days or an average of three days in 7 animals, while in 9 animals sugar did not become positive until a period of one to three days or an average of two days after ketones and 2 animals exhibited both sugar and ketones on the same day.

(2) Ketonuria. This phenomenon was observed in 20 of the 28 injected animals (Table 1, and Figs. 4, 6-8, 10-17, 20-27). It developed between the third day in Rabbits 8 and 13 and the eleventh day in Rabbit 29 and on the sixth day on the average. The excretion of ketones rose to a peak and thereafter fell to zero and such a rise and fall occurred both in the animals receiving constant extract and in those injected/

injected with increasing extract. The increase in ketone excretion was uniformly rapid in most animals, but in some it was slow initially and later rapid or proceeded throughout at a medium rate. Similarly, the decline of ketone excretion was, as a rule, uniformly rapid, although sometimes rapid at first and later more slow or occasionally throughout of medium pace. Ketone excretion reached its peak between the fifth day for Rabbit 18 and the eleventh day for Rabbits 7, 29 and 31 and on the eight day on the average for the animals in which complete ketonuric curves were obtained. The height of the peak varied within wide limits. Thus, Rabbit 30 excreted only 15 mg. ketones per 24 hr. at most, while at the peak of its curve, Rabbit 31 passed 1706 mg. ketones per 24 hr. The animals injected with constant extract passed an average maximum of 476 mg. ketones per 24 hr. compared with 601 mg. ketones per 24 hr. for those receiving increasing extract and the average peak for the series was 510 mg. per 24 hr. The period over which ketones were excreted also varied considerably. Thus, whereas it lasted for only one day in Rabbits 4 and 18, ketonuria continued with or without occasional ketone-free days for eight days in Rabbits 10, 11, 12 and 13. The animals injected with constant extract excreted ketones for an average of four days against slightly more than five days for the animals receiving increasing extract and the average period of ketonuria for the series was 4.5 days/

days. The average curve of ketone excretion thus began on the sixth day of treatment, attained a maximum of 510 mg. per 24 hr. by the eigth day and returned to normal slightly later than the tenth day of injection. Eighteen of the rabbits, as already mentioned, excreted both ketones and sugar.

(3) Re-injection. Three rabbits which had shown transitory phases of glycosuria and ketonuria were re-injected after they had regained their strength. Rabbit 14 (Fig. 14) received 32.2 g. gland in constant daily amounts of 1.5 g. gland per kg. body weight between the sixth and sixteenth days and excreted sugar and ketones for nine days and two days respectively. Re-injection consisted in the administration of 15.3 g. gland in daily quantities of the same magnitude between the thirty-seventh and forth-second days. Rabbit 10 (Fig.10) received 41.7 g. gland between the tenth and twenty-fourth days and the daily amount in this case was increased at intervals of five days from 1 g. per kg. to 2 g. per kg. Sugar and ketones were excreted for ten and eight days respectively. The animal was re-injected between the fifty-third and sixty-second days of the experiment and given 26.1 g. gland in daily amounts which were increased after five days from 1 g. per kg. to 1.5 g. per kg. Re-injection of Rabbits 14 and 10 covered the period within which both had previously developed glycosuria and ketonuria, yet no sugar or ketones appeared in the urine of either of them/

them as a result of the second course of treatment. Rabbit 12 was given 55.1 g. gland in increasing daily amounts between the tenth and twenty-fifth days of the experiment and showed transitory phases of glycosuria and ketonuria. A second course of treatment was started on the fifty-eighth day, but the animal about a minute after the first injection died in a collapsed, dyspnoeic condition.

(4) Sugar Tolerance. (a) Single method. Eight rabbits were investigated from the point of view of sugar tolerance by the single method above described. The test was carried cut in the normal animal and also during and after the diabetic phase in two rabbits, while in the remainder it was performed in the intact animal and either during or after the glycosuric period. The results are given in Table II and collectively illustrated by Fig. 29. The curve of normal sugar tolerance based on the average of eight rabbits rises swiftly from a fasting level of 131 mg. per cent to a peak of 268 mg. per cent in 5 minutes. The blood sugar then falls at a uniformly rapid rate to 202 mg. per cent at 20 minutes. The difference in the levels of the blood sugar at 20 and 30 minutes is 33 mg. compared with 50 mg. for the previous 10 minutes so that the rate of fall between 20 and 30 minutes shows a definite decrease. The blood sugar after 30 minutes continues to fall at a uniformly moderate rate to reach 129 mg. at 50 minutes. Based on the average/

average of seven rabbits, the curve of sugar tolerance during the diabetic phase begins at a fasting level of 174 mg. per cent which is 43 mg. per cent more than the average normal fasting level. Its peak of 300 mg. per cent at 5 minutes is also 32 mg. per cent higher than that of the control curve, although a rise of only 126 mg. per cent compared with 137 mg. per cent for the normal curve suggests that some of the original peaks have been missed. The curve of the diabetic phase thereafter declines at a rate comparable with the normal to reach 250 mg. per cent at 20 minutes. The fall in blood sugar between 20 and 30 minutes is only 17 mg. per cent compared with 35 mg. per cent for the previous 10 minutes and 33 mg. per cent during the same period of the normal curve. The blood sugar between 20 and 30 minutes, therefore, falls not only at an abnormally reduced rate compared with its previous speed, but also at about half the rate of the normal curve. The fall in blood sugar between 30 and 50 minutes is only 8 mg. per cent against a normal decline of 40 mg. per cent and compared with the normal the blood sugar at 50 mimutes is higher by 100 mg. per cent. The rate of absorption during this final period consequently shows a marked progressive diminution and is, indeed, reduced to one-eighth of the normal. Thus, the sugar tolerance curve of the diabetic phase is during the first 20 minutes of the test similar to that of normal tolerance at a higher level, while it falls at only half the normal rate between/

11 a.

T A B L E II

SUGAR TOLERANCE - SINGLE METHOD

Rabbit	Stage	BLOOD SUGAR in mg. per cent								
		Fasting	5 min.	10 min.	15 min	20 min	25 min	30 min	40 min	50 m
24	Control	126	298	286	270	250	235 *	214	183 †	156 †
	Diabetes	140	311	286	280 *	276	264	260	260	260 *
	Recovery	-	-	-	-	-	-	-	-	-
25	Control	103	235	207	178 **	158 *	138 **	126	114	101 †
	Diabetes	140	228	207	201 *	185 *	178	178	183	183
	Recovery	-	-	-	-	-	-	-	-	-
26	Control	133	282	241	212	190 *	169	158	138	124
	Diabetes	209	311	304	296	284	270	270	270	256 ††
	Recovery	-	-	-	-	-	-	-	-	-
28	Control	158	272	256	230	224	203	194	163	151
	Diabetes	222	321	296	272	262	245	243	239	239
	Recovery	-	-	-	-	-	-	-	-	-
29	Control	133	249	239	212	194 *	176	162	145	140
	Diabetes	-	-	-	-	-	-	-	-	-
	Recovery	121	230 *	215 *	201	174 *	153 †	140 *	119 *	109 *
30	Control	114	249	231	212	187	171	140	119	107
	Diabetes	168	311	294	276	262	254	242	235	230
	Recovery	-	-	-	-	-	-	-	-	-
31	Control	160	295	270	252	226	218 *	194	158	128
	Diabetes	203	338	306	278	258	239	235	230	225
	Recovery	130	296	252	212	184 †	162 *	148	119 *	99
32	Control	117	260	256	218	187	176	160	142	128
	Diabetes	135	282	260	251 *	226	211	203	194	185
	Recovery	96	192 *	176	158	133 †	124	121	105	96 *
Averages	Control	131	268	248	223	202	186	169	145	129
	Diabetes	174	300	279	265	250	237	233	230	225
	Recovery	116	239	214	190	164	146	136	114	101

* + 1 minute

** + 3 minutes

† + 2 minutes

†† + 5 minutes

12 a.

TABLE III

SUGAR TOLERANCE - CONSECUTIVE METHOD

Rabbit	Stage	BLOOD SUGAR in mg. per cent								
		Fasting	5min	28min	35min	58min	65min	88min	95min	118min
7	Control	110	274	163	270	151	264	133	254	160
	Diabetes	-	-	-	-	-	-	-	-	-
	Recovery*	98	218	154	231	156	313	169	349	170
9	Control	-	-	-	-	-	-	-	-	-
	Diabetes	-	-	-	-	-	-	-	-	-
	Recovery†	110	214	147	239	156	264	163	266	174
10	Control	131	268	205	224	131	189	169	201	172
	Diabetes	191	289	236	330	255	340	312	408	316
	Recovery	122	262	192	278	171	239	144	258	140
11	Control	129	282	212	345	224	351	230	363	224
	Diabetes	171	306	252	395	311	452	306	513	345
	Recovery	119	268	183	315	199	319	203	306	172
12**	Control	105	499	282	556	366	520	385	454	345
	Diabetes	-	-	-	-	-	-	-	-	-
	Recovery	101	463	245	494	286	509	247	539	296
Averages of 7, 9 10 & 11	Control	123	275	193	280	169	268	177	273	185
	Diabetes	181	298	244	363	283	396	309	461	331
	Recovery	121	265	188	297	185	279	174	282	156

* Performed one day after last day of glycosuria.

† Performed two days after last day of glycosuria.

** This animal received four half-hourly injections of 5 c.c. of a 100 per cent glucose solution instead of 5 c.c. of a 20 per cent glucose solution as in Rabbits 7, 9, 10 and 11.

†† Average of 10 and 11 only.

between 20 and 30 minutes and between 30 and 50 minutes at only one-eigth of the normal. The result is that at the end of the test the blood sugar remains higher than the control level by as much as 100 mg. per cent. Based on the average of three rabbits, the curve of sugar tolerance after the diabetic phase is similar to that of normal tolerance except that it is placed at a lower level. Its lower level is probably explained by the fact that the animals have become accustomed to manipulative measures such as would tend to stimulate the sympathetic nervous system and produce hyperglycaemia during the earlier tests. Sugar tolerance after the diabetic phase may, therefore, be regarded as again of normal order.

(b) Consecutive method. The sugar tolerance of five rabbits was investigated by this method. Each animal was tested in the control stage and also during and/or after the diabetic phase. The results are set forth in Table III and illustrated by Fig. 30. The curve of normal sugar tolerance is based on the average of figures obtained from Rabbits 7, 10 and 11 and takes the form of an alternately rising and falling line, the trend of which is on the average slightly downward. Two of the three component graphs show more clearly this falling character, but the third definitely rises and so masks the effect of the others. The interpretation of the average falling graph is that each of the last three amounts of glucose injected intravenously has been removed from the circulation/

circulation in a slightly more adequate manner than its predecessor. This effect which is known as the Staub-Traugott phenomenon was first described by Hamman and Hirschman (1919) and is regarded by Himsworth (1934) as one of the most delicate reactions in carbohydrate metabolism. The curve of tolerance during the diabetic phase is based on the average of Rabbits 10 and 11 and has on the average a distinctly upward direction. The explanation of such a curve is found principally in the fact that the blood sugar after each injection fails to fall to the same degree as it does in the course of the normal tolerance test. Thus, whereas in the normal tolerance curve the blood sugar after the first three injections falls 82, 111 and 91 mg. per cent respectively, reductions of 54, 80 and 87 mg. per cent respectively occur in the curve of sugar tolerance during the diabetic phase. The reverse degree of fall after the fourth injection is undoubtedly due to experimental error. A curve of such rising character, indeed, is in keeping with the results of the single method, since this method revealed that the blood sugar between 20 and 30 minutes fell at only half the control rate and must, therefore, be abnormally elevated at 28 minutes when a second intravenous injection of glucose is given in the consecutive method. The consecutive method thus yields a graph which is merely a reduplicated version of/

of that obtained by the single method and which similarly indicates that the diabetic phase is accompanied by a definitely lowered sugar tolerance.

Sugar tolerance was estimated in Rabbits 7 and 9 one and two days respectively <u>after</u> the cessation of glycosuria and also thereafter in Rabbits 10 and 11 at intervals of twenty-two and twenty-three days respectively. The graph yielded by Rabbit 7 is definitely rising in character, while that of Rabbit 9 shows a moderate rise. Both graphs indicate that the sugar tolerance of these animals is still abnormally low. The graph constructed from the average of Rabbits 10 and 11, on the other hand, practically duplicates that of normal tolerance and, like it, shows on the average that slightly downward trend indicative of an increasing adequacy to deal with sugar. These findings justify the conclusion that sugar tolerance remains depressed for a short time even after the cessation of glycosuria, but that at about three weeks thereafter tolerance for sugar has returned to within definitely normal limits. Finally, the sugar tolerance of Rabbit 12 was investigated by means of a 100 per cent glucose solution instead of the usual 5 per cent solution. Allowing for experimental errors in the control experiment the graph gauging sugar tolerance 24 days after the diabetic phase was again similar to that of normal tolerance.

(5) <u>Insulin Sensitivity</u>. Six rabbits were investigated/

investigated from the point of view of insulin sensitivity by the method defined above. Each was tested in the control stage and during the diabetic phase, while three were also assessed after the glycosuric period. The results are set out in Table IV and collectively illustrated by Fig. 31. The curve of normal insulin sensitivity based on the average of the six animals begins at a fasting level of 132 mg. per cent and falls, after a short initial delay, rapidly and uniformly to 85 mg. per cent at 20 minutes. The blood sugar subsequently declines progressively more slowly and reaches 74 mg. per cent by 30 minutes. The curve then rises slowly and steadily to 80 mg. at 50 minutes. The blood sugar falls an absolute average of 58 mg. per cent (44 per cent) in 30 minutes, while the extremes are 41 mg. per cent in Rabbit 22 and 87 mg. per cent for Rabbit 18. Based on the average of the six animals the curve of insulin sensitivity during the diabetic phase starts at a fasting level of 172 mg. per cent which is 40 mg. per cent higher than the average control blood sugar. It shows no response for almost 10 minutes and then falls slowly to 154 mg. per cent after 25 minutes. The curve remains about the same level for 10 minutes and then rises at a slow steady rate to 164 mg. per cent at the end of 50 minutes. The average absolute fall is 18 mg. per cent (10 per cent) in 25 minutes, the extremes being an actual rise of 25 mg. per cent in Rabbit 13 and a fall of 47 mg./

15 a

TABLE IV

INSULIN SENSITIVITY

Rabbit	Stage	BLOOD SUGAR in mg. per cent								
		Fasting	5min	10min	15min	20min	25min	30min	40min	50min
13	Control	115	100	80	74	64	-	69 †	78 †	78 †
	Diabetes 1	131	142*	145†	149 *	156 *	-	151 †	149**	147
	2	117	112*	126*	112	117 *	117	117 *	109	-
	Recovery	-	-	-	-	-	-	-	-	-
14	Control	145	145*	135	122 *	103	83**	74	65	73
	Diabetes	165	168 *	156	158	158	154	161	159 †	156
	Recovery	87	82†	82	67 *	53	51	46	40	37
15	Control	151	145*	128	101 *	96	98	101	109	115
	Diabetes 1	183	183*	183	183	171	165	172	194	194
	2	187	178†	174	176	183	185	190 †	183**	189
	Recovery	-	-	-	-	-	-	-	-	-
18	Control	133	136	110†	101	85	73	58	46	47 ††
	Diabetes	245	237*	230	233	226	224	212	212	212
	Recovery	-	-	-	-	-	-	-	-	-
21	Control	127	119*	108*	94	81	69	63	69	75
	Diabetes	154	147*	136*	122	121	115*	110	115	119
	Recovery	112	109*	103	96	83	74	67	56	51
22	Control	119	115*	109	98 *	83 †	80	78	89	92
	Diabetes 1 ***	160	165*	160	151	142	136	135	133	138
	2	163	180*	171	163*	160	142*	140 *	133	149
	3	162	162*	156	147**	145*	140	147	160	178
	Recovery	138	105†	100	94*	74*	69	62	71	78*
Averages	Control	132	127	112	98	85	81	74	76	80
	Diabetes	172	172	167	163	161	154	157	158	164
	Recovery	112	99	95	86	70	65	58	56	55

* + 1 minute

† + 2 minutes

** + 3 minutes †† + 4 minutes.

*** Sugar excretion during day of test = (1) 5.3 g.; (2) 15.8 g. ; and (3) 4.1 g.

47 mg. per cent in Rabbit 22. Rabbit 22 is further instructive in that its blood sugar falls 22, 27 and 47 mg. per cent relative to a sugar excretion of 4.1 g., 5.3 g. and 15.8 g. per 24 hr. The significance of these reactions will be considered later, but the conclusion can now be made that since the percentage fall in response to insulin normally and during the diabetic phase is 44 per cent and 10 per cent respectively, insulin is at least four times less efficient in lowering the blood sugar in the diabetic as compared with the intact animal. The curve of insulin sensitivity after the diabetic phase is based on the average of Rabbits 14, 21 and 22 which were tested 18, 5 and 4 days respectively after the cessation of glycosuria and 18, 5 and 3 days respectively after the last injection. It begins at a fasting blood sugar of 112 mg. per cent and falls uniformly and fairly rapidly to 58 mg. per cent in half an hour. It declines thereafter in a scarcely perceptible manner until it reaches 55 mg. per cent at the end of the test. This curve differs from that of normal insulin sensitivity in that it is placed at a slightly lower level and fails to show any terminal recovery, but resembles it both in general form and in its fall of 57 mg. per cent (51 per cent) which is close to the normal response of 58 mg. per cent (44 per cent). The lower level of the curve is probably due to the fact that the animals have become accustomed to manipulative measures, while the curve

of/

of one of them shows a definite terminal recovery. Insulin tolerance after the diabetic phase can, therefore, be regarded as having returned to within normal range.

(6) Urine Volume. Excluding two which developed diarrhoea, twenty-one of the twenty-eight rabbits reacted to the initial injections of extract by excreting less urine. The degree of oliguria varied. Thus, three rabbits continued to pass more than 100 c.c. urine per 24 hr., while seven excreted between 40 and 65 c.c., eight between 20 and 40 c.c. and three less than 20 c.c. per 24 hr. Two of the last group of three were the most extreme examples in that each passed no urine for a period of 24 hr. The initial fall in urine volume was followed by a variety of reactions. Three animals continued to excrete a progressively less amount of urine, while the output of another three remained on the average at the level to which it had fallen. Fifteen rabbits increased their urine volume. The improvement usually began immediately after the initial fall, but was sometimes delayed for a period of days. In spite of it, three animals continued to excrete a subnormal amount of urine. Three, however, returned to normal excretion levels by the end of treatment and at this point nine rabbits even passed more copious urine than they ever did under control. Three of the remainder showed no significant change in urinary output during treatment, while the excretion/

excretion of another was normal at first and later excessive. Finally, several animals which remained oliguric during extract treatment immediately became polyuric on the cessation of injections. Polyuria, however, was in no case marked.

