THE ISLETS OF LANGERHANS IN RELATION TO DIABETES

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The work recorded in the following paper was undertaken with a view to testing the hypothesis frequently brought forward that the islets of Langerhans of the pancreas yield an internal secretion whose function has some relation to the utilization of dextrose in the vertebrate organism. The primary cause of diabetes is, according to Macleod,¹ the 'want of disruption of the dextrose molecule and its consequent non-utilization by the organism.' Further, it is well established from the experiments of von Mering and Minkowski and others that total extirpation of the pancreas induces violent diabetes in dogs, cats, pigs, and frogs, whilst the supplying of ordinary pancreas *per os* fails to alleviate the condition.

Now, this relation between pancreas and diabetes is held by many to depend more particularly upon the epithelial cell groups, commonly termed 'islets of Langerhans,' which are a characteristic of the pancreas in all vertebrates. These islets have a rich blood supply, and have been held by various writers to be elements *sui generis*. Comparatively recently the view has been advanced (not for the first time by any means) that they are not a distinct tissue, but simply a *phase* of ordinary pancreatic tissue. The present is not an appropriate opportunity upon which to discuss the merits of these opposing views; that is reserved for another occasion. Reference is made to them here simply to clear the ground for what follows. One of us² has shown that in Teleostei, at all events, these

1. 'Recent advances in Physiology and Bio-Chemistry,' p. 340, et seq., 1906.

2. Rennie, *Quarterly Journal of Microscopical Science*, 1903.

islets are independent of pancreas proper, and that in several species there exists a particular islet which from its definite position and constancy of occurrence may be termed a 'principal islet.' This islet is in certain fishes of relatively large size, and this, coupled with the fact that in Aberdeen Fish Market we were able to secure exceptional supplies, particularly throughout the winter months, yielded our opportunity. Numbers of *Lophius piscatorius* and other fishes were obtained almost daily, and from these the larger islets were cut out and supplied for consumption to patients suffering from diabetes. They were generally given in the form of a boiled extract; in one case considerable quantities were consumed in the raw state. In each case will be found indicated the particular form in which the islet substance was taken.

Our facts are submitted as a contribution to the problem suggested by the title of this paper. The work was undertaken in view of the known relation between the pancreas and diabetes, and also in view of the frequently assumed relation between these islets when pathologically affected and this disease. While the experiments as they stand cannot be regarded as conclusive in establishing a connection it is well to bear in mind that a decisive answer is scarcely to be looked for from experiments such as these alone. This is so mainly because—

(1) Under the most favourable circumstances we have been able to use *only a very small quantity of islet substance*, e.g., in Case III (period 6), where 4 grams per day were given, but this was maintained only once for a week on end.

(2) There is a possibility that the metabolism of the cold-blooded animals (Teleostei) whose islets were used may differ from that of man to such a degree as to materially affect their action in the cases tested.

(3) With one exception the cases treated were all well established, and of a severe type.

(4) Some difficulty was experienced, as will be seen, in inducing patients to continue under treatment for a sufficient period.

An account has already been published¹ giving the results of experiments testing the action of islet substance *in vitro* upon dextrose, when negative results were obtained.

The sugar estimations in the following cases were made by the Pavy or the yeast methods. In some cases duplicate tests were made by the House Physician at the Infirmary.

Case I.—J. H., aet. 18, with a record of this disease for about two years previously, having twice been in Aberdeen Royal Infirmary during that time. Ten months before the commencement of the present treatment he was passing about 400 ounces urine daily, containing about 4,000 grains sugar. This was in the winter of 1901-2. He applied for dispensary treatment and in November, 1902, his urine per 24 hours was 560 ounces, containing 21,500 grains sugar. He had gone almost blind, and was very weak. This was the first case to be treated with these islets and at this time supplies were very limited. Indeed, during the first sixty days of the experiment, the total quantity taken by the patient amounted to only 34·25 grams, or an average of ·57 gram daily. The islets were taken from *Hippoglossus vulgaris*, *Anarrhichas lupus*, and *Lophius piscatorius* at first, latterly, entirely from *Lophius*. They were macerated in a mortar and digested for some time at 40° C. The patient was on ordinary diet, except starch, and took the islets three times daily between meals. The following notes indicate the progress of the case :—

1902.

Nov. 13—Patient received ·6 gram islets.

„ 19—Urine about 400 ounces. Patient feeling better.

„ 25—Patient in good spirits and his thirst is distinctly diminished. Urine 320 ounces; Sugar 11,187 grains.