(7) Food Consumption. Nineteen of the twenty-eight rabbits were investigated from the point of view of food consumption. Only one continued during treatment to eat the same amount of food as it did while being controlled. On the other hand, seventeen reacted immediately to extract therapy by eating less cabbage or bran or both. Two rabbits continued to have a constantly or increasingly poor appetite during the rest of their treatment. The remaining sixteen animals, however, after a variable period of days showed an improvement of appetite usually first in the direction of cabbage and then bran. Six rabbits despite such improvement still ate a subnormal diet by the end of treatment. Five recovered their usual appetite and five even entered on a phase of excessive food consumption. A normal or excessive appetite was sometimes acquired as early as the middle of treatment, but was in other cases delayed until just after the cessation of injections.

(8) Islet Tissue. (a) Histological Examination. A comparison of the pancreases of the injected rabbits with those of normal animals revealed two changes referable to the islet tissue. First, the average size of the islets in a proportion of the injected animals/

animals was distinctly greater than the average of the largest islets in the control series and the deduction, therefore, was drawn that the average size of the islets in the entire injected series was probably greater than the average of the islets in the whole control group. The enlarged islets were structurally normal and consisted of the usual proportion of A- and B-cells. They thus showed no degranulation, hydrops or hyalinisation, the production of which formed one of the aims of the research. They were also devoid of mitotic figures despite the fact that their enlarged condition was obviously the result of division and increase of their component cells. Secondly, the islets so far as could be gauged by mere visual examination of sections were normal in number throughout the entire injected series with the exception of Rabbit 2. An observation supporting the normality of the islets as regards number was the fact that the small ducts in the pancreases of all the injected animals except Rabbit 2 were normal in number and distribution and in the character of their lining epithelium.

Rabbit 2 differed from all the others of the injected group in that the pancreas showed the following changes. Whereas they occur singly or in pairs normally, the small pancreatic ducts in Rabbit 2 were found in conspicuous groups, frequently of about half-a-dozen (Figs. 32 and 33). The exact number of ducts in any group, however, was difficult

to/

to determine since the new channels usually twisted among the acini of the surrounding pancreatic tissue and were sectioned in various planes. Nevertheless, the occurrence of the channels in such groups was absolute evidence of a focal formation of entirely new ducts. The new channels were occasionally placed in immediate relation to and had obviously budded from a larger interlobular duct. No such relationship, however, was usually observed and the origin of the new ducts, therefore, was attributed to a local proliferation of the original small intralobular channels. The cells lining the proliferated ducts were often finely vacuolated or almost filled by a single large globule of fluid. They were consequently swollen into large cubical or even columnar structures, while the flattening of their nucleus against the cell base had often led to the formation of signet ring forms. The lumen of the ducts was also correspondingly reduced in size, but sometimes still contained acidophile secretion. Isolated ducts throughout the pancreas showed varying degrees of the same hydropic vacuolation and swelling of their epithelium. A frequent feature in relation to the swollen ducts, whether isolated or in groups, was the presence of masses of islet tissue (Figs. 34 - 39). These masses ranged in size between small collections of about six cells and islets which were almost as large as any in the tissue. They also varied/

varied in number. Thus, isolated ducts and some groups of ducts showed only one related islet, while the islets numbered from six to nine in other groups of ducts. The islets usually lay in juxtaposition to the ducts, but ducts were occasionally observed to be completely surrounded by islet tissue and direct continuity, moreover, was sometimes observed between the cells lining the ducts and those of the islets. The islet tissue in specially stained sections consisted of the usual proportion of A- and B- cells (Figs. 40 - 41). The excess of islets in relation to the proliferated ducts clearly indicated a formation of new islets, yet no mitotic figures were found in the epithelium of either ducts or islets. Microscopical examination of the pancreases of the injected rabbits and a comparison with control material thus indicated that the islets of the injected series were on the average enlarged, but not increased numerically, except in Rabbit 2 which showed a proliferation of its ducts and a differentiation therefrom of entirely new islets. These histological conclusions necessitated more accurate assessment and led to the following quantitative investigation.

(b) Quantitative Estimation. Results relative to weight of pancreas, weight of islet tissue, average weight of islets and number of islets for the twenty-eight injected rabbits and for ten control animals/

animals are given in Tables V and VI respectively. The following points are noteworthy regarding the series of injected rabbits. The pancreas weighed from 1.0 g. in Rabbit 32 to 6.2 g. in Rabbit 10 and averaged 3.47 g. The islet tissue varied between 0.02 g. in Rabbit 32 and 0.32 g. in Rabbit 25 and was 0.09 g. on the average. The average weight of the islets as regards upper and lower limits was 0.217 ɣ in Rabbits 5 and 6 and 1.123 ɣ in Rabbit 26 respectively and had a mean value of 0.451 ɣ . Finally, the islets were as few as 44,000 in Rabbit 32 and as numerous as 442,000 in Rabbit 25, while the average number for the series was 202,000. The control series, on the other hand, yielded the following figures. The pancreas weighed from 1.95 g. in Rabbit 9 to 4.65 g. in Rabbit 4 and3.02 g. on the average. The islet tissue varied between 0.03 g. in Rabbits 6 and 9 and 0.09 g. in Rabbit 8 and averaged 0.05 g. The average weight of the islets was at least 0.128 ɣ in Rabbit 2 and at most 0.390 ɣ in Rabbit 8 and had a mean value of 0.230 ɣ . Finally, the islets numbered from 133,000 in Rabbit 9 to 402,000 in Rabbit 3, while their average number for the series was 240,000. The considerable variation in the weight of the pancreas of both injected and control rabbits suggests that the lowest and highest weights probably involve equivalent experimental errors as is to be expected from the difficulties/

22 a.

TABLE V.

ISLET TISSUE OF INJECTED RABBITS

Rabbit	Weight of Pancreas	Weight of Islet Tissue	Average weight of Islets	Number of Islets
1	2.71 g.	0.04 g.	0.274 ɣ	146,000
2	2.34 g.	0.08 g.	0.340 ɣ	235,000
3	5.69 g.	0.06 g.	0.568 ɣ	108,000
4	2.76 g.	0.07 g.	0.253 ɣ	277,000
5	2.93 g.	0.06 g.	0.217 ɣ	277,000
6	3.12 g.	0.05 g.	0.217 ɣ	230,000
7	3.06 g.	0.04 g.	0.340 ɣ	118,000
8	3.70 g.	0.07 g.	0.445 ɣ	152,000
9	2.96 g.	0.08 g.	0.474 ɣ	159,000
10	6.20 g.	0.15 g.	0.504 ɣ	305,000
11	3.45 g.	0.05 g.	0.317 ɣ	151,000
12	3.71 g.	0.07 g.	0.568 ɣ	119,000
13	1.86 g.	0.03 g.	0.365 ɣ	79,000
14	2.48 g.	0.06 g.	0.235 ɣ	257,000
15	4.09 g.	0.17 g.	0.445 ɣ	376,000
17	3.18 g.	0.05 g.	0.365 ɣ	142,000
18	3.33 g.	0.13 g.	0.713 ɣ	175,000
20	1.74 g.	0.04 g.	0.274 ɣ	131,000
21	2.20 g.	0.05 g.	0.295 ɣ	169,000
22	4.90 g.	0.17 g.	0.474 ɣ	347,000
24	2.42 g.	0.05 g.	0.390 ɣ	123,000
25	6.08 g.	0.32 g.	0.713 ɣ	442,000
26	5.89 g.	0.29 g.	1.123 ɣ	261,000
28	3.76 g.	0.15 g.	0.880 ɣ	173,000
29	4.95 g.	0.09 g.	0.274 ɣ	334,000
30	3.03 g.	0.07 g.	0.675 ɣ	104,000
31	3.70 g.	0.10 g.	0.474 ɣ	212,000
32	1.00 g.	0.02 g.	0.445 ɣ	44,000
Average	3.47 g.	0.09 g.	0.451 ɣ	202,000
Standard Error	± 0.25	± 0.014	± 0.040 ɣ	± 18,000

22 b.

T A B L E VI

ISLET TISSUE OF CONTROL RABBITS

Rabbit	Weight of Pancreas	Weight of Islet Tissue	Average weight of Islets	Number of Islets
1	3.10 g.	0.06 g.	0.365 γ	172,000
2	2.43 g.	0.04 g.	0.128 γ	334,000
3	4.07 g.	0.06 g.	0.154 γ	402,000
4	4.65 g.	0.06 g.	0.217 γ	276,000
5	3.57 g.	0.05 g.	0.184 γ	268,000
6	2.40 g.	0.03 g.	0.168 γ	186,000
7	2.80 g.	0.06 g.	0.274 γ	225,000
8	3.00 g.	0.09 g.	0.390 γ	234,000
9	1.95 g.	0.03 g.	0.200 γ	133,000
10	2.19 g.	0.04 g.	0.217 γ	176,000
Average	3.02 g.	0.05 g.	0.230 γ	240,000
Standard Error	± 0.17	± 0.004	± 0.017 γ	± 16,000

difficulties of the technique. Such a statement also applies to the other data, but the averages of both series, nevertheless, are regarded as fairly accurate estimates.

The average weights of the pancreases of the injected and control rabbits were sufficiently similar to indicate no substantial change in the weight of the organ in the experimental animals. On the other hand, the injected series had an average of 0.09 g. of islet tissue compared with 0.05 g. for the control animals. The injected rabbits thus had on the average approximately twice as much islet tissue as the control group. Again, the average weight of the islets in the injected group was 0.451 γ and 0.230 γ for the control series. The islets of the injected animals as in the previous instance were thus on the average approximately twice as much in weight as those of the control rabbits (Figs. 42 and 43). The injected rabbits, finally, had an average of 202,000 compared with 240,000 in the control series. Considering the wide control variation, these figures indicated that the number of islets in the injected group was within normal range. The data thus justified the conclusions that the injected animals had approximately twice their normal weight of islet tissue and that this increase was due to an enlargement of the islets to approximately twice their original weight, while the islets/

islets remained constant in number. Such quantitative conclusions confirmed the assessment of the islet tissue made on microscopical examination. The latter, however, was additionally valuable in that it showed how the increase of islet tissue in Rabbit 2 involved not only hypertrophy of the islets, but also an increase in their number.

DISCUSSION.

The 28 rabbits which formed the basis of this investigation reacted in one or other of four ways to crude extract treatment and are consequently divisible into four groups. A first group of 18 rabbits was characterised by both glycosuria and ketonuria ; a second group of 5 rabbits showed glycosuria, but no ketonuria ; a third group of 2 rabbits manifested itself in ketonuria, but no glycosuria; and a fourth group of 3 rabbits exhibited neither glycosuria nor ketonuria. A total of 23 rabbits or 82 per cent of the series thus excreted sugar. The production of pituitary diabetes in rabbits has been attempted on a few previous occasions. Baumann and Marine (1932) using a crude saline extract produced glycosuria in each of 4 rabbits. Houssay, Biasotti and Rietti (1934) administered an alkaline extract to two rabbits without any effect in the way of sugar excretion. Finally, Young (1938) giving a crude extract by both subcutaneous and intraperitoneal/

intraperitoneal routes observed glycosuria in about 75 per cent of nearly 100 rabbits. The results of this and previous investigations thus indicate that in showing glycosuria as a response to extract treatment rabbits react positively in a proportion of cases only. Such a conclusion regarding rabbits may be compared with the reaction of other species. For example, Houssay, Biasotti and Rietti (1934) produced glycosuria in all of 22 dogs, while in 25 dogs Young (1938 A) recorded only one failure. Using cats, Houssay et al (1934) observed glycosuria in both of two cases and Young (1938 A) in four of eight animals. Houssay et al (1934) effected the excretion of sugar in each of 4 guinea-pigs, but no glycosuria appeared in any of the guinea-pigs treated by Young (1938 A). Finally, Houssay et al (1934) failed to observe glycosuria in groups of 10 rats and 5 mice and in both of these species Young (1938 A) obtained closely similar results. Such reports and the findings with regard to rabbits in this investigation indicate that the above-mentioned species, according to their susceptibility to diabetogenic anterior pituitary extract, may be divided into three groups - (1) dogs which are highly susceptible; (2) cats, rabbits and guinea-pigs which react in a percentage of cases ; and (3) rats and mice which are practically insensitive.

Young (1938 A), as already stated, produced glycosuria/

glycosuria in about 75 per cent of nearly 100 rabbits, but in only 50 per cent to the extent of more than 2 g. sugar per day and also observed an equivalent response on the part of the component Dutch, Himalayan, Belgian hare and sandy lop-eared strains. 85 per cent of the English rabbits in this research showed glycosuria and 74 per cent excreted more than 2 g. sugar per day. The English strain would thus appear to be definitely more reactive than several other strains of rabbit. The present rabbits, moreover, showed marked individual variation in their diabetic response. This response thus varied in onset between the second and ninth day of treatment and from three to twenty-three days in duration, while its peak occurred from the sixth to the twenty-second day of treatment and amounted to between 1.1 g. and 32.7 g. sugar per 24 hr. The conclusion already reached regarding variation in susceptibility of different species may consequently be broadened to apply also to strains and individual animals of the same strain.

The highest amounts of sugar excreted were 22.6 g., 27.5 g., and 32.7 g. per 24 hr. Baumann and Marine (1932) observed a maximum glycosuria of 34.9 g. per 24 hr., but Young (1938 A) recorded a peak sugar excretion of only 13.4 g. per 24 hr. The highest excretion of sugar in the present series was thus/

thus comparable with that observed by Baumann and Marine. No matter its severity or its duration, however, the glycosuria inevitably disappeared and this proved to be the case under treatment with a daily amount of extract which was both maintained constant and considerably increased at intervals of a few days. The only differences were that the animals receiving constant extract excreted sugar on the average for nine days and showed an average maximum glycosuria of 11.2 g. per 24 hr. compared with corresponding averages of eleven days and 8.6 g. per 24 hr. for the animals injected with increasing extract. Moreover, re-injection after the diabetic phase failed both in rabbits which had received constant and increasing extract to effect any further excretion of sugar. Baumann and Marine (1932) treated their 4 rabbits with constant extract and likewise produced in each case a glycosuria lasting at most 14 days. Young (1937, 1938 A) administering constant extract to dogs observed a transitory glycosuria. By increasing the extract, however, he caused the glycosuria to reappear only to disappear again after a few days. He was then able by increasing the extract at intervals to prevent subsidence of the glycosuria and ultimately to establish a marked glycosuria which persisted even after the withdrawal of extract. The rabbit thus differs materially from the dog in that both constant

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and increasing extract is capable of rendering the rabbit permanently resistant to its diabetogenic influence. The development of such resistance might be explained in two ways. On the one hand, Collip and Anderson (1934, 1935) and Anderson and Collip (1934) have shown that animals treated with thyrotropic hormone develop in their serum a substance which neutralises the action of the hormone and the transitory nature of the glycosuria in the present rabbits might conceivably have been due to the development of an antihormone to the diabetogenic factor. The antithyrotropic hormone, however, takes on the average twenty-one days to develop and annul the action of the hormone, whereas the average duration of the glycosuria in this investigation was only eleven days. The definitely shorter duration of the glycosuria indicated the participation of a factor other than an antihormone, although that such an antihormone played at least some part cannot be completely discountenanced. On the other hand, Richardson and Young (1938) observed unusual mitotic activity in the islets of a dog which had become refractory to a crude diabetogenic extract and Rabbit 2 of this series showed a local proliferation of the small ducts in its pancreas and a differentiation therefrom of entirely new islets. These observations suggested that the transitoriness of the glycosuria in the English rabbit might find its explanation in an increase/

increase of islet tissue and consequently an enhanced source of insulin. This deduction was proved to be the case by a quantitative method which, although open to criticism in many ways, is nevertheless more reliable than any other known technique. The injected rabbits transpired to have a weight of islet tissue approximately twice that of the control series. This increase in the weight of islet tissue, moreover, was found to be due to an enlargement of the islets to approximately twice their original weight, while the islets remained constant in number. Rabbit 2 was an exception to this conclusion in that, as already stated, it showed evidence microscopically of a formation of new islets, but it was unique in this respect and must consequently be regarded as fortuitous. No evidence of mitotic division was found in the hypertrophied islets of any of the injected rabbits despite the fact that the islets must in many cases have been undergoing further enlargement at the time of the animal's death. The same statement is even applicable to Rabbit 2 in which active hyperplasia of ducts and islets was undoubtedly in progress when the animal died of acute pneumonia. Such a negative observation is in contrast with the frequency with which mitotic division was observed by Richardson and Young (1938), Richardson (1940) and Best, Campbell, Haist and Ham (1942) in the islets of diabetic or refractory dogs. Mitotic activity/

activity in the dogs, however, was associated with degranulation and hydrops of the beta cells and these degenerative phenomena may explain at least in part the occurrence of such unusual mitotic division. On the other hand, no degenerative changes were ever found in the islets of the present rabbits so that the original aims of the research as stated at the beginning were without success.

The increase of islet tissue in these rabbits is interesting in relation to the changes described in rats treated with anterior lobe extracts. Anselmino, Herold and Hoffmann (1933) injected rats for a few days with a watery extract of acetone-dried fresh anterior pituitary glands and claimed that this procedure effected a marked increase in the size and number of the pancreatic islets. They based their observations regarding the size and number of the islets merely on the microscopical examination of sections of the pancreases which is a method obviously conducive to faulty interpretation. Moreover, Richardson and Young (1937) were unable to support Anselmino et al with regard to the action of an extract prepared from acetone-dried material, but nevertheless showed by using a quantitative method for the assay of islet tissue that, when rats were treated daily for between two and three weeks with a saline extract of fresh anterior lobe, the islet tissue was doubled. They could not state

from/

from their method of assay, however, whether the increase of islet tissue was due to an increase in the size or number of the islets or both. The degree of islet tissue increase in the present rabbits thus duplicates that produced in rats by Richardson and Young (1937) and further proves that the increase is due to hypertrophy of the islets and occasionally also to an increase in their number. Marks and Young (1939, 1940) subsequently proved that the daily administration of a crude anterior lobe extract to rats for two weeks leads to a rise in the insulin content of the pancreas to about twice the control value. This observation indicates that the hyperplastic islet tissue in the rat and presumably therefore in the rabbit is functionally active. It does not necessarily mean, however, that insulin is being secreted into the circulation at an abnormally rapid rate. Indeed, Richardson and Young (1937) found that the fasting blood sugar of their injected rats remained within normal range and a similar observation was made in some of the present rabbits after they had become refractory. Moreover, sugar tolerance tests carried out in the post-diabetic stage were normal. Even when Rabbit 12 was specially strained by using a 100 per cent glucose solution in the consecutive method, its sugar tolerance was of the same measure after as before the diabetic phase. The hyperplastic islet tissue, in other words, reacted merely to the required degree

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and no more. Nevertheless, the fact that it represented a greater quantity and source of insulin readily explained how re-injection of refractory rabbits failed to produce any further glycosuria. This point has also been discussed by Best, Haist and Ridout (1939).

The increase of islet tissue may have been compensatory to hyperglycaemia or brought about under the influence of a pancreotropic factor in the extract. Consideration in deciding between these alternatives must be given to the following facts. Five of the present rabbits never excreted sugar and presumably therefore maintained more or less normal blood sugars and yet, with one exception, had islets the average weight of which was greater than that of the islets of the control series. Rabbit 2 was one of these animals and besides having islets larger than the average showed a definite proliferation of its pancreatic ducts and a formation of entirely new islets. Richardson and Young (1937), moreover, found in their rats that the extract which increased the amount of islet tissue to twice that of controls had little or no effect on the level of the blood sugar. Finally, Best, Campbell, Haist and Ham (1942) noted that the simultaneous administration of anterior lobe extract and insulin tended to prevent degenerative islet changes, but did not eliminate the occurrence of mitotic figures. These combined observations indicate that the increase of islet tissue/

tissue is not compensatory to any hyperglycaemia, but probably due to the action of an independent pancreotropic factor. Marks and Young (1940) distinguish between the pancreotropic factor which increases the amount of islet tissue and the insulin-increasing factor which augments the quantity of extractable insulin. Since they are so closely related in action, these two factors, however, may fairly be assumed to be one and the same substance. The pancreotropic factor on the basis of this and other investigations is thus apparently able to stimulate (1) proliferation of the ducts of the pancreas; (2) differentiation from the proliferated ducts of new islets; (3) division of the islet cells with resultant hypertrophy of original islets; and (4) formation of insulin by the islet tissue.

The foregoing suggests that the variation in the reaction of different species such as the dog, rabbit and rat to diabetogenic anterior lobe extract depends in part on the relative susceptibility of the species to the diabetogenic and pancreotropic factors. Thus, the dog would appear to be highly susceptible to the diabetogenic factor and only slightly to the pancreotropic substance. The result is that the dog almost always reacts with marked hyperglycaemia and glycosuria and the islets endeavouring to compensate become degenerated and depleted of insulin [Campbell, Keenan and Best (1939); Best, Campbell and Haist (1939); Marks and Young (1939)] . The English rabbit is less affected/

affected by the diabetogenic substance and more by the pancreotropic factor. It consequently shows glycosuria in 85 per cent of cases, but the excretion of sugar is always neutralised by an increase in the amount of islet tissue to about double the normal. Finally, the rat appears to be practically insensitive to the diabetogenic factor and conversely sensitive to the pancreotropic substance. The effect is that it practically never excretes sugar and yet shows a marked increase in the amount both of islet tissue and pancreatic insulin.

That susceptibility to diabetogenic extract is also related in part to the original amount of pancreatic islet tissue is suggested by the following facts. Young (1941) found that puppies tolerate doses of crude anterior lobe extract greatly in excess of those required to produce glycosuria in adult dogs without exhibiting any signs of diabetes. Such a difference in susceptibility could be explained on the ground that puppies have relatively more islet tissue per kilogram of body weight than adult dogs and Ogilvie (1937) in support of this possibility has shown that human infants and adults have their islet tissue apportioned in this way. Lukens and Dohan (1942) using cats were able by partial pancreatectomy and subsequent extract treatment constantly to render them diabetic, whereas Young (1938 A) could make only 50 per cent of his cats glycosuric by extract alone.

In/

In this research, re-injection of rabbits which had shown transitory diabetes with more than originally effective amounts of extract failed to produce any further diabetes, presumably because the animals had by then acquired more islet tissue, and, therefore, available insulin. Variation in the reaction to diabetogenic extract thus apparently depends in part on relative susceptibility to the diabetogenic and pancreatropic factors and in part on the original amount of islet tissue and available insulin. This combination of influences, moreover, probably explains the variable reaction to diabetogenic extract not only of different species but also of different strains and different animals of the same strain.

The existence in ox anterior lobe extract of a pancreotropic factor suggests that the human anterior hypophysis may secrete a similar agent and a certain amount of evidence, indeed, exists to support this deduction. In the developing human pancreas, for example, the ducts according to Maximow and Bloom (1938) proliferate and differentiate into acini and islets. The islets continue to increase in number until the third year of postnatal life and growth of the islet tissue thereafter is effected merely by hypertrophy of existing islets (Ogilvie, 1937). These developmental features, as already seen, are essentially pancreotropic effects and the deduction,/

deduction, therefore, may reasonably be made that a pancreotropic factor is responsible for their production. It is also noteworthy that the anterior lobe extract in English rabbits produced hypertrophy of the islets much more commonly than an increase in their number. The cells of the existing islets, in other words, are more susceptible to the proliferative action of the pancreotropic factor than the cells of the ducts. This difference in susceptibility is perhaps natural since differentiation of islets from ducts comes to an end a long time before the islets cease to hypertrophy and presumably is correspondingly difficult to bring back into being as a generative mechanism. Hypertrophied islets also occur in obese subjects (Ogilvie, 1933, 1935) and in diabetics (Warren, 1938), and Young (1941, 1942 A & B) taking it as an indication of pancreotropic hyperfunction has incorporated this finding in a theory regarding the etiology of obesity.

The diminution of sugar tolerance during the diabetic phase as demonstrated by both single and consecutive methods confirms the observations of Houssay (1936) and Young (1939). The form of the single tolerance curve obtained during the diabetic phase means that the islets discharge sufficient insulin to cope adequately with the injected glucose during the first 20 minutes of the test, but that the supply of insulin thereafter rapidly and progressively/

progressively diminishes until only a very small amount of secretion is being passed out by the islets. Again, the falling character of the consecutive tolerance curve in the intact animal is a sign that each dose of glucose successively stimulates an increased secretion of insulin by the islets and the rising curve obtained in the diabetic animal indicates conversely that each subsequent dose of glucose is followed by a diminished output of insulin. These deductions regarding the secretion of insulin in turn suggest two observations concerning the state of the islets. First, the islets during the diabetic phase probably contain less than their normal amount of insulin. This idea is supported by the fact that Young (1940) observed a fall in the insulin content of the rabbit pancreas after extract treatment. This finding would at first appear to contradict what has already been said regarding an increase in the amount of islet tissue and presumably, therefore, of insulin in the rabbit pancreas. The two statements, however, are compatible in that a fall of pancreatic insulin may occur during the stage of diabetes whereas after recovery from the diabetogenic factor a rise is to be anticipated along with the increase in islet tissue. Secondly, the islets during the diabetic phase must be greatly depleted in regard of their ability to manufacture and secrete insulin. Both points/

points indicate that in attempting to overcome the action of the diabetogenic factor the islets have been reduced to a state of semi-exhaustion which, in the absence of their susceptibility to the pancreotropic factor, might have ended in severe degenerative changes as in the dog. Nevertheless, the fact that normal sugar tolerance curves were obtained by both single and consecutive methods three weeks after the diabetic phase is evidence of ultimate complete functional recovery of the islets. It is noteworthy that the sugar tolerance of two rabbits as determined during the first two days of the post-diabetic period was diminished. Recovery of the islets cannot, therefore, coincide with the cessation of glycosuria, but must be a relatively gradual process requiring several days. The significance of a normal sugar tolerance curve in the presence of an increased quantity of islet tissue has already been mentioned in relation to the rate of secretion of insulin by the hyperplastic tissue.

The diminished sensitivity to the hypoglycaemic action of insulin such as was observed during the diabetic phase in several animals confirms the findings of Houssay and Potick (1929), Benedetto (1933), Cope and Marks (1935) and Young (1938 B). The degree of insensitivity was variable. It was occasionally absolute, but on the average such that insulin/

insulin was at least four times less effective in lowering the blood sugar of the diabetic compared with the intact animal. The three responses of Rabbit 22 to the test dose of insulin, however, were instructive in that they varied inversely as the degree of glycosuria. The anti-insulin activity of anterior lobe extracts according to Cope and Marks (1935) and Young (1938 B, 1939) may also be observed at a time when the blood sugar is not significantly altered as, for example, in the dog during the latent period between the beginning of extract treatment and the development of glycosuria. These observations together indicate that diminution in the hypoglycaemic action of insulin is not an effect of any diabetogenic factor in the extract. Young (1938 B) has found that the responsible agent is also not identical with prolactin or with the thyrotropic or gonadotropic hormones and has suggested (Young, 1936) that it be known as the glycotropic factor. This factor, he believes, is the direct antagonist of insulin. Since insulin has a three-fold action in that it inhibits the formation of sugar from glycogen in the liver, facilitates the synthesis of glycogen from sugar in the muscles, and stimulates the oxidation of sugar by the peripheral tissues [Cori, Cori and Goltz (1923); Cori (1931); Best, Dale, Hoet and Marks (1926)] , the glycotropic factor must, therefore, be regarded as having functions of an/

an opposite nature.

The fact that ketonuria occurred in about 70 per cent of the present animals agrees with the frequency with which Young (1938 A) observed the same phenomenon in his rabbits. Ketonuria resembled glycosuria in that it developed on the average on the sixth day and also ran a transitory course no matter whether the animal was treated with constant or increasing extract. Its duration, however, was slightly less than half that of the glycosuria so that the ketones had disappeared from the urine shortly before the glycosuria had reached its peak. The transitoriness of the ketonuria indicates just as in the case of the glycosuria that the animals developed a resistance to the mechanism whereby the extract effects the excessive production of ketones in the blood and the fact that re-injected animals failed to show any further ketonuria proves that within the scope of these experiments such refractoriness is permanent. The development of resistance to the ketogenic action of anterior pituitary extract has also been noted in rats by Black, Collip and Thomson (1934). On the other hand, Young (1939) in permanently diabetic dogs observed a progressive increase in ketonuria over periods of a year or more. The English rabbit and the dog thus differ markedly in that whereas the rabbit acquires permanent resistance to both the diabetogenic and ketogenic actions of the extract, the dog

under/

under intensive treatment fails in both of these respects. Three of the rabbits in this investigation excreted more than 1,000 mg. and six rabbits more than 500 mg. of total ketones per 24 hr. These amounts compared with normal ketone excretion in the English rabbit indicate a substantially increased ketonuria and contrast with the statement by Young (1938 A) that the ketonuria in his rabbits was never very striking. Apart from the rabbit, ketonuria has been produced by anterior pituitary extracts in the rat [Burn and Ling (1930); Best and Campbell (1938); Gray (1938); Shipley and Long (1938)] , dog [Rietti (1934) ; Young (1937, 1938 A)] , guinea pig [Best and Campbell (1938) ; Young (1938 A)] and cat (Young, 1938 A). No agreement exists at the moment regarding the mechanism whereby anterior pituitary extract stimulates ketogenesis. Thus, Black, Collip and Thomson (1934) attribute the phenomenon to a specific ketogenic factor in the extract, while Shipley and Long (1938) believe that it is due to the inhibitory action of the extract on carbohydrate and protein catabolism.

The frequency of oliguria and the moderate degree of polyuria even in those rabbits exhibiting a urinary increase were noteworthy findings. The oliguria occurred despite considerable simultaneous glycosuria and polyuria was associated with glycosuria in only four animals. Such observations confirm/

confirm the results of Young (1938 A), but are not in agreement with those of Baumann and Marine (1932) who reported a marked polyuria in their treated rabbits. The urinary changes in the present investigation were distinctly related to dietary fluctuations. Thus, the oliguria occurring immediately after the start of treatment was always associated with a reduced food consumption, while the subsequent excretion of a normal or excessive amount of urine was accompanied by a corresponding increase in the intake of food. Young (1938 A) noted a similar diminution in the food consumption of his rabbits.

CONCLUSIONS.

(1) Twenty-eight rabbits of which twenty-seven were English and one Dutchreceived daily subcutaneous or intraperitoneal treatment with a crude saline extract of fresh ox anterior pituitary gland.

(2) Eighteen rabbits showed both glycosuria and ketonuria, five glycosuria only, two ketonuria only, and three neither glycosuria nor ketonuria.

(3) Both glycosuria and ketonuria were transitory despite intensive therapy and later treatment failed to produce any further phase of either phenomenon.

(4) Sugar tolerance and insulin sensitivity were definitely decreased during the diabetic phase, but/

but both tests were thereafter within normal range.

(5) The injected rabbits had approximately twice the weight of islet tissue compared with controls. This increase was due to a hypertrophy of the islets to about twice their original weight, while the number of islets remained constant. One rabbit was an exception in that the pancreas also showed a proliferation of its small ducts and a differentiation therefrom of entirely new islets.

(6) Crude anterior lobe extract has diabetogenic, pancreotropic, glycotropic and ketogenic actions. The incidence of experimental pituitary diabetes depends partly on the original amount of islet tissue and partly on relative species, strain and individual susceptibility to the diabetogenic and pancreotropic actions.

(7) Urine volume as a result of extract treatment is usually diminished at first and later either normal or moderately increased. The variations in urine volume are due to corresponding changes in food consumption.

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Protocols.

Rabbit 1. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
9.5.40	1828	85	-	-	-	-	-
10.5.40	1785	153	-	-	-	-	-
11.5.40	1814	110	-	-	-	-	-
12.5.40	1842	103	-	-	-	-	-
13.5.40	1817	100	-	-	-	-	-
14.5.40	1842	108	-	-	-	-	-
15.5.40	1857	145	-	-	-	-	0.5 g. per kg. (1.9 cc)
16.5.40	1814	86	-	-	-	-	0.5 g. per kg. (1.9cc.)
17.5.40	1871	105	-	-	-	-	0.5 g. per kg. (1.9 cc.)
18.5.40	1871	30	-	-	-	-	0.5 g. per kg. (1.9 cc.)
19.5.40	1814	60	-	-	-	-	0.5 g. per kg. (1.9 cc.)
20.5.40	1814	61	-	-	-	-	1 g. per kg. (3.6 cc.)
21.5.40	1814	91	-	-	-	-	1 g. per kg. (3.6 cc.)
22.5.40	1871	51	-	-	-	-	1 g. per kg. (3.8 cc.)
23.5.40	1814	123	-	-	-	-	1 g. per kg. (3.6 cc.)
24.5.40	1817	53	-	-	-	-	1 g. per kg. (3.8 cc.)
25.5.40	1899	83	-	-	-	-	1 g. per kg. (3.8 cc.)
26.5.40	1871	155	-	-	-	-	1 g. per kg. (3.8 cc.)

Date.	Body Weight in g.	Urine Volume in cc.	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.
27.5.40	1814	78	-	-	-	-	1.5 g. per kg. (5.4 cc.)
28.5.40	1785	72	-	-	-	-	1.5 g. per kg. (5.4 cc.)
29.5.40	1842	170	-	-	-	-	1.5 g. per kg. (5.7 cc.)
30.5.40	1700	107	-	-	-	-	1.5 g. per kg. (5.2 cc.)
31.5.40	1700	90	-	-	-	-	1.5 g. per kg. (5.2 cc.)
1.6.40	1700	93	-	-	-	-	1.5 g. per kg. (5.2 cc.)
2.6.40	1700	146	-	-	-	-	-
3.6.40	1700	95	-	-	-	-	-
4.6.40	1587	88	-	-	-	-	2 g. per kg. (6.4 cc.)
5.6.40	1530	113	-	-	-	-	2 g. per kg. (6.4 cc.)
6.6.40	1516	69	-	-	-	-	2 g. per kg. (6.4cc.)
7.6.40	1530	92	-	-	-	KILLED (PERITONITIS)	

Rabbit 2. (Female)

Date	Body Weight in g.	Urine Volume in cc.	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.
22.6.40	1899	185	-	-	-	-	-
23.6.40	1871	185	-	-	-	-	-
24.6.40	1842	195	-	-	-	-	-
25.6.40	1871	150	-	-	-	-	1 g. per kg. (3.8 cc)
26.6.40	1871	127	-	-	-	-	1 g. per kg. (3.8 cc.)
27.6.40	1885	150	-	-	-	-	1 g. per kg. (3.8 cc.)
28.6.40	1857	191	-	-	-	-	1 g. per kg. (3.8 cc.)
29.6.40	1814	242	-	-	-	-	2 g. per kg. (7.2 cc.)
30.6.40	1814	276	-	-	-	-	-
1.7.40	1814	230	-	-	-	-	1.5 g. per kg. (5.4 cc.)
2.7.40	1842	200	-	-	-	-	1.5 g. per kg. (5.4 cc.)
3.7.40	1757	283	-	-	-	-	1.5 g. per kg. (5.4 cc.)
4.7.40	1700	238	-	-	-	-	1.5 g. per kg. (5.2 cc.)
5.7.40	1700	298	-	-	-	-	1.5 g. per kg. (5.2 cc.)
6.7.40	1700	260	-	-	-	-	2 x 1.5 g. per kg. (9 cc.)
7.7.40	1615	227	-	-	-	-	-
8.7.40	1530	259	-	-	KILLED (Ac. Bronchopneumonia).		

Rabbit 3. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
1.7.40	1615	136	-	-	-	-	-
2.7.40	1615	138	-	-	-	-	-
3.7.40	1587	158	-	-	-	-	-
4.7.40	1573	152	-	-	-	-	-
5.7.40	1615	89	-	-	-	-	-
6.7.40	1644	120	-	-	-	-	-
7.7.40	1644	183	-	-	-	-	-
8.7.40	1644	128	-	-	-	-	-
9.7.40	1700	170	-	-	-	-	-
10.7.40	1644	149	-	-	-	-	-
11.7.40	1700	190	-	-	-	-	1 g. per kg. (3.4 cc.)
12.7.40	1644	194	-	-	-	-	1 g. per kg. (3.4 cc.)
13.7.40	1700	118	-	-	-	-	2 g. per kg. (6.8 cc.)
14.7.40	1700	157	-	-	-	-	-
15.7.40	1672	174	-	-	-	-	1 g. per kg. (3.4 cc.)
16.7.40	1700	133	0.05	0.06	-	-	1 g. per kg. (3.4 cc.)

MED (Peritonitis).

Rabbit 4. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
14.7.40	1502	85	-	-	-	-	-
15.7.40	1473	162	-	-	-	-	-
16.7.40	1473	130	-	-	-	-	-
17.7.40	1502	153	-	-	-	-	-
18.7.40	1530	141	-	-	-	-	-
19.7.40	1530	122	-	-	-	-	1 g. per kg. (3.1 cc.)
20.7.40	1530	153	-	-	-	-	2 g. per kg. (6.2 cc.)
21.7.40	1530	132	-	-	-	-	-
22.7.40	1530	137	-	-	-	-	1 g. per kg. (3.1 cc.)
23.7.40	1530	58	-	-	-	-	1g. per kg. (3.1 cc.)
24.7.40	1544	146	-	-	-	-	1 g. per kg. (3.1 cc.)
25.7.40	1587	153	-	-	-	-	1.5 g. per kg. (4.8 cc.)
26.7.40	1587	107	-	-	-	-	1.5 g. per kg. (4.8 cc.)
27.7.40	5173	147	-	-	-	-	2 x 1.5 g. per kg. (9.6 cc.)
28.7.40	1587	122	-	-	-	-	-
29.7.40	1643	132	-	-	-	-	1.5 g. per kg. (4.8 cc.)
30.7.40	1700	113	-	-	-	-	1.5 g. per kg. (4.8 cc.)
31.7.40	1643	195	-	-	-	-	2 g. per kg. (6.4 cc)

1.8.40/

Date.	Body Weight in g.	Urine Volume in cc.	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.
1.8.40	1729	120	-	-	-	-	2 g. per kg. (6.4 cc.)
2.8.40	1700	135	-	-	-	-	2 g. per kg. (6.4 cc.)
3.8.40	1587	274	-	-	-	-	2 x 2 g. per kg. (12.8 cc.)
4.8.40	1587	55	-	-	-	-	-
5.8.40	1587	270	-	-	-	-	2 g. per kg. (6.4 cc.)
6.8.40	1587	252	-	-	-	-	2 g. per kg. (6.4 cc.)
7.8.40	1530	160	-	-	-	-	2.5 g. per kg. (7.6 cc.)
8.8.40	1473	73	-	-	-	DIED	(Exhaustion)

Rabbit 5. (Female)

	Body Weight in g.	Urine Volume in cc.	Blood Sugar in mg.%	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.
1.7.40	1729	176	-	-	-	-	-	-
2.8.40	1785	234	-	-	-	-	-	-
3.8.40	1757	200	-	-	-	-	-	-
4.8.40	1700	165	-	-	-	-	-	-
5.8.40	1729	168	-	-	-	-	-	-
6.8.40	1757	183	-	-	-	-	-	-
7.8.40	1757	197	-	-	-	-	-	-
8.8.40	1757	265	-	-	-	-	-	-
9.8.40	1757	185	152	-	-	-	-	-
10.8.40	1757	164	-	-	-	-	-	1 g. per kg. (3.6 cc.)
11.8.40	1814	167	155	-	-	-	-	2 x 1 g. per kg. (7.2 cc.)
12.8.40	1785	118	-	-	-	-	-	-
13.8.40	1842	150	-	-	-	-	-	1 g. per kg. (3.8 cc.)
14.8.40	1842	157	-	-	-	-	-	1 g. per kg. (3.8 cc.)
15.8.40	1814	212	-	0.05	0.1	-	-	1 g. per kg. (3.6 cc.)
16.8.40	1871	150	-	0.1	0.2	-	-	1.5 g. per kg. (5.7 cc.)
17.8.40	1899	148	-	0.1	0.2	-	-	1.5 g. per kg. (5.7 cc.)
18.8.40	1885	180	166	0.2	0.3	-	-	2 x 1.5 g. per kg. (11.4 cc.)
19.8.40	1814	225	-	0.06	0.1	-	-	-
20.8.40	1814	138	-	0.1	0.2	-	-	1.5 g. per kg. (5.4 cc.)
21.8.40	1814	136	-	0.2	0.2	-	-	1.5 g. per kg. (5.4 cc.)

	Body Weight in g.	Urine Volume in cc.	Blood Sugar in mg.%	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.
1.8.40	1842	206	-	0.5	1.0	-	-	2 g. per kg. (7.2 cc.)
2.8.40	1871	145	-	0.4	0.6	-	-	2 g. per kg. (7.4 cc.)
3.8.40	1871	156	232	2.0	3.1	-	-	2 g. per kg. (7.4 cc.)
4.8.40	1814	188	-	3.1	5.8	-	-	2 g. per kg. (7.3 cc.)
5.8.40	1814	166	-	3.0	5.0	-	-	2.5 g. per kg. (9.0 cc.)
6.8.40	1785	213	-	0.6	1.4	-	-	2.5 g. per kg. (9.0 cc.)
7.8.40	1757	230	-	0.7	1.5	-	-	-
8.8.40	1672	160	-	0.1	0.2	-	-	-
9.8.40	1587	257	95	-	-	-	KILLED.	

Rabbit 6. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
20.9.40	2041	139	-	-	-	-	-
21.9.40	2027	202	-	-	-	-	-
22.9.40	2041	93	-	-	-	-	-
23.9.40	1998	240	-	-	-	-	-
24.9.40	2069	270	-	-	-	-	-
25.9.40	2041	220	-	-	-	-	-
26.9.40	2097	142	-	-	-	-	-
27.9.40	1984	140	-	-	-	-	-
28.9.40	2012	101	-	-	-	-	-
29.9.40	2041	191	-	-	-	-	-
30.9.40	2055	81	-	-	-	-	-
1.10.40	2041	108	-	-	-	-	1 g. per kg. (4 cc.)
2.10.40	2097	100	-	-	-	-	1 g. per kg. (4.2 cc.)
3.10.40	1984	115	-	-	-	-	1 g. per kg. (4 cc.)
4.10.40	1927	64	-	-	-	-	1 g. per kg. (3.8 cc.)
5.10.40	1998	134	-	-	-	-	2 x 1 g.per kg. (8 cc.)
6.10.40	-	34	-	-	+	+	-
7.10.40	1927	140	-	-	-	-	1.5 g. per kg. (5.8 cc.)
8.10.40	1984	76	-	-	+	+	1.5 g. per kg. (6 cc.)
9.10.40	1927	95	-	-	-	-	1.5 g. per kg. (5.7 cc.)
10.10.40	1927	110	-	-	-	-	1.5 g. per kg. (5.7 cc.)
11.10.40	1899	95	-	-	-	-	1.5 g. per kg. (5.7 cc.)

Date.	Body Weight in g.	Urine Volume in cc.	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.
12.10.40	1927	112	-	-	-	-	2 x 2.0 g.per kg. (15.2cc).
13.10.40	1814	149	-	-	-	-	-
14.10.40	1842	172	-	-	-	-	2.0 g. per kg. (7.2 cc.)
15.10.40	1899	178	-	-	-	-	2.0 g. perkg. (7.6 cc.)
16.10.40	1956	85	-	-	-	-	2.0 g. per kg. (8 cc.)
17.10.40	1729	340	-	-	-	-	2.5 g. per kg. (9.0 cc.)
18.10.40	1714	392	-	-	-	-	2.5 g. per kg. (8.6 cc.)
19.10.40	1757	289	-	-	-	-	2 x 2.5 g. per kg. (18 cc.)
20.10.40	-	520	-	-	-	-	-
21.10.40	1743	134	-	-	-	-	-
22.10.40	1558	360	-	-	-	-	KILLED.

Rabbit 7. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
9.10.40.	1771	236	-	-	-	-	-
20.10.40	1778	196	-	-	-	-	-
21.10.40	1785	101	-	-	-	-	-
22.10.40	1799	258	-	-	-	-	-
23.10.40	1806	147	-	-	-	-	-
24.10.40	1785	200	-	-	Blank = 20 *	-	-
25.10.40	1700	67	-	-	-	-	-
26.10.40	1771	120	-	-	-	-	-
27.10.40	1793	200	-	-	-	-	-
28.10.40	1814	139	-	-	-	-	-
29.10.40	1785	191	-	-	-	-	1.0 g. per kg. (3.6 cc.)
30.10.40	1857	151	-	-	-	-	1.0 g. per kg. (3.8 cc.)
31.10.40	1842	110	-	-	-	-	1.0 g. per kg. (3.8 cc.)
1.11.40	1871	76	-	-	-	-	1.0 g. per kg. (3.8 cc.)
2.11.40	1871	144	-	-	-	-	2.5 g. per kg. (9.6 cc.)
3.11.40	-	74	-	-	-	-	-
4.11.40	1842	141	-	-	-	-	1.5 g. per kg. (5.8 cc.)
5.11.40	1814	91	-	-	100	91	1.5 g. per kg. (5.4 cc.)
6.11.40	1814	125	0.1	0.1	134	168	1.5 g. per kg. (5.4 cc.)
7.11.40	1842	121	3.0	3.6	109	132	2.0 g. per kg. (7.6 cc.)
8.11.40	1842	133	5.5	7.3	154	205	2.0 g. per kg. (7.6 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
9.11.40	1871	172	0.8	1.4	-	-	2.0 g. per kg. (7.6 cc.)
10.11.40	-	183	0.1	0.2	-	-	2.0 g. per kg. (7.6 cc.)
11.11.40	1871	233	0.1	0.2	-	-	2.5 g. per kg. (9.5 cc.)
12.11.40	1871	248	0.1	0.1	-	-	2.45 g. per kg. (9.1 cc.)
13.11.40	1842	198	-	-	-	-	-
14.11.40	1814	145	0.2	0.2	-	-	-

LIED.

SUGAR TOLERANCE :

CONSECUTIVE METHOD.

Date.	Blood Sugar in mg. per cent.								
	Fasting.	5 min.	28 min.	35 min.	58 min.	65 min.	88 min.	95 min.	118m.
10.40	110	274	163	270	151	264	133	254	160
11.40	98	218	154	231	156	313	169	349	170

Rabbit 8. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
12.11.40	2260	95	-	-	-	-	-
13.11.40	2239	239	-	-	-	-	-
14.11.40	2239	172	-	-	Blank = 30*	-	-
15.11.40	2239	180	-	-	-	-	-
16.11.40	2239	204	-	-	-	-	-
17.11.40	-	228	-	-	-	-	-
18.11.40	2183	194	-	-	-	-	-
19.11.40	2154	174	-	-	-	-	-
20.11.40	2154	187	-	-	-	-	-
21.11.40	2211	176	-	-	-	-	1.0 g. per kg. (4.4 cc.)
22.11.40	2211	170	-	-	-	-	1.0 g. per kg. (4.4 cc.)
23.11.40	2154	129	-	-	140	181	2 x 1.0 g. per kg. (8.4 cc.)
24.11.40	-	23	0.20	0.05	294	68	-
25.11.40	2097	28	0.08	0.02	106	30	1.0 g. per kg. (4.2 cc.)
26.11.40	2097	32	0.06	0.02	99	32	-

MED.

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

Rabbit 9. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
27.11.40	1615	138	-	-	-	-	-
28.11.40	1587	208	-	-	-	-	-
29.11.40	1615	178	-	-	-	-	-
30.11.40	1558	148	-	-	-	-	-
1.12.40	-	150	-	-	-	-	-
2.12.40	1558	194	-	-	-	-	-
3.12.40	1615	164	-	-	-	-	-
4.12.20	1643	169	-	-	-	-	1.0 g. per kg. (3.2 cc.)
5.12.40	1757	108	-	-	-	-	1.0 g. per kg. (3.6 cc.)
6.12.40	1729	143	-	-	-	-	1.0 g. per kg. (3.4 cc.)
7.12.40	1643	230	-	-	-	-	2 x 1.0 g. per kg. (6.4 cc.)
8.12.40	-	50	-	-	-	-	-
9.12.40	1672	120	-	-	-	-	1.5 g. per kg. (5.2 cc.)
10.12.40	1700	128	-	-	-	-	1.5 g. per kg. (5.2 cc.)
11.12.40	1729	181	-	-	-	-	1.5 g. per kg. (5.2 cc.)
12.12.40	1729	170	0.3	0.6	-	-	1.5 g. per kg. (5.2 cc.)
13.12.40	1700	31	-	-	-	-	1.5 g. per kg. (5.2 cc.)
14.12.40	1785	169	0.4	0.6	-	-	2.0 g. per kg. (7.2 cc.)
15.12.40	-	180	0.3	0.6	-	-	-
16.12.40	1757	265	-	-	-	-	2.0 g. per kg. (6.8 cc.)

Date.	Body Weight in g.	Urine Volume in cc.	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.
17.12.40	1785	180	-	-	-	-	2.0 g. per kg. (7.2cc.)
18.12.40	1814	241	2.5	6.0	-	-	2.0 g. per kg. (7.2 cc.)
19.12.40	1814	221	2.3	5.1	-	-	2.0 g. per kg. (7.2 cc.)
20.12.40	1785	232	6.6	15.3	-	-	2.0 g. per kg. (7.2 cc.)
21.12.40	1785	205	3.3	6.8	-	-	2.5 g. per kg. (9 cc.)
22.12.40	-	218	0.3	0.7	-	-	2.5 g. per kg. (9 cc.)
23.12.40	1814	217	-	-	-	-	2.5 g. per kg. (9 cc.)
24.12.40	1799	201	-	-	-	-	2.5 g. per kg. (9 cc.)
25.12.40	1806	209	-	-	-	-	-
26.12.40	1785	218	-	-	-	-	-
27.12.40	1785	182	-	-	-	KILLED.	

SUGAR TOLERANCE CURVE :

CONSECUTIVE METHOD.

e.	Blood Sugar in mg. per cent.								
	Fasting	5 min.	28min.	35min.	58min.	65min.	88 min.	95min.	118min.
.12.40	110	214	147	239	156	264	163	266	174

Rabbit 10. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
31.12.40	1814	152	-	-	-	-	-
1.1.41	1814	180	-	-	-	-	-
2.1.41	1871	174	-	-	-	-	-
3.1.41	1956	151	-	-	Blank = 35*	-	-
4.1.41	1871	170	-	-	-	-	-
5.1.41	-	185	-	-	-	-	-
6.1.41	1956	173	-	-	-	-	-
7.1.41	1927	181	-	-	-	-	-
8.1.41	1956	122	-	-	-	-	-
9.1.41	1984	131	-	-	-	-	1.0 g. per kg. (4 cc.)
10.1.41	1984	109	-	-	-	-	1.0 g. per kg. (4 cc.)
11.1.41	1927	110	-	-	-	-	2 x 1.0 g. per kg. (7.6 cc.)
12.1.41	-	83	-	-	12	10	-
13.1.41	1956	106	-	-	-	-	1.0 g. per kg. (3.8 cc.)
14.1.41	1871	80	0.7	0.6	10	8	1.5 g. per kg. (5.8 cc.)
15.1.41	1871	65	1.8	1.2	184	120	1.5 g. per kg. (5.8 cc.)
16.1.41	1842	101	3.7	3.7	539	544	1.5 g. per kg. (5.8 cc.)
17.1.41	1757	60	6.7	4.0	159	95	1.5 g. per kg. (5.4 cc.)
18.1.41	1814	80	2.0	1.6	131	105	1.5 g. per kg. (5.4 cc.)
19.1.41	-	106	2.8	3.0	54	57	1.5 g. per kg. (5.4 cc.)
20.1.41	1871	129	3.3	4.3	-	-	2.0 g. per kg. (7.6 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
21.1.41	1899	110	1.9	2.1	-	-	2.0 g. per kg. (7.6 cc.)
22.1.41	1927	146	2.3	3.4	-	-	2.0 g. per kg. (7.6 cc.)
23.1.41	1927	114	0.9	1.0	-	-	2.0 g. per kg. (7.6 cc.)
24.1.41	1814	143	-	-	-	-	-
25.1.41	1530	190	-	-	-	-	-
26.1.41	-	140	-	-	-	-	-
27.1.41	1643	72	-	-	-	-	-
28.1.41	1700	47	-	-	-	-	-
29.1.41	1700	143	-	-	-	-	-
30.1.41	1729	110	-	-	-	-	-
31.1.41	1757	90	-	-	-	-	-
1.2.41	1757	66	-	-	-	-	-
2.2.41	-	116	-	-	-	-	-
3.2.41	1814	73	-	-	-	-	-
4.2.41	1785	196	-	-	-	-	-
5.2.41	1814	185	-	-	-	-	-
6.2.41	1814	115	-	-	-	-	-
7.2.41	1814	147	-	-	-	-	-
8.2.41	1871	84	-	-	-	-	-
9.2.41	-	169	-	-	-	-	-
10.2.41	1871	111	-	-	-	-	-
11.2.41	1871	169	-	-	-	-	-
12.2.41	1814	134	-	-	-	-	-
13.2.41	1871	116	-	-	-	-	-
14.2.41	1814	88	-	-	-	-	-

Date.	Body Weight in g.	Urine Volume in cc.	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.
15.2.41	1899	83	-	-	-	-	-
16.2.41	-	158	-	-	-	-	-
17.2.41	1956	160	-	-	-	-	-
18.2.41	1984	117	-	-	-	-	-
19.2.41	1984	197	-	-	-	-	-
20.2.41	1956	180	-	-	-	-	-
21.2.41	1984	156	-	-	-	-	1.0 g. per kg. (4 cc.)
22.2.41	2041	95	-	-	-	-	2 x 1.0 g. per kg. (8 cc.)
23.2.41	-	100	-	-	-	-	-
24.2.41	2055	96	-	-	-	-	1.0 g. per kg. (4 cc.)
25.2.41	2069	105	-	-	-	-	1.0 g. per kg. (4.2 cc.)
26.2.41	2083	152	-	-	-	-	1.5 g. per kg. (6.4 cc.)
27.2.41	2097	127	-	-	-	-	1.5 g. per kg. (6.4 cc.)
28.2.41	2097	228	-	-	-	-	1.5 g. per kg. (6. 4 cc.)
1.3.41	2069	136	-	-	-	-	1.5 g. per kg. (6.4 cc.)
2.3.41	-	162	-	-	-	-	1.5 g. per kg. (6.4 cc.)
3.3.41	1984	23	-	-	-	DIED.	

SUGAR TOLERANCE CURVE. (Rabbit 10)

CONSECUTIVE METHOD.

te.	Blood Sugar in mg. per cent.								
	Fasting	5min.	28min.	35min.	58min.	65min.	88min.	95min.	118min.
1.4	131	268	205	224	131	189	169	201	172
.1.41	191	289	236	330	255	340	312	408	316
.241	122	262	192	278	171	239	144	258	140

Rabbit 11. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
15.1.41	1700	68	-	-	-	-	-
16.1.41	1672	140	-	-	-	-	-
17.1.41	1643	130	-	-	-	-	-
18.1.41	1643	111	-	-	Blank = 40*	-	-
19.1.41	-	133	-	-	-	-	-
20.1.41	1700	115	-	-	-	-	-
21.1.41	1700	146	-	-	-	-	-
22.1.41	1700	151	-	-	-	-	-
23.1.41	1700	94	-	-	-	-	-
24.1.41	1700	106	-	-	-	-	-
25.1.41	1729	142	-	-	-	-	-
26.1.41	-	151	-	-	-	-	-
27.1.41	1729	95	-	-	-	-	-
28.1.41	1700	72	-	-	-	-	-
29.1.41	1729	100	-	-	-	-	1.0 g. per kg. (3.4 cc.)
30.1.41	1700	38	-	-	-	-	1.0 g. per kg. (3.4 cc.)
31.1.41	1700	58	-	-	-	-	1.0 g. per kg. (3.4 cc.)
1.2.41	1700	20	-	-	-	-	2 x 1 g.per kg. (6.8 cc.)
2.2.41	-	61	-	-	124	51	-
3.2.41	1757	170	-	-	-	-	1.5 g. per kg. (5.4 cc.)
4.2.41	1757	136	7.7	10.5	129	121	1.5 g. per kg. (5.4 cc.)
5.2.41	1757	157	9.4	14.8	232	201	1.5 g. per kg. (5.4 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
6.2.41	1757	125	6.0	7.5	527	609	1.5 g. per kg. (5.4 cc.)
7.2.41	1700	63	5.3	3.3	701	404	1.5 g. per kg. (5.4 cc.)
8.2.41	1729	80	5.0	4.0	86	37	1.5 g. per kg. (5.4 cc.)
9.2.41	-	64	6.7	4.3	55	10	1.5 gper kg. (5.4 cc.)
10.2.41	1785	105	7.0	7.4	30	-	1.5 g. per kg. (5.4 cc.)
11.2.41	1785	156	5.5	8.6	-	-	1.5 g. per kg. (5.4 cc.)
12.2.41	1814	152	2.8	4.3	-	-	1.5 g. per kg. (5.4 cc.)
13.2.41	1757	116	3.0	3.5	-	-	1.5 g. per kg. (5.4 cc.)
14.2.41	1871	51	1.1	0.6	-	-	1.5 g. per kg. (5.8 cc.)
15.2.41	1757	181	0.9	1.6	-	-	1.5 g. per kg. (5.4 cc.)
16.2.41	-	127	0.04	0.1	-	-	1.5 g. per kg. (5.4 cc.)
17.2.41	1814	87	0.5	0.4	-	-	1.5 g. per kg. (5.4 cc.)
18.2.41	1814	111	-	-	-	-	2.0 g. per kg. (7.2 cc.)
19.2.41	1814	128	-	-	-	-	2.0 g. per kg. (7.2 cc.)
20.2.41	1814	139	-	-	-	-	2.0 g. per kg. (7.2 cc.)
21.2.41	1700	35	-	-	-	-	-
22.2.41	1714	200	-	-	-	-	-
23.2.41	-	143	-	-	-	-	-
24.2.41	1601	86	-	-	-	-	-

Date.	Body Weight in g.	Urine Volume in cc.	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.
25.2.41	1629	76	-	-	-	-	-
26.2.41	1643	60	-	-	-	-	-
27.2.41	1587	43	-	-	-	-	-
28.2.41	1587	35	-	-	-	-	-
13.3. 41	KILLED.						

SUGAR TOLERANCE CURVE:

CONSECUTIVE METHOD.

ate.	Blood Sugar in mg. per cent								
	Fasting	5min.	28min.	35min.	58min.	65min.	88min.	95min.	118min.
.1.41	129	282	212	345	224	351	230	363	224
2.41	171	306	252	395	311	452	306	513	345
. 3.41	119	268	183	315	199	319	203	306	172

Rabbit 12. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
25.2.41	2197	210	-	-	-	-	-
26.2.41	2239	172	-	-	-	-	-
27.2.41	2253	181	-	-	Blank = 14*	-	-
28.2.41	2211	180	-	-	-	-	-
1.3.41	2168	191	-	-	-	-	-
2.3.41	-	11	-	-	-	-	-
3.3.41	2183	232	-	-	-	-	-
4.3.41	2211	130	-	-	-	-	-
5.3.41	2126	124	-	-	-	-	-
6.3.41	2154	72	-	-	-	-	1.0 g. per kg. (4.2 cc.)
7.3.41	2211	50	-	-	-	-	1.0 g. per kg. (4.4 cc).
8.3.41	2211	54	-	-	-	-	2 x 1.0 g. per kg. (8.8 cc.)
9.3.41	-	40	-	-	-	-	-
10.3.41	2211	174	2.0	3.5	-	-	1.0 g. per kg. (4.4 cc.)
11.3.41	2267	68	5.8	4.0	330	215	1.5 g. per kg. (6.8 cc.)
12.3.41	2211	66	2.3	1.5	798	518	1.5 g. per kg. (6.4 cc.)
13.3.41	2239	67	1.8	1.2	413	267	1.5 g. per kg. (6.6 cc.)
14.3.41	2267	75	2.0	1.5	985	728	1.5 g. per kg. (6.8 cc.)
15.3.41	2211	102	1.2	1.2	1040	1047	1.5 g. per kg. (6.4 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
16.3.41	-	67	0.7	0.5	98	56	2.0 g. per kg. (8.8 cc.)
17.3.41	2239	131	0.2	0.3	58	58	2.0 g. per kg. (8.8 cc.)
18.3.41	2211	120	-	-	20	7	2.0 g. per kg. (8.8 cc.)
19.3.41	2211	138	-	-	-	-	2.0 g. per kg. (8.8 cc.)
20.3.41	2267	92	-	-	-	-	2.0 g. per kg. (9.0 cc.)
21.3.41	2295	125	-	-	-	-	2.5 g. per kg. (11.2 cc.)
22.3.41	2267	138	-	-	-	-	-
23.3.41	-	116	-	-	-	-	-
24.3.41	2041	93	-	-	-	-	-
25.3.41	1984	260	-	-	-	-	-
26.3.41	2041	153	-	-	-	-	-
24.4.41	DIED.						

SUGAR TOLERANCE CURVE:

CONSECUTIVE METHOD.

te.	Blood Sugar in mg. per cent.								
	Fasting.	5min.	28min.	35min.	58min.	65 min.	88min.	95min.	118min.
3.41 *	105	499	282	556	360	520	385	454	345
4.41	101	463	245	494	286	509	247	539	296

* This animal received four half-hourly injections of 5 cc. of a 100 per cent glucose solution instead of 5 cc. of a 20 per cent glucose solution as in Rabbits 7, 9, 10 and 11.

Rabbit 13. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
18.3.41	2126	159	-	-	-	-	-
19.3.41	2069	162	-	-	-	-	-
20.3.41	2069	160	-	-	-	-	-
21.3.41	2097	172	-	-	-	-	-
22.3.41	2041	112	-	-	-	-	-
23.3.41	-	131	-	-	Blank = 28*	-	-
24.3.41	2183	114	-	-	-	-	-
25.3.41	2097	295	-	-	-	-	-
26.3.41	2097	112	-	-	-	-	-
27.3.41	2097	115	-	-	-	-	-
28.3.41	2097	145	-	-	-	-	-
29.3.41	2069	162	-	-	-	-	-
30.3.41	-	170	-	-	-	-	-
31.3.41	2041	203	-	-	-	-	-
1.4.41	2041	136	-	-	-	-	-
2.4.41	2012	61	-	-	-	-	-
3.4.41	2041	64	-	-	-	-	-
4.4.41	2041	35	-	-	-	-	-
5.4.41	2069	116	-	-	-	-	-
6.4.41	-	-	-	-	-	-	-
7.4.41	2069	104	-	-	-	-	1.5 g. per kg. (6.3 cc.)
8.4.41	2041	149	-	-	-	-	1.0 g. per kg. (4.6 cc.)
9.4.41	2041	67	-	-	260	155	1.5 g. per kg. (6.0 cc.)
10.4.41	2097	59	-	-	552	309	1.5 g. per kg. (6.3 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
11.4.41	2097	78	-	-	20	0	1.5 g. per kg. (6.3 cc.)
12.4.41	2183	123	6.2	7.6	52	30	1.5 g. per kg. (6.6. cc.)
13.4.41	-	112	8.8	9.9	750	809	1.5 g. per kg. (6.6 cc.)
14.4.41	2154	139	9.8	13.6	932	1257	1.5 g. per kg. (6.3 cc.)
15.4.41	2154	187	0.2	0.3	53	47	1.5 g. per kg. (6.3 cc.)
16.4.41	2126	130	0.1	0.1	34	8	1.5 g. per kg. (6.3 cc.)
17.4.41	2154	110	-	-	-	-	1.5 g. per kg. (6.3 cc.)
18.4.41	2183	132	0.2	0.3	-	-	1.5 g. per kg. (6.3 cc.)
19.4.41	2154	260	-	-	-	-	1.5 g. per kg. (6.3cc.)
20.4.41	-	221	-	-	-	-	1.5 g. per kg. (6.3 cc.)
21.4.41	2154	246	-	-	-	-	1.5 g. per kg. (6.3 cc.)
22.4.41	2183	192	-	-	-	-	1.5 g. per kg. (6.3 cc.)
23.4.41	2069	279	-	-	-	-	1.5 g. per kg. (6.3 cc.)
24.4.41	2041	360	-	-	-	-	-
25.4.41	1956	136	-	-	-	-	-
26.4.41	1984	286	-	-	-	-	-
27.4.41	1956	235	-	-	-	-	-
28.4.41	1927	196	-	-	-	-	-
29.4.41	1955	202	-	-	-	-	-
30.4.41	1955	215	-	-	-	-	-
1. 5. 41	1842	253	-	-	-	-	-

Date.	Body Weight in g.	Urine Volume in cc.	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.
3.5.41	-	-	-	-	KILLED.		

INSULIN SENSITIVITY.

ate.	Blood Sugar in mg. per cent.									
	Fasting.	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.	60min
4.41	115	100	80	74	64	-	69†	78†	78†	-
4.41	131	142**	145†	149**	156**	-	151†	149††	147	151
4.41	117	112**	126**	112*	117**	117*	117**	109**		

* + ½ minute

** + 1 minute

† + 2 minutes

†† + 3 minutes

Rabbit 14. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
25.4.41	2012	140	-	-	-	-	-
26.4.41	2012	167	-	-	-	-	-
27.4.41	-	115	-	-	Blank= 9 *	-	-
28.4.41	1984	155	-	-	-	-	-
29.4.41	1984	148	-	-	-	-	-
30.4.41	1899	37	-	-	-	-	1.5 g. per kg. (6 cc.)
1.5.41	1927	66	-	-	-	-	1.5 g. per kg. (5.7 cc.)
2.5.41	1984	130	0.9	1.1	-	-	1.5 g. per kg. (6 cc.)
3.5.41	1984	203	1.9	3.9	-	-	1.5 g. per kg. (6 cc.)
4.5.41	-	188	5.0	9.4	-	-	1.5 g. per kg. (6 cc.)
5.5.41	1927	110	0.4	0.4	64	61	1.5 g. per kg. (5.8 cc.)
6.5.41	1956	160	-	-	32	37	1.5 g. per kg. (5.8 cc.)
7.5.41	1927	160	4.7	7.5	-	-	1.5 g. per kg. (5.8 cc.)
8.5.41	1927	226	4.4	10.0	-	-	1.5 g. per kg. (5.8 cc.)
9.5.41	1927	115	6.2	7.1	-	-	1.5 g. per kg. (5.8 cc.)
10.5.41	1899	148	0.9	1.3	-	-	1.5 g. per kg. (5.7 cc.)
11.5.41	-	220	-	-	-	-	-
12.5.41	1842	220	-	-	-	-	-
13.5.41	1814	197	-	-	-	-	-
14.5.41	1814	151	-	-	-	-	-

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
15.5.41	1814	228	-	-	-	-	-
16.5.41	1757	156	-	-	-	-	-
17.5.41	1785	84	-	-	-	-	-
18.5.41	-	224	-	-	-	-	-
19.5.41	1757	248	-	-	-	-	-
20.5.41	1757	165	-	-	-	-	-
21.5.41	1757	140	-	-	-	-	-
22.5.41	1757	129	-	-	-	-	-
23.5.41	1729	122	-	-	-	-	-
24.5.41	1757	142	-	-	-	-	-
25.5.41	-	157	-	-	-	-	-
26.5.41	1700	85	-	-	-	-	-
27.5.41	1700	79	-	-	-	-	-
28.5.41	1700	128	-	-	-	-	-
29.5.41	1700	100	-	-	-	-	-
30.5.41	1672	127	-	-	-	-	-
31.5.41	1672	133	-	-	-	-	1.5 g. per kg. (5.1 cc.)
1.6.41	-	62	-	-	-	-	1.5 g. per kg. (5.1 cc.)
2.6.41	1700	170	-	-	-	-	1.5 g. per kg. (5.1 cc.)
3.6.41	1729	142	-	-	-	-	1.5 g. per kg. (5.1 cc.)
4.6.41	1700	103	-	-	-	-	1.5 g. per kg. (5.1 cc.)
5.6.41	1729	204	-	-	-	-	1.5 g. per kg. (5.1 cc.)
6.6.41	1700	121	-	-	-	-	-
7.6.41	1672	132	-	-	-	-	-

Date.	Body Weight in g.	Urine Volume in cc.	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.
8.6.41	-	161	-	-	-	-	-
9.6.41	1729	150	-	-	-	-	-
10.6.41	1672	132	-	-	-	KILLED.	

INSULIN SENSITIVITY.

Date.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
4.41	145	145 *	135	122 *	103	83 ‡‡	74	65	73
5.41	165	168 *	156	158	158	154	161	159 †	156
5.41	87	82 †	82	67 *	53	51	46	40	37

* 1 minute ‡‡ 3 minutes

† 2 minutes

Rabbit 15. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
13.5.41	1984	39	-	-	-	-	-
14.5.41	2183	152	-	-	-	-	-
15.5.41	2154	135	-	-	-	-	-
16.5.41	2126	198	-	-	Blank = 20 *	-	-
17.5.41	2154	140	-	-	-	-	-
18.5.41	-	122	-	-	-	-	-
19.5.41	2154	210	-	-	-	-	1.5 g. per kg. (6 cc.)
20.5.41	2239	80	-	-	-	-	1.5 g. per kg. (6.6 cc.)
21.5.41	2211	62	-	-	-	-	1.5 g. per kg. (6.6 cc.)
22.5.41	2211	27	-	-	78	16	1.5.g. per kg. (6.6 cc.)
23.5.41	2183	59	-	-	190	100	1.5 g. per kg. (6.6 cc.)
24.5.41	2126	80	0.3	0.2	148	118	1.5 g. per kg. (6.3cc.)
25.5.41	-	97	0.6	0.6	238	212	1.5 g. per kg. (6.3 cc.)
26.5.41	2097	72	1.9	1.4	249	165	1.5 g. per kg. (6.3 cc.)
27.5.41	2069	68	3.3	2.3	195	119	1.5 g. per kg. (6.3 cc.)
28.5.41	2154	103	1.1	1.1	32	12	1.5 g. per kg. (6.0 cc.)
29.5.41	2097	87	0.9	0.8	-	-	1.5 g. per kg. (6.3 cc.)
30.5.41	2097	90	-	-	-	DIED.	

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

Rabbit 15.

INSULIN SENSITIVITY.

te.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.5.41	151	145*	128	101*	96	98	101	109	115
.5.41	183	183*	183	183	171	165	172	194	194
.5.41	187	178†	174	176	183	185	190†	183††	189

* + 1 minute

† + 2 minutes

†† + 3 minutes.

Rabbit 17. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
25.6.41	1814	170	-	-	-	-	-
26.6.41	1785	135	-	-	-	-	-
27.6.41	1814	248	-	-	Blank = 20*	-	-
28.6.41	1842	246	-	-	-	-	-
29.6.41	-	160	-	-	-	-	-
30.6.41	1814	280	-	-	-	-	-
1.7.41	1814	175	-	-	-	-	-
2.7.41	1700	162	-	-	-	-	-
3.7.41	1700	180	-	-	-	-	1.5 g. per kg. (5 cc.)
4.7.41	1814	52	-	-	-	-	1.5 g. per kg. (5.4 cc.)
5.7.41	1899	94	-	-	-	-	1.5 g. per kg. (5.6 cc.)
6.7;41	1814	115	0.1	0.1	39	22	1.5 g. per kg. (5.4 cc.)
7.7.41	1643	147	-	-	63	63	1.5 g. per kg. (4.8 cc.)
8.7.41	1558	63	-	-	20	-	-

DIE D.

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

Rabbit 18. (Female).

Date.	Body Weight in g.	Urine Volume in cc.	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.
6.7.41	1814	175	-	-	-	-	-
7.7.41	1899	151	-	-	-	-	-
8.7.41	1927	130	-	-	Blank = 15 *	-	-
9.7.41	1814	210	-	-	-	-	-
10.7.41	1814	221	-	-	-	-	-
11.7.41	1927	249	-	-	-	-	-
12.7.41	1871	266	-	-	-	-	-
13.7.41	-	310	-	-	-	-	-
14.7.41	1899	182	-	-	-	-	-
15.7.41	1984	308	-	-	-	-	-
16.7.41	1956	170	-	-	-	-	1.5 g. per kg. (5.6 cc.)
17.7.41	2012	187	-	-	-	-	1.5 g. per kg. (6 cc.)
18.7.41	1984	222	-	-	-	-	1.5 g. per kg. (5.9 cc.)
19.7.41	1984	253	-	-	-	-	1.5 g. per kg. (5.6 cc.)
20.7.41	-	174	-	-	134	207	-
21.7.41	1927	338	-	-	-	-	1.5 g. per kg. (5.7 cc.)
22.7.41	2012	265	-	-	-	-	1.5 g. per kg. (5.9 cc.)
23.7.41	2012	316	0.1	0.4	-	-	1.5 g. per kg. (5.9 cc.)
24.7.41	2012	296	0.7	2.0	-	-	1.5 g. per kg. (5.9 cc.)
25.7.41	2041	118	-	-	-	-	1.5 g. per kg. (5.9 cc.)
26.7.41	2012	282	1.5	4.2	-	-	1.5 g. per kg. (5.9 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
27.7.41	-	159	1.8	2.9	-	-	1.5 g. per kg. (5.9 cc.)
28.7.41	2041	280	4.4	12.3	-	-	1.5 g. per kg. (6.0 cc.)
29.7.41	1984	147	0.8	1.2	-	-	1.5 g. per kg. (5.9 cc.)
30.7.41	2041	119	-	-	-	-	1.5 g. per kg. (6.0 cc.)
31.7.41	1984	172	-	-	-	-	-
1.8.41	1984	297	-	-	-	-	-
2.8.41	1984	112	-	-	-	-	-
3.8.41	1984	355	-	-	-	-	-
4.8.41	1984	222	-	-	-	DIED.	

INSULIN SENSITIVITY.

te.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.41	133	136	110 †	101	85	73	58	46	47 ‡‡
7.41	205	203 **	196 *	172	156	140 †	136 *	126	120
7.41	245	237 *	230	233	226	224	212	212	212

* + 1 minute

† + 2 minutes

* * + 3 minutes

‡‡ + 4 minutes

Rabbit 20. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
3.8.41	1814	148	-	-	-	-	-
4.8.41	1785	313	-	-	-	-	-
5.8.41	1814	115	-	-	-	-	-
6.8.41	1757	200	-	-	-	-	-
7.8.41	1757	204	-	-	-	-	-
8.8.41	1530	133	-	-	-	-	-
9.8.41	1643	62	-	-	-	-	1.5 g. per kg. (4.8 cc.)
10.8.41	-	40	-	-	-	-	1.5 g. per kg. (4.8 cc.)
11.8.41	1785	100	-	-	-	-	1.5 g. per kg. (5.4 cc.)
12.8.41	1757	263	-	-	-	-	1.5 g. per kg. (5.2 cc.)
13.8.41	1643	79	-	-	-	-	1.5 g. per kg. (4.8 cc.)
14.8.41	1587	41	-	-	-	-	1.5 g. per kg. (4.8 cc.)
15.8.41	1530	8	-	-	-	-	1.5 g. per kg. (4.5 cc.)
16.8.41	1587	59	-	-	-	-	1.5 g. per kg. (4.8 cc.)
17.8.41	-	115	-	-	-	-	1.5 g. per kg. (4.8 cc.)
18.8.41	1530	200	-	-	-	-	1.5 g. per kg. (4.5 cc.)
19.8.41	1473	295	-	-	-	-	-
20.8.41	1473	91	-	-	-	-	-
21.8.41	1417	143	-	-	-	-	-
22.8.41	1360	87	-	-	-	KILLED.	

Rabbit 21. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
23.9.41	1984	149	-	-	-	-	-
24.9.41	1984	94	-	-	-	-	-
25.9.41	2041	178	-	-	-	-	-
26.9.41	1984	151	-	-	-	-	-
27.9.41	1984	123	-	-	-	-	-
28.9.41	-	62	-	-	-	-	-
29.9.41	1927	230	-	-	-	-	-
30.9.41	1956	83	-	-	-	-	-
1.10.41	2126	120	-	-	-	-	-
2.10.41	2183	194	-	-	-	-	1.5 g. per kg. (6.8 cc.)
3.10.41	2154	68	-	-	-	-	1.5 g. per kg. (6.3 cc.)
4.10.41	2097	98	-	-	-	-	1.5 g. per kg. (6.2 cc.)
5.10.41	-	159	-	-	-	-	1.5 g. per kg. (6.2 cc.)
6.10.41	2041	233	-	-	-	-	1.5 g. per kg. (6.0 cc.)
7.10.41	2097	73	-	-	-	-	1.5 g. per kg. (6.2 cc.)
8.10.41	2041	129	-	-	-	-	1.5 g. per kg. (6.0 cc.)
9.10.41	2154	125	0.7	0.9	-	-	1.5 g. per kg. (6.0 cc.)
10.10.41	2211	179	4.4	7.9	-	-	1.5 g. per kg. (6.6 cc.)
11.10.41	2154	187	2.8	5.1	-	-	1.5 g. per kg. (6.0 cc.)
12.10.41	-	199	0.1	0.2	-	-	1.5 g. per kg. (6.0 cc.)
13.10.41	2211	164	1.1	1.8	-	-	1.5 g. per kg. (6.2 cc.)

Date.	Body Weight in g.	Urine Volume in cc.	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.
14.10.41	2239	269	0.6	1.7	-	-	1.5 g. per kg. (6.6 cc.)
15.10.41	2267	209	1.6	3.3	-	-	1.5 g. per kg. (6.6 cc.)
16.10.41	2239	240	0.2	0.5	-	-	1.5 g. per kg. (6.6 cc.)
17.10.41	2154	235	-	-	-	-	-
18.10.41	2126	140	-	-	-	-	-
19.10.41	-	112	-	-	-	-	-
20.10.41	1927	295	-	-	-	-	-
21.10.41	1842	255	-	-	-	-	-
22.10.41	1757	89	-	-	-	KILLED.	

INSULIN SENSITIVITY.

Date.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.8.41	127	119*	108*	94	81	69	63	69	80
.10.41	154	147*	136*	122	121	115*	110	115	119
.10.41	112	109*	103	96	83	74	67	56	51

* + 1 minute.

Rabbit 22. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
14.10.41	2211	158	-	-	-	-	-
15.10.41	2097	205	-	-	-	-	-
16.10.41	2154	244	-	-	-	-	-
17.10.41	2211	186	-	-	-	-	-
18.10.41	2211	166	-	-	Blank= 20*	-	-
19.10.41	-	112	-	-	-	-	-
20.10.41	2211	115	-	-	-	-	-
21.10.41	2154	179	-	-	-	-	-
22.10.41	2211	82	-	-	-	-	-
23.10.41	2267	98	-	-	-	-	1.5 g. per kg. (6.8 cc.)
24.10.41	2183	130	-	-	-	-	1.5 g. per kg. (6.4 cc.)
25.10.41	2183	21	-	-	-	-	1.5 g. per kg. (6.4 cc.)
26.10.41	-	13	-	-	-	-	1.5 g. per kg. (6. 4 cc.)
27.10.41	2211	93	-	-	-	-	1.5 g. per kg. (6.6 cc.)
28.10.41	2211	57	0.06	0.03	-	-	1.5 g. per kg. (6.6 cc.)
29.10.41	2239	108	1.3	1.4	-	-	1.5 g. per kg. (6.6 cc.)
30.10.41	2154	62	1.4	0.9	-	-	1.5 g. per kg. (6.3 cc.)
31.10.41	2154	112	4.7	5.3	-	-	1.5 g. per kg. (6.3 cc.)
1.11.41	2154	171	6.2	10.6	166	250	1.5 g. per kg. (6.3 cc.)
2.11.41	-	285	6.6	18.7	105	242	1.5 g. per kg. (6.3 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
3.11.41	2097	282	8.0	22.6	65	127	1.5 g. per kg. (6.2 cc.)
4.11.41	2097	237	6.7	15.8	65	107	1.5 g. per kg. (6.2 cc.)
5.11.41	2183	171	7.2	12.2	-	-	1.5 g. per kg. (6.3 cc.)
6.11.41	2154	271	3.3	9.0	-	-	1.5 g. per kg. (6.3 cc.)
7.11.41	2211	170	2.4	4.1	-	-	1.5 g. per kg. (6.6. cc.)
8.11.41	2154	226	1.3	2.9	-	-	1.5 g. per kg. (6.3 cc.)
9.11.41	-	310	-	-	-	-	1.5 g. per kg. (6.3 cc.)
10.11.41	1927	124	-	-	-	-	-
11.11.41	2012	127	-	-	-	-	-
12.11.41	1927	120	-	-	-	-	-
13.11.41	1984	92	-	-	-	-	-
14.11.41	2041	194	-	-	-	-	-
15.11.41	2041	170	-	-	-	-	-
16.11.41	-	109	-	-	-	-	-
17.11.41	2012	230	-	-	-	-	-
18.11.41	2041	99	-	-	-	-	-

KILLED.

Rabbit 22.

INSULIN SENSITIVITY.

te.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.10.41	119	115*	109	98*	83**	80	78	89	92
10.41	160	165*	160	151	142	136	135	133	138
11.41	163	180*	171	163*	160	142*	140	133	149
11.41	162	162*	156	147†	145*	140	147	160	178
11.41	138	105**	100	94*	74*	69	62	71	78*

* + 1 minute

** + 2 minutes

† + 3 minutes

Rabbit 24. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
14.2.42	1927	119	-	-	-	-	-
15.2.42	-	84	-	-	-	-	-
16.2.42	1956	64	-	-	Blank = 22*	-	-
17.2.42	1927	56	-	-	-	-	1.5 g. per kg. (5.7 cc.)
18.2.42	1871	48	-	-	-	-	1.5 g. per kg. (5.6 cc.)
19.2.42	1927	-	-	-	-	-	1.5 g. per kg. (5.7 cc.)
20.2.42	1899	54	-	-	-	-	1.5 g. per kg. (5.7 cc.)
21.2.42	1899	100	0.3	0.3	173	151	1.5 g. per kg. (5.7 cc.)
22.2.42	-	197	0.1	0.2	140	233	1.5 g. per kg. (5.7 cc.)
23.2.42	1871	6	-	-	75	3	1.5 g. per kg. (5.6 cc.)
24.2.42	1871	172	0.3	0.5	-	-	1.5 g. per kg. (5.6 cc.)
25.2.42	1814	50	0.7	0.3	98	38	1.5 g. per kg. (5.6 cc.)
26.2.42	1814	64	0.5	0.3	-	-	1.5 g. per kg. (5.6 cc.)
27.2.42	1814	97	-	-	-	-	-
28.2.42	1814	115	1.4	1.7	-	-	-
1.3.42	-	175	1.1	1.9	-	-	1.5 g. per kg. (5.6 cc.)
2.3.42	1757	78	-	-	-	-	1.5 g. per kg. (5.4 cc.)
3.3.42	1814	95	-	-	-	-	1.5 g. per kg. (5.6 cc.)
4.3.42	1814	98	-	-	-	-	1.5 g. per kg. (5.6 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
5.3.42	1814	98	0.5	0.5	-	-	1.5 g. per kg. (5.2 cc.)
6.3.42	1814	126	0.1	0.2	-	-	1.5 g. per kg. (5.6 cc.)
7.3.42	1814	165	1.1	1.8	-	-	1.5 g. per kg. (5.6 cc.)
8.3.42	-	137	2.3	3.2	-	-	1.5 g. per kg. (5.6 cc.)
9.3.42	1814	166	2.5	4.2	-	-	1.1 g. per kg. (3.9 cc.)
10.3.42	1814	211	2.6	5.5	-	-	1.5 g. per kg. (5.6 cc.)
11.3.42	1871	115	2.9	3.3	-	-	1.0 g. per kg. (4 cc.)
12.3.42	1814	262	0.8	2.0	-	-	-
13.3.42	1814	153	0.4	0.6	-	-	-
14.3.42	1871	135	0.2	0.3	-	-	-
15.3.42	1814	262	0.1	0.2	-	-	-
16.3.42	1814	161	-	-	-	-	-
17.3.42	1814	199	-	-	-	-	-
18.3.42	1814	131	-	-	-	-	-
19.3.42	1814	59			DIED.		

SUGAR TOLERANCE:

SINGLE METHOD.

te.	Blood Sugar in mg. per cent.								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
2.42	126	298	286	270	250	235 *	214	183 †	156 †
2.42	140	311	286	280 *	276	264	260	260	260 *

* + 1 minute † + 2 minutes.

Rabbit 25. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
18.2.42	2041	96	-	-	-	-	-
19.2.42	2012	157	-	-	-	-	-
20.2.42	2041	186	-	-	-	-	-
21.2.42	2041	122	-	-	Blank = 28 *	-	-
22.2.42	-	183	-	-	-	-	-
23.2.42	2041	149	-	-	-	-	-
24.2.42	2041	84	-	-	-	-	-
25.2.42	2041	130	-	-	-	-	-
26.2.42	2069	135	-	-	-	-	-
27.2.42	2041	142	-	-	-	-	1.5 g. per kg. (6 cc.)
28.2.42	2012	82	-	-	-	-	1.5 g. per kg. (6 cc.)
1.3.42	-	126	-	-	-	-	1.5 g. per kg. (6 cc.)
2.3.42	1984	-	-	-	-	-	1.5 g. per kg. (6 cc.)
3.3.42	1927	53	-	-	379	186	1.5 g. per kg. (5.7 cc.)
4.3.42	1927	18	-	-	70	8	1.5 g. per kg. (5.7 cc.)
5.3.42	1871	66	0.6	0.4	620	391	1.5 g. per kg. (5.6 cc.)
6.3.42	1814	27	-	-	129	27	1.5 g. per kg. (5.6 cc.)
7.3.42	1814	43	0.7	0.3	143	50	1.5 g. per kg. (5.6 cc.)
8.3.42	-	34	2.6	0.9	110	28	1.5 g. per kg. (5.6 cc.)
9.3.42	1927	70	1.6	1.1	-	-	-

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
10.3.42	1927	74	0.3	0.2	-	-	-
11.3.42	1984	110	0.1	0.1	-	-	-
12.3.42	2012	183	-	-	-	-	-
13.3.42	1927	194	-	-	-	-	-
14.3.42	1984	168	-	-	-	-	-
15.3.42	-	170	-	-	-	-	-
16.3.42	1956	185	-	-	-	-	-
17.3.42	1927	178	-	-	-	-	-
18.3.42	1984	195	-	-	-	-	-
19.3.42	1984	145	-	-	-	-	-
7.4.42				DIED.			

SUGAR TOLERANCE:

SINGLE METHOD.

.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.42	103	235	207	178 **	158 *	138 **	126	114	101 †
.42	140	228	207	201 *	185 *	178	178	183	183

* + 1 minute ** + 3 minutes

† + 2 minutes

Rabbit 26. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
1.4.42	2097	92	-	-	-	-	-
2.4.42	2097	92	-	-	-	-	-
3.4.42	2041	181	-	-	-	-	-
4.4.42	2041	217	-	-	Blank = 50 *	-	-
5.4.42	-	98	-	-	-	-	-
6.4.42	2041	103	-	-	-	-	-
7.4.42	1984	150	-	-	-	-	1.5 g. per kg. (6 cc.)
8.4.42	2041	53	2.1	1.1	-	-	1.5 g. per kg. (6 cc.)
9.4.42	2041	44	6.7	2.9	-	-	1.5 g. per kg. (6 cc.)
10.4.42	2012	56	3.8	2.1	-	-	1.5 g. per kg. (6 cc.)
11.4.42	2041	47	3.4	1.6	-	-	1.5 g. per kg. (6 cc.)
12.4.42	-	89	3.5	3.1	820	695	1.5 g. per kg. (6 cc.)
13.4.42	2069	98	3.4	3.3	-	-	1.5 g. per kg. (6 cc.)
14.4.42	2069	54	6.5	3.5	450	216	1.5 g. per kg. (6 cc.)
15.4.42	2041	147	3.0	4.4.	-	-	1.5 g. per kg. (6 cc.)
16.4.42	2154	50	2.3	1.2	-	-	1.5 g. per kg. (6 cc.)
17.4.42	2211	66	0.8	0.6	-	-	1.5 g. per kg. (6.3 cc.)

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

Rabbit 26.

SUGAR TOLERANCE:

SINGLE METHOD.

...te.	Blood Sugar in mg. per cent								
	Fasting	5 min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
4.42	133	282	241	212	190 *	169	158	138	124
4.42	209	311	304	296	284	270	270	270	256 †

* + 1 minute. † + 5 minutes.

Rabbit 28 (Female).

Date.	Body Weight in g.	Urine Volume in cc.	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.
23.4.42	2324	59	-	-	-	-	-
24.4.42	2324	142	-	-	Blank = 29*	-	-
25.4.42	2324	252	-	-	-	-	1.5 g. per kg. (6.7 cc.)
26.4.42	-	64	-	-	-	-	1.5 g. per kg. (6.7 cc.)
27.4.42	2352	150	-	-	-	-	1.5 g. per kg. (7 cc.)
28.4.42	2380	90	-	-	-	-	1.5 g. per kg. (7 cc.)
29.4.42	2380	80	-	-	364	268	1.5 g. per kg. (7 cc.)
30.4.42	2267	110	0.5	0.5	42	14	1.5 g. per kg. (6.7 cc.)
1.5.42	2267	70	0.5	0.4	-	-	1.5 g. per kg. (6.7 cc.)
2.5.42	2267	54	3.4	1.8	115	46	-

DIED.

SUGAR TOLERANCE:

SINGLE METHOD.

Date.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.4.42	158	272	256	230	224	203	194	163	151
.5.42	222	321	296	272	262	245	243	239	239

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

Rabbit 29. (Female).

Date.	Body Weight in g.	Urine Volume in cc.	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.
27.4.42	1984	160	-	-	-	-	-
28.4.42	2041	147	-	-	Blank = 41*	-	-
29.4.42	2012	83	-	-	-	-	-
30.4.42	2012	125	-	-	-	-	-
1.5.42	2041	175	-	-	-	-	-
2.5.42	2012	126	-	-	-	-	1.5 g. per kg. (6 cc.)
3.5.42	-	28	-	-	-	-	1.5 g. per kg. (6 cc.)
4.5.42	1984	96	-	-	-	-	1.5 g. per kg. (6 cc.)
5.5.42	1956	56	-	-	-	-	1.5 g. per kg. (5.7 cc.)
6.5.42	2041	50	-	-	-	-	1.5 g. per kg. (6 cc.)
7.5.42	2041	57	-	-	-	-	1.5 g. per kg. (6 cc.)
8.5.42	2012	75	2.7	2.0	-	-	1.5 g. per kg. (6 cc.)
9.5.42	1984	94	0.1	0.1	-	-	1.5 g. per kg. (6 cc.)
10.5.42	-	89	1.8	1.6	-	-	1.5 g. per kg. (6 cc.)
11.5.42	1956	22	-	-	-	-	1.5 g. per kg. (5.7 cc.)
12.5.42	1956	34	-	-	637	213	1.5 g. per kg. (5.7 cc.)
13.5.42	1899	26	-	-	390	91	1.5 g. per kg. (5.7 cc.)
14.5.42	1899	248	-	-	-	-	-
15.5.42	1927	225	-	-	-	-	-

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
16.5.42	1927	212	-	-	-	-	-
17.5.42	-	143	-	-	-	-	-
18.5.42	1956	103	-	-	-	-	-
19.5.42	1956	101	-	-	-	-	-
20.5.42	1956	178	-	-	-	-	-
21.5.42	1984	165	-	-	-	-	-
22.5.42	1970	140	-	-	-	-	-
23.5.42	1927	124	-	-	-	-	-
24.5.42	-	128	-	-	-	-	-
25.5.42	1956	110	-	-	-	-	-
26.5.42	1984	89	-	-	-	-	-
27.5.42	1984	163	-	-	-	-	-
28.5.42	1984	73	-	-	-	-	-
29.5.42	1984	115	-	-	-	-	-
30.5.42	1956	171	-	-	-	-	-
31.5.42	-	-	-	-	-	-	-
1.6.42	1984	-	-	-	-	-	-
20.6.42		KILLED.					

SUGAR TOLERANCE:

SINGLE METHOD.

te	Blood Sugar in mg. per cent								
	Fasting	5 min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
.42	133	249	239	212	194 *	176	162	145	140
.42	121	230 *	215 *	201	174 *	153 †	140 *	119 *	109 *

* + 1 minute. † + 2 minutes.

Rabbit 30. (Female)

Date.	Body Weight in g.	Urine Volume in cc.	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.
4.5.42	1927	121	-	-	-	-	-
5.5.42	1984	91	-	-	-	-	-
6.5.42	1927	148	-	-	-	-	-
7.5.42	1984	56	-	-	Blank = 42*	-	-
8.5.42	1984	142	-	-	-	-	-
9.5.42	1984	95	-	-	-	-	-
10.5.42	-	170	-	-	-	-	-
11.5.42	2012	36	-	-	-	-	-
12.5.42	1984	47	-	-	-	-	-
13.5.42	1927	79	-	-	-	-	-
14.5.42	1927	169	-	-	-	-	1.5 g. per kg. (5.7 cc.)
15.5.42	1927	114	-	-	-	-	1.5 g.per kg. (5.7 cc.)
16.5.42	1956	92	-	-	-	-	1.5 g. per kg. (5.7 cc.)
17.5.42	-	34	-	-	-	-	1.5 g. per kg. (5.7 cc.)
18.5.42	1899	120	-	-	-	-	1.5 g. per kg. (5.7 cc.)
19.5.42	1984	25	1.7	0.4	-	-	1.5 g. per kg. (6 cc.)
20.5.42	1871	108	3.7	4.0	-	-	1.5 g. per kg. (5.6 cc.)
21.5.42	1899	31	1.0	0.3	75	10	1.5 g. per kg. (5.7 cc.)
22.5.42	1927	39	2.8	1.1	81	15	1.5 g. per kg. (5.7 cc.)
23.5.42	1956	48	1.1	0.5	-	-	1.5 g. per kg. (5.8 cc.)

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
24.5.42	-	70	0.9	0.7	-	-	-
25.5.42	1927	67	0.6	0.4	-	DIED.	

SUGAR TOLERANCE:

SINGLE METHOD.

e.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
5.42	114	249	231	212	187	171	140	119	107
5.42	168	311	294	276	262	254	242	235	230

Rabbit 31. (Female).

Date.	Body Weight in g.	Urine Volume in cc.	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.
19.5.42	2239	34	-	-	-	-	-
20.5.42	2239	143	-	-	-	-	-
21.5.42	2211	114	-	-	-	-	-
22.5.42	2211	80	-	-	Blank = 45*	-	-
23.5.42	2211	90	-	-	-	-	-
24.5.42	-	90	-	-	-	-	-
25.5.42	2126	116	-	-	-	-	1.5 g. per kg. (6.3 cc.)
26.5.42	2154	62	-	-	-	-	1.5 g. per kg. (6.3 cc.)
27.5.42	2154	160	1.3	2.1	-	-	1.5 g. per kg. (6.3 cc.)
28.5.42	2097	72	0.2	0.1	-	-	1.5 g. per kg. (6.3 cc.)
29.5.42	2097	55	2.5	1.4	-	-	1.5 g. per kg. (6.3 cc.)
30.5.42	2097	69	1.1	0.7	-	-	1.5 g. per kg. (6.3 cc.)
31.5.42	-	155	4.4	6.9	-	-	1.5 g. per kg. (6.3 cc.)
1.6.42	2211	196	7.0	13.7	189	282	1.5 g. per kg. (6.6 cc.)
2.6.42	2197	292	6.4	18.8	334	843	1.5 g. per kg. (6.6 cc.)
3.6.42	2211	288	7.3	21.1	465	1210	1.5 g. per kg. (6.6 cc.)
4.6.42	2154	330	9.9	32.7	562	1706	-
5.6.42	2239	114	4.4	5.0	-	-	-
6.6.42	2183	200	-	-	-	-	-
7.6.42	-	150	-	-	-	-	-
8.6.42	2126	180	-	-	-	-	-

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
9.6.42	2168	178	-	-	-	-	-
10.6.42	2069	200	-	-	-	-	-
11.6.42	2083	129	-	-	-	-	-
12.6.42	2069	87	-	-	-	-	-
13.6.42	2097	123	-	-	-	-	-
13.7.42		KILLED.					

SUGAR TOLERANCE:

SINGLE METHOD.

ate.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
5.42	160	295	270	252	226	218*	194	158	128
6.42	203	338	306	278	258	239	235	230*	225
7.42	130	296	252	212	184†	162*	148	119*	99

* + 1 minute. † + 2 minutes.

Rabbit 32. (Male)

Date.	Body Weight in g.	Urine Volume in cc.	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.
29.5.42	2211	150	-	-	-	-	-
30.5.42	2183	145	-	-	-	-	-
31.5.42	-	313	-	-	-	-	-
1.6.42	2239	136	-	-	Blank = 34*	-	-
2.6.42	2267	210	-	-	-	-	-
3.6.42	2295	208	-	-	-	-	-
4.6.42	2295	293	-	-	-	-	-
5.6.42	2352	271	-	-	-	-	-
6.6.42	2352	253	-	-	-	-	1.5 g. per kg. (6.9 cc.)
7.6.42	-	126	-	-	-	-	1.5 g. per kg. (6.9 cc.)
8.6.42	2380	140	0.5	0.7	-	-	1.5 g. per kg. (7.1 cc.)
9.6.42	2366	283	0.1	0.4	-	-	1.5 g. per kg. (6.9 cc.)
10.6.42	2352	240	0.5	1.1	-	-	1.5 g. per kg. (6.9 cc.)
11.6.42	2437	263	4.9	12.9	-	-	1.5 g. per kg. (7.2 cc.)
12.6.42	2437	257	4.9	12.6	-	-	1.5 g. per kg. (7.2 cc.)
13.6.42	2437	282	7.8	21.9	-	-	1.5 g. per kg. (7.2 cc.)
14.6.42	-	285	9.7	27.5	-	-	1.5 g. per kg. (7.2 cc.)
15.6.42	2380	234	2.5	5.9	-	-	1.5 g. per kg. (7 cc.)
16.6.42	2395	190	0.3	0.5	-	-	-
17.6.42	2380	265	-	-	-	-	-

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

Date.	Body Weight in g.	Urine Volume in cc.	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.
18.6.42	2352	225	-	-	-	-	-
19.6.42	2395	152	-	-	-	-	-
20.6.42	2395	119	-	-	-	-	-
21.6.42	-	210	-	-	-	-	-
22.6.42	2437	99	-	-	-	-	-
23.6.42	2437	218	-	-	-	-	-
24.6.42	2437	165	-	-	-	-	-
25.6.42	2437	120	-	-	-	-	-
13.7.42	DIED.						

SUGAR TOLERANCE:

SINGLE METHOD.

.6.	Blood Sugar in mg. per cent								
	Fasting	5min.	10min.	15min.	20min.	25min.	30min.	40min.	50min.
642	117	260	256	218	187	176	160	142	128
.42	135	282	260	251 *	226	211	203	194	185
.42	96	192 *	176	158	133 †	124	121	105	96 *

* + 1 minute. † + 2 minutes.

Quantitative Estimation

of

Pancreatic Islet Tissue.

Rabbit	ISLETS				ACINAR TISSUE				% age Islets Tissue
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.cm.	
1. H.**	4.06	0.14	530.3	18.3	24.47	10.3	3181.8	1337.7	1.3
B.	4.04	0.64	"	84.0	97.87	44.3	12727.2	5759.1	1.4
T.	4.07	0.35	"	45.6	44.72	18.8	5833.3	2453.4	1.8
2. H.	4.07	0.88	"	115.7	65.36	27.8	8484.8	3606.7	3.2
B.	8.12	1.54	2x"	201.1	69.35	29.4	9015.1	3819.1	5.2
T.	4.02	0.24	530.3	31.7	32.85	12.5	4242.4	1611.9	1.9
3. H.	4.03	0.26	"	34.2	27.99	18.1	3712.1	2399.6	1.0
B.	3.98	0.26	"	34.6	35.8 +2C*	20.0 +2C	4772.7 +2C	3073.3	1.1
T.	3.99	0.30	"	39.9	39.86	25.6	5303.0	3402.4	1.1
4. H.	4.07	0.82	"	106.8	61.57	36.6	7954.5	4726.2	2.2
B.	4.14	0.33	"	42.3	41.07	24.4	5303.0	3148.3	1.3
T.	8.11	1.81	2x"	236.8	75.83	46.3	10075.7	6154.6	3.8
5. H.	3.98	0.37	530.3	49.3	39.97	22.5	5303.0	2982.9	1.6
B.	4.00	0.51	"	67.6	59.90	30.7	7954.0	4076.6	1.6
T.	4.02	0.83	"	109.5	60.1	34.4	7954.0	4552.7	2.4
6. H.	4.08	0.51	"	66.3	36.2 + 8C	18.9 + 8C	4772.7 + 8C	4119.8	1.6
B.	4.05	0.25	"	32.7	28.3 + 3C	17.1 + 3C	3712.1 + 3C	2853.5	1.1
T.	4.02	0.86	"	113.4	48.4 + 7C	29.2 + 7C	6363.6 + 7C	5263.7	2.1
7. H.	3.98	0.27	"	36.0	24.2 +9C	13.2 +9C	3181.8 +9C	3567.0	1.0
B	3.99	1.0	"	132.9	52.2 +25C	28.3 +25C	6893.9 + 25C	8825.0	1.0
T.	4.04	0.24	"	31.5	28.1 +13C	14.9 +13C	3712.1 + 13C	4613.3	1.4
8 H.	3.99	0.37	"	49.2	28.2	16.3	3712.1	2145.7	2.2
B.	3.96	0.14	"	18.7	28.0 +2C	16.2 +2C	3712.1 +2C	2554.7	0.7
T.	4.10	0.71	"	91.8	32.1 +8C	15.9 + 8C	4242.4 + 8C	3729.4	2.4

C = area of one field = 203.5 sq.cm. = 1.54 g.

** H, B & T = head, body and tail of pancreas.

Age	Islet Tissue		Wt. Pancreas in g.	Wt. Islet Tissue in g.	No. Islets counted	Av. Area one Islet in sq.cm.		Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets.
a nar sue sq.cm										
37.7	1.37				27	0.68				
59.1	1.46	1.56	2.71	0.04	97	0.87	0.74	0.261	0.274	146,000
53.4	1.86				67	0.68				
06.7	3.21				147	0.79				
19.1	5.27	3.48	2.34	0.08	189	1.06	0.86	0.324	0.340	235,000
11.9	1.97				44	0.72				
99.6	1.01				31	1.10				
73.3	1.13	1.08	5.69	0.06	25	1.38	1.22	0.541	0.568	108,000
02.4	1.11				34	1.17				
26.2	2.26				152	0.70				
48.3	1.34	2.48	2.76	0.07	90	0.46	0.68	0.241	0.253	277,000
54.6	3.84				270	0.88				
82.9	1.65				80	0.62				
76.6	1.66	1.91	2.93	0.06	137	0.49	0.63	0.207	0.217	277,000
52.7	2.41				138	0.79				
19.8	1.61				125	0.53				
53.5	1.15	1.64	3.12	0.05	54	0.61	0.62	0.207	0.217	230,000
63.7	2.15				156	0.73				
67.0	1.01				53	0.68				
25.0	1.05	1.17	3.06	0.04	132	1.00	0.86	0.324	0.340	118,000
13.3	1.46				35	0.90				
45.7	2.29				49	1.00				
54.7	0.73	1.83	3.70	0.07	20	0.94	1.03	0.424	0.445	152,000
89.4	2.46				80	1.15				

Rabbit.	ISLETS				ACINAR TISSUE			
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.cm.
9. H.	3.97	0.81	530.3	108.2	32.1 +13C	14.8 +13C	4242.4 +13C	8849.9
B.	3.99	1.18	"	156.8	76.3 + 3C	43.5 + 3C	10075.7 + 3C	6354.8
T.	3.97	1.44	"	192.4	52.3 + 3C	32.2 + 3C	6893.9 + 3C	4854.9
10. H.	3.98	0.51	"	68.0	32.4	18.0	4242.4	2356.9
B.	4.08	0.70	"	91.0	40.3	25.0	5303.0	3289.7
T.	3.97	0.40	"	53.4	36.3	22.8	4772.7	2997.7
11. H.	3.98	0.46	"	61.3	44.3 +16C	24.7 +16C	5833.3 +16C	6508.4
B	4.03	0.40	"	52.6	24.2 + 9C	13.4 + 9C	3181.8 + 9C	3593.5
T.	4.03	0.69	"	90.8	44.2 + 8C	26.8 + 8C	5833.3 + 8C	5164.9
12. H.	4.06	0.27	"	35.3	24.1 + 3C	14.1 + 3C	3181.8 + 3C	2472.1
B.	4.07	0.40	"	52.1	36.1 + 1C	22.2 + 1C	4772.7 + 1C	3138.5
T.	4.03	1.40	"	184.2	44.4 +22C	25.3 +22C	5833.3 +22C	7778.4
13. H.	3.97	0.48	"	64.1	28.1 +16C	16.0 +16C	3712.1 +16C	5369.7
B.	4.04	0.21	"	27.6	44.3 +11C	26.3 +11C	5833.3 +11C	5701.6
T.	4.00	0.66	"	87.5	16.1 + 9C	8.3 + 9C	2121.2 + 9C	2925.0
14. H.	4.01	0.66	"	87.3	40.2 + 6C	23.0 + 6C	5303.0 + 6C	4255.1
B.	3.90	0.49	"	66.6	40.2	21.7	5303.0	2862.6
T.	4.09	0.93	"	120.6	44.4 + 3C	26.5 + 3C	5833.3 + 3C	4092.1
15. H.	4.04	0.92	"	120.8	24.2 + 9C	12.7 + 9C	3181.8 + 9C	3501.3
B.	4.03	0.73	"	96.1	28.3 + 4C	16.4 + 4C	3712.1 + 4C	2965.2
T.	4.05	1.00	"	130.9	16.2 + 6C	8.6 + 6C	2121.2 + 6C	2347.1

Age Islet Tissue		Wt. Pancreas in g.	Wt. Islet Tissue in g.	No. Islets counted	Av. Area one Islet in sq.cm.		Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets.
1.22				112	0.97				
2.47	2.55	2.96	0.08	150	1.05	1.07	0.451	0.474	159,000
3.96				161	1.20				
2.89				60	1.13				
2.77	2.48	6.20	0.15	70	1.30	1.10	0.480	0.504	305,000
1.78				61	0.88				
0.94				110	0.56				
1.46	1.39	3.45	0.05	55	0.96	0.83	0.302	0.317	151,000
1.76				93	0.38				
1.43				31	1.14				
1.66	1.82	3.71	0.07	47	1.11	1.21	0.541	0.568	119,000
2.37				133	1.38				
1.19				72	0.89				
0.48	1.55	1.86	0.03	60	0.46	0.88	0.348	0.365	79,000
2.99				68	1.29				
2.05				149	0.59				
2.33	2.44	2.48	0.06	91	0.73	0.65	0.224	0.235	257,000
2.95				188	0.64				
3.45				133	0.91				
3.24	4.09	4.09	0.17	90	1.07	1.05	0.424	0.445	376,000
5.58				112	1.17				

Rabbit	ISLETS				ACINAR TISSUE			
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.cm.
17. H.	3.97	0.35	530.3	46.8	20.0 +2C	12.5 +2C	2651.2 + 2C	2064.0
B.	3.96	0.20	"	26.8	27.9 +5C	15.5 +5C	3712.1 + 5C	3079.8
T.	4.01	0.35	"	46.3	28.0 +2C	16.9 +2C	3712.1 + 2C	2647.5
18. H.	4.05	0.55	"	72.0	28.2	16.5	3712.1	2172.0
B.	4.08	0.62	"	80.6	44.3	24.7	5833.3	3252.4
T.	4.07	1.19	"	155.1	36.2	21.7	4772.7	2861.0
20. H.	4.06	0.37	"	48.3	32.2	20.3	4242.4	2674.6
B.	4.04	0.41	"	53.8	32.4	20.4	4242.4	2671.1
T.	4.02	0.51	"	67.3	28.2 +3C	16.7 +3C	3712.1 +3C	2808.8
21. H.	3.99	0.36	"	47.9	24.3	14.7	3181.8	1924.8
B.	4.01	0.40	"	52.9	28.6 +3C	17.7 +3C	3712.1 + 3C	2907.8
T.	4.14	0.66	"	84.5	32.9 + 3C	21.5 +3C	4242.4 +3C	3382.9
22.H.	8.22	2.16	2x "	278.7	28.5 +24C	14.5 +24C	3712.1 +24C	6772.6
B.	4.05	0.70	530.3	91.7	28.8 + 7C	16.5 +7C	3712.1 + 7C	3551.2
T.	8.32	1.68	2x "	214.2	32.5 +19C	18.8 +19C	4242.4 +19C	6320.6
24 H.	3.96	0.33	530.3	44.2	28.2	18.2	3712.1	2395.8
B.	4.03	0.21	"	27.6	32.1 +2C	19.7 +2C	4242.4 + 2C	3010.6
T.	3.97	1.09	"	145.6	32.4 +11C	18.0 +11C	4242.4 + 11C	4595.4
25 H.	3.96	0.35	"	46.9	12.1	7.6	1590.9	999.2
B.	3.97	0.86	"	114.9	28.3 + 2C	18.2 + 2C	3712.1 + 2C	2794.3
T.	12.17	3.85	3x "	503.3	40.2 +21C	24.3 +21C	5303.0 + 21C	7479.0

%age Islet Tissue		Wt. Pancreas in g.	Wt. Islet Tissue in g.	No. Islets counted	Av. Area one Islet in sq.cm.		Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets.
2.27				49	0.96				
0.87	1.63	3.18	0.05	33	0.81	0.89	0.348	0.365	142,000
1.75				51	0.91				
3.31				51	1.41				
2.48	3.74	3.33	0.13	65	1.24	1.41	0.679	0.713	175,000
5.42				98	1.58				
1.81				73	0.66				
2.01	2.07	1.74	0.04	73	0.74	0.71	0.261	0.274	131,000
2.40				94	0.72				
2.49				68	0.70				
1.82	2.27	2.20	0.05	74	0.71	0.77	0.281	0.295	169,000
2.50				93	0.91				
4.12				270	1.03				
2.58	3.36	4.90	0.17	80	1.15	1.07	0.451	0.474	347,000
3.39				205	1.04				
1.84				50	0.88				
0.92	1.98	2.42	0.05	42	0.66	0.90	0.372	0.390	123,000
3.17				127	1.15				
4.69				37	1.27				
4.11	5.18	6.08	0.32	83	1.38	1.41	0.679	0.713	442,000
6.73				317	1.59				

Rabbit	ISLETS				ACINAR TISSUE			
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.
26. H.	4.06	1.33	530.3	173.7	40.1	25.5	5303.0	3372.
B.	3.96	0.75	"	100.4	32.1	19.7	4242.4	2603.
T.	3.98	1.64	"	218.5	40.1	27.9	5303.0	3689.
28. H.	4.05	0.41	"	53.7	20.1	12.0	2651.5	1583.
B.	4.06	0.75	"	98.0	32.0 +3C	20.4 + 3C	4242.4 + 3C	3315.
T.	3.99	1.33	"	176.8	24.1 + 5C	15.3 + 5C	3181.8 + 5C	3037.
29. H	4.06	0.25	"	32.7	20.1	12.1	2651.5	1596.
B.	3.98	0.16	"	21.3	20.1	13.1	2651.5	1728.
T.	3.95	0.49	"	65.8	24.2 +4C	16.0 + 4C	3181.8 + 4C	2917.
30. H.	3.96	0.29	"	38.8	20.0	13.4	2651.5	1776.
B.	4.05	0.44	"	57.6	24.2 + 1C	16.5 + 1C	3181.8 + 1C	2372.9
T.	4.08	0.39	"	50.7	28.2	16.6	3712.1	2185.
31. H.	3.99	0.57	"	75.8	32.3 + 7C	19.0 + 7C	4242.4 +7C	3920.0
B.	4.07	0.62	"	80.8	40.2	25.4	5303.0	3350.7
T.	4.03	0.69	"	90.8	16.1 + 5C	10.5 + 5C	2121.2 + 5C	2400.9
32. H.	3.97	0.76	"	101.5	24.2 +8C	12.6 +8C	3181.8 +8C	3284.6
B.	4.02	0.20	"	26.4	20.1 +1C	12.9 +1C	2651.5 +1C	1905.2
T.	4.04	0.13	"	17.1	16.1	9.0	2121.2	1185.8

rea cinar issue n sq.	%age Islet Tissue		Wt. Pan-creas in g.	Wt. Islet Tissue in g.	No. Islets Counted	Av. Area one Islet. in sq.cm.		Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets.
372.	5.15				89	1.95				
603.	3.86	4.98	5.89	0.29	56	1.79	1.85	1.070	1.123	261,000
689.	5.92				121	1.81				
583.	3.39				37	1.45				
315.	2.96	4.06	3.76	0.15	61	1.61	1.59	0.838	0.880	173,000
037.	5.82				104	1.70				
596.	2.05				42	0.78				
728.	1.23	1.85	4.95	0.09	40	0.53	0.71	0.261	0.274	334,000
917.	2.26				79	0.83				
776.	2.18				28	1.39				
372.	2.43	2.31	3.03	0.07	45	1.28	1.32	0.643	0.675	104,000
185.	2.32				39	1.30				
920.	1.93				74	1.02				
350.	2.41	2.71	3.70	0.10	69	1.17	1.06	0.451	0.474	212,000
400.	3.78				91	1.00				
284.	3.09				87	1.17				
905.	1.39	1.97	1.00	0.02	25	1.06	1.04	0.424	0.445	44,000
185.	1.44				19	0.90				

Control.	ISLETS				ACINAR TISSUE			
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.c
1.H.	4.04	0.21	530.3	27.6	20.2	13.4	2651.5	1758.9
B.	4.00	0.40	"	53.0	24.1	15.6	3181.8	2059.6
T.	4.01	0.29	"	38.4	24.2	15.2	3181.8	1998.5
2. H.	4.05	0.26	"	34.0	24.1	14.3	3181.8	1887.9
B.	4.05	0.16	"	21.0	20.1	12.5	2651.5	1648.9
T.	4.05	0.41	"	53.7	24.1 +2C	15.3 +2C	3181.8 + 2C	2427.0
3. H.	4.07	0.15	"	19.5	20.1	10.7	2651.5	1411.5
B	4.04	0.22	"	28.9	28.1	18.2	3712.1	2404.2
T	3.99	0.27	"	35.9	20.2	13.8	2651.5	1811.4
4. H	4.04	0.26	"	34.2	24.1	15.4	3181.8	2033.2
B	4.03	0.22	"	29.0	24.1	15.7	3181.8	2072.8
T	4.05	0.15	"	19.6	28.1	18.6	3712.1	2457.1
5. H	4.09	0.18	"	23.3	20.1	11.5	2651.5	1517.0
B	4.07	0.07	"	9.1	20.1	14.4	2651.5	1899.6
T	4.07	0.37	"	48.2	20.1 + 3C	12.5 + 3C	2651.5 + 3C	2259.4
6.H	4.04	0.19	"	24.9	20.2 +5C	10.7 + 5C	2651.5 + 5C	2422.0
B	4.64	0.29	521.6	32.6	18.7 +9C	11.5 + 9C	2086.4 + 9C	3114.6
T.	4.68	0.76	"	84.7	23.5 +16C	12.8 +16C	2608.0 +16C	4676.5
7. H	4.70	0.77	"	85.5	42.0	29.0	4694.4	3241.4
B	4.64	0.20	"	22.5	28.2	18.7	3129.6	2075.3
T	4.73	0.93	"	102.6	37.6 +5C	23.0 +5C	4172.8 + 5C	3570.0

Page Islet Tissue		Wt. Pancreas in g.	Wt. Islet Tissue in g.	No. Islets Counted	Av. Area one Islet in sq.cm.		Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets
1.57				40	0.69				
2.57	2.02	3.10	0.06	44	1.20	0.89	0.348	0.365	172,000
1.92				50	0.77				
1.80				84	0.41				
1.27	1.76	2.43	0.04	54	0.39	0.43	0.122	0.128	334,000
2.21				107	0.50				
1.38				43	0.45				
1.20	1.52	4.07	0.06	62	0.47	0.49	0.147	0.154	402,000
1.98				64	0.56				
1.68				53	0.65				
1.40	1.29	4.65	0.06	40	0.73	0.64	0.207	0.217	276,000
0.80				36	0.54				
1.52				42	0.55				
0.48	1.38	3.57	0.05	17	0.54	0.58	0.175	0.184	268,000
2.13				73	0.66				
1.03				49	0.51				
1.05	1.30	2.40	0.03	61	0.53	0.54	0.160	0.168	186,000
1.81				147	0.58				
2.64				105	0.81				
1.08	2.20	2.80	0.06	41	0.56	0.72	0.261	0.274	225,000
2.87				129	0.80				

Control	ISLETS				ACINAR TISSUE			
	Wt. Sheet in g.	Wt. Islets in g.	Area Sheet in sq.cm.	Area Islets in sq.cm.	Wt. Sheets in g.	Wt. Acinar Tissue in g.	Area Sheets in sq.cm.	Area Acinar Tissue in sq.cm.
8.H.,	4.66	0.75	521.6	83.9	28.0 +4C	17.6 + 4C	3129.6 + 4C	2781.2
B,	4.64	0.51	"	57.3	23.5 +2C	14.0 + 2C	2608.0 + 2C	1960.7
T,	4.68	1.11	"	123.7	37.7 +6C	24.2 +6C	4172.8 + 6C	3899.6
9. H,	4.65	0.69	"	77.4	32.8 + 8C	20.5 +8C	3651.2 + 8C	3910.0
B,	4.60	0.27	"	30.6	37.1 + 1C	23.9 +1C	4172.8 + 1C	2891.6
T,	4.65	0.18	"	20.2	27.7	17.2	3129.6	1943.3
10.H,	4.60	0.54	"	61.2	32.3	19.5	3651.2	2204.3
B,	4.63	0.20	"	22.5	27.9	16.7	3129.6	1873.3
T,	4.68	0.24	"	26.7	27.9	19.0	3129.6	2130.6

%age Islet Tissue		Wt. Pancreas in g.	Wt. Islet Tissue in g.	No. Islets Counted	Av. Area one Islet in sq.cm.	Av. Vol. one Islet c.μ.	Av. Wt. one Islet in γ	Total No. of Islets.
3.02				87	0.96			
2.92	3.04	3.00	0.09	59	0.97 0.94	0.372	0.390	234,000
3.17				137	0.90			
1.98				106	0.73			
1.06	1.36	1.95	0.03	60	0.51 0.61	0.190	0.200	133,000
1.04				35	0.58			
2.78				75	0.82			
1.20	1.74	2.19	0.04	44	0.51 0.63	0.207	0.217	176,000
1.25				47	0.57			

SECTION V.

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

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SECTION V.

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

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/

TABLE I.

		Group 1	Group 2	Group 3	Entire Series
mber of animals		7	4	4	15
ation of treatment		15 days	10 days	10 days	12 days
erage amount of A.P.G.* per animal		43.5 g.	31.5 g.	28.6 g.	36.3 g.
dy ght.	Av. per day	7.3 g.	-0 g.	-12.1 g.	1.8 g.
	Total	5.7 %	-0 %	- 5.9 %	1.1 %
erage caloric intake er day relative to ontrol.		65 %	65 %	39 %	58 %
erage urinary volume per day relative to ontrol.		87 %	90 %	47 %	77 %
to s- ia.	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
on- a.	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.

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

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/

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 cc. 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 cc. 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/

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
verage	0.113	0.494	218,000
tandard 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/

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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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 250 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.)
.1140	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.

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.
.11.40	1842	141	0 g.bran 125 g.cab.	23	-	-	-	-	1.5 g.per kg. (5.8 c.c.)
.11.40	1814	91	0 g.bran 100 g.cab.	19	-	-	100	91	1.5 g.per kg. (5.4 cc.)
.11.40	1814	125	20 g.bran 190 g.cab.	88	0.1	0.1	134	168	1.5 g.per kg. (5.4 c.c.)
.11.40	1842	121	50 g.bran 165 g.cab.	162	3.0	3.6	109	132	2.0 g.per kg. (7.6 c.c.)
.11.40	1842	133	60 g.bran 200 g.cab.	231	5.5	7.3	154	205	2.0 g.per kg. (7.6 c.c.)
.11.40	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	-	-	-

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Rabbit 9. (Male)

Date.	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.
7.11.40	1615	138	100 g.bran 250 g.cab.	308	-	-	-	-	-
28.1140	1587	208	100 g.bran 250 g.cab.	308	-	-	-	-	-
9.11.40	1615	178	100 g.bran 250 g.cab.	308	-	-	-	-	-
0.11.40	1558	148	100 g.bran 250 g.cab.	308	-	-	-	-	-
12.40	-	150	100 g.bran 250 g.cab.	308	-	-	-	-	-
12.40	1558	194	100 g.bran 250 g.cab.	308	-	-	-	-	-
12.40	1615	164	100 g.bran 250 g.cab.	308	-	-	-	-	-
12.40	1643	169	100 g.bran 250 g.cab.	308	-	-	-	-	1.0 g. per kg. (3.2 c.c.)
12.40	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.)
12.40	-	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.)

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.
5.12.40	-	180	100 g.bran 250 g.cab.	308	0.3	0.6	-	-	-
6.12.40	1757	265	100 g.bran 250 g.cab.	308	-	-	-	-	2.0 g. per kg. (6.8 c.c.)
7.12.40	1785	180	100 g.bran 250 g.cab.	308	-	-	-	-	2.0 g. per kg. (7.2 cc.)
8.12.40	1814	241	100 g.bran 250 g.cab.	308	2.5	6.0	-	-	2.0 g. per kg. (7.2 c.c.)
9.12.40	1814	221	100 g.bran 250 g.cab.	308	2.3	5.1	-	-	2.0 g. per kg. (7.2 c.c.)
10.12.40	1785	232	100 g.bran 250 g.cab.	308	6.6	15.3	-	-	2.0 g. per kg. (7.2 c.c.)
11.12.40	1785	205	100 g.bran 250 g.cab.	308	3.3	6.8	-	-	2.5 g. per kg. (9 c.c.)
12.12.40	-	218	80 g.bran 250 g.cab.	256	0.3	0.7	-	-	2.5 g. per kg. (9 c.c.)
13.12.40	1814	217	100 g.bran 250 g.cab.	308	-	-	-	-	2.5 g. per kg. (9 c.c.)
14.12.40	1799	201	100 g.bran 250 g.cab.	308	-	-	-	-	2.5 g. per kg. (9 c.c.)
15.12.40	1806	209	100 g.bran 250 g.cab.	308	-	-	-	-	-
16.12.40	1785	218	100 g.bran 250 g.cab.	308	-	-	-	-	-
17.12.40	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	-	-	-	-	-
1.40	1814	180	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.40	1871	174	100 g.bran 300 g.cab.	318	-	-	Blank - 35*	-	-
1.40	1956	151	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.40	1871	170	70 g.bran 290 g.cab.	237	-	-	-	-	-
1.40	-	185	100 g.bran 300 g.cab.	318	-	-	-	-	-
1.40	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.

ge.	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)

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.
.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	-	-	-	-	-
9.141	1729	100	100 g.bran 300 g.cab.	318	-	-	-	-	1.0 g.per kg. (4.3 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.)
.241	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.)

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.
9.2.41	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	-	-	-	-	-
.241	1587	43	-	-	-	-	-	-	-
2.41	1587	35	-	-	-	-	-	-	-

Rabbit 12. (Female)

Date.	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.
3.2.41	2197	210	100 g.bran 300 g.cab.	318	-	-	-	-	-
5.2.41	2239	172	100 g.bran 300 g.cab.	318	-	-	-	-	-
7.2.41	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	-	-	-	-	-
.41	2211	130	100 g.bran 300 g.cab.	318	-	-	-	-	-
.41	2126	124	fasting	-	-	-	-	-	-
.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	-	-	-	-	-
0.3.41	2211	174	50 g.bran 300 g.cab.	187	2.0	3.5	-	-	1.0 g. per kg. (4.4.c.c.)
1.3.41	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.)
3.3.41	2239	67	-	-	1.8	1.2	413	267	1.5 g. per kg. (6.6 c.c.0
4.3.41	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

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.
.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.
4.41	2069	116	50 g.bran 290 g.cab.	185	-	-	-	-	-
4.41	-	-	-	-	-	-	-	-	-
4.41	2069	104	100 g.bran 150 g.cab.	290	-	-	-	-	1.5 g. per kg. (6.3 c.c.)
4.41	2041	149	0 g.bran 190 g.cab.	35	-	-	-	-	1.0 g. per kg. (4.6 c.c.)
4.41	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.)

to	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	-	-	-	-	-
4.41	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.)
.5.41	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.
2.5.41	1842	220	80 g.bran 300 g.cab.	265	-	-	-	-	-
3.5.41	1814	197	20 g.bran 300 g.cab.	108	-	-	-	-	-
4.5.41	1814	151	30 g.bran 330 g.cab.	140	-	-	-	-	-
0.5.41	1814	228	60 g.bran 388 g.cab.	229	-	-	-	-	-

Rabbit 15. (Male)

	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	-	-	-	-	-
5.5.41	2154	135	90 g.bran 280 g.cab.	288	-	-	-	-	-
6.5.41	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)

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.
.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)

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.
.10.41	2211	158	100 g.bran 110 g.cab.	282	-	-	-	-	-
5.10.41	2097	205	150 g.bran 200 g.cab.	430	-	-	-	-	-
6.10.41	2154	244	150 g.bran 250 g.cab.	439	-	-	-	-	-
7.10.41	2211	186	200 g.bran 300 g.cab.	580	-	-	-	-	-
.10.41	2211	166	200 g.bran 300 g.cab.	580	-	-	-	-	-
9.10.41	-	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	-	-	-	-	-
0.10.41	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.)
3.10.41	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.)
8.10.41	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.)
11.41	2154	171	110 g.bran 170 g.cab.	320	6.2	10.6	166	250	1.5 g. per kg. (6.3 c.c.)
11.41	-	285	100 g.bran 300 g.cab.	318	6.6	18.7	105	242	1.5 g. per kg. (6.3 c.c.)
11.41	2097	282	162 g.bran 260 g.cab.	473	8.0	22.6	65	127	1.5 g. per kg. (6.2 c.c.)
11.41	2097	237	120 g.bran 300 g.cab.	370	6.7	15.8	65	107	1.5 g. per kg. (6.2 c.c.)
11.41	2183	171	160 g.bran 300 g.cab.	475	7.2	12.2	-	-	1.5 g. per kg. (6.3 c.c.)
11.41	2154	271	150 g.bran 300 g.cab.	449	3.3	9.0	-	-	1.5 g. per kg. (6.3 c.c.)
11.41	2211	170	120 g.bran 290 g.cab.	368	2.4	4.1	-	-	1.5 g. per kg. (6.6 c.c.)
11.41	2154	226	90 g.bran 380 g.cab.	306	1.3	2.9	-	-	1.5 g. per kg. (6.3 c.c.)
11.41	-	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.
3.42	-	34	20 g.bran 190 g.cab.	88	2.6	0.9	110	28	1.5 g. per kg. (5.6 c.c.)
3.42	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	-	-	-
.342	2012	183	100 g.bran 200 g.cab.	299	-	-	-	-	-
.3.42	1927	194	100 g.bran 285 g.cab.	315	-	-	-	-	-
.342	1984	168	100 g.bran 270 g.cab.	312	-	-	-	-	-
.3.42	-	170	100 g.bran 280 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)

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.
4.42	2097	92	85 g.bran 200 g.cab. 20 g.hay	290	-	-	-	-	-
4.42	2097	92	70 g.bran 190 g.cab. 20 g.hay	249	-	-	-	-	-
4.42	2041	181	90 g.bran 230 g.cab. 20 g.hay	308	-	-	-	-	-
4.42	2041	217	30 g.bran 170 g.cab. 20 g.hay	140	-	-	Blank = 50*	-	-
4.42	-	98	50 g.bran 200 g.cab. 20 g.hay	198	-	-	-	-	-
4.42	2041	103	80 g.bran 250 g.cab. 20 g.hay	286	-	-	-	-	-
4.42	1984	150	100 g.bran 270 g.cab. 20 g.hay	342	-	-	-	-	1.5 g. per kg. (6 c.c.)
4.42	2041	53	50 g.bran 200 g.cab. 20 g.hay	198	2.1	1.1	-	-	1.5 g. per kg. (6 c.c.)
4.42	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.
5.42	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.
5.42	1927	121	50 g.bran 260 g.cab. 20 g.hay	209	-	-	-	-	-
5.42	1984	91	40 g.bran 270 g.cab. 20 g.hay	185	-	-	-	-	-
5.42	1927	148	30 g.bran 275 g.cab. 20 g.hay	160	-	-	-	-	-
5.42	1984	56	0 g.bran 175g.cab. 20 g.hay	62	-	-	Blank= 42*	-	-
5.42	1984	142	50 g.bran 275 g.cab. 20 g.hay	212	-	-	-	-	-
5.42	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	-	-	-	-	-
6.42	2239	136	100 g.bran 300 g.cab. 20 g.hay	348	-	-	Blank = 34*	-	-
6.42	2267	210	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
6.42	2295	208	100 g.bran 300 g.cab. 20 g.hay	348	-	-	-	-	-
.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/

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/

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/

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/

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/

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 rôle 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 refrattory 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, according 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/

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.

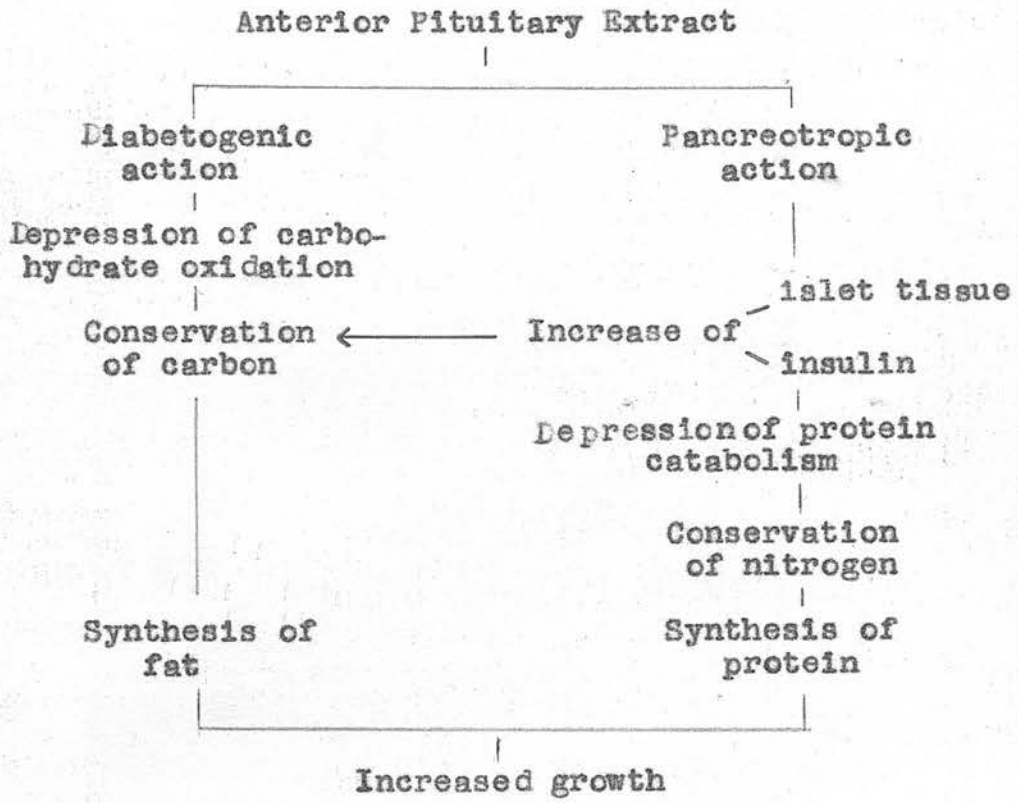
The obese subject, as Dunlop and Murray-Lyon (1931) have shown, does not put on weight continuously. The amount of overweight instead is largely determined during the first five years or less and thereafter an equilibrium is maintained for many years. Loss of weight finally occurs with the onset of diabetes. 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/

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 affected 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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