„ 26 to Jan. 10—During this period the quantity of urine per day was about 320 ounces, only twice was it as high as 400. The quantity of sugar did not show much fluctuation, an average sample containing 12,288 grains. About the beginning of January it was rather less. The patient's health was somewhat varied and apart from the reduction in the quantity of urine and sugar, and the continued relief from distressing thirst, there were no other features suggestive of improvement.

Jan. 10 to 26—Patient somewhat stronger and showing signs of improvement. Polyuria gradually diminished so that daily quantity is at 260 ounces, and total sugar about 8,240 grains.

„ 27 to 30—Supplies of islets withheld. Urine rose to 320 ounces and thirst was doubtfully increased.

1. Rennie, Zentralblatt f. Physiologie, Bd. xviii., No. 13.

Jan. 30 to Feb. 8—With slight fluctuation the urine fell to 240 ounces and patient appeared improved.

Feb. 9 to 24—During this period no islet substance was supplied. On the whole the general health appeared good, the urine, with the exception of a rise to 280 ounces on the 13th and 14th, slowly fell to 220 ounces. On 19th the sugar amounted to 7,700 grains. Notwithstanding this reduction the patient seemed weaker, and he stated that his blindness was increasing.

„ 25 to Mar. 23—With little fluctuation, the urine fell slowly and steadily during this period. In first week of March his appetite was that of a person in health, and his thirst distinctly reduced. Sugar, on Feb. 26th, was 7,200 grains, on Mar. 4th, 7,000, and on the 19th, about 6,600. On the 23rd the supply of islet substance failed.

Mar. 24 to April 3—No more islet substance obtainable. From the 21st onward he did not feel well, and complained of sickness and failing appetite. On April 1st he went out a short distance, it was a very cold day, and on that evening he complained of severe headache and racking pains in his bones. Ill and in bed till morning of 3rd, when he died.

Note.—It will be seen from the introductory note that this was a hopelessly bad case, in which all the known methods of diabetic treatment had effected no result. Little was expected of islet treatment in such a case, but it was the only case available at the time, and the results are as given above.

Case II.—Female, aet 45, admitted 28th Jan., 1903, to Royal Infirmary. From 29th Jan. to 12th Feb. patient was under no special treatment. The following particulars regarding her condition during this time were noted :—

Date 1903.	Ounces Urine.	Grains Sugar.	Remarks.
Jan. 29	164	654	Wt. 9 st. 2½ lbs.
30	92	—	
31	182	—	
Feb. 2	120	—	Wt. 8 st. 12 lbs.
3	62	1054	
4	83	—	
8	66	1122	
9	76	—	
10	67	—	
11	—	2848	Wt. 8st. 12 lbs.
12	—	—	

During this period it will be observed that the output of sugar steadily increased, while the patient also lost weight. Supplies of islet substance, prepared as in Case I,

equal to about $1\frac{1}{2}$ grams per day, were commenced on the 13th, and were prepared and given in the usual way. Annexed are the details recorded for the time the treatment was in use :—

Date 1903.		Ounces Urine.		Grains Sugar.		Remarks.
Feb. 18	...	35	...	700	...	Wt. 9 st. $0\frac{1}{2}$ lb.
19	...	51	...	1071	...	
20	...	68	...	1564	...	
22	...	68	...	1560	...	
23	...	63	...	1827	...	
24	...	53	...	1219	...	
25	...	58	...	870	...	
26	...	49	...	980	...	Wt. 9 st. $0\frac{3}{4}$ lbs.
27	...	65	...	1235	...	
28	...	67	...	1139	...	
Mar. 1	...	88	...	1496	...	
2	...	67	...	1330	...	
3	...	40	...	1040	...	
4	...	73	...	876	...	
5	...	54	...	1404	...	
8	...	66	...	924	...	Wt. 9 st. $3\frac{1}{4}$ lbs.
9	...	59	...	885	...	
10	...	52	...	780	...	
11	...	59	...	531	...	
12	...	51	...	714	...	Wt. 9 st. $3\frac{1}{4}$ lbs.
15	...	46	...	—	...	
16	...	53	...	954	...	
21	...	53	...	530	...	Wt. 9 st. 4 lbs.
22	...	36	...	—	...	
24	...	54	...	702	...	

During this period it will be noted that the sugar is distinctly diminished, while at the same time the weight is increased.

On the 24th our supply of islets was exhausted and no more could at this time be obtained. The patient was kept under observation for some little time longer but could not be induced to remain after the beginning of April. The following are the observations made during this period :—

Date 1903.		Ounces Urine.		Grains Sugar.		Remarks.
Mar. 25	...	66	...	858	...	
26	...	88	...	1144	...	Wt. 9 st. 4 lbs.
27	...	83	...	—	...	
28	...	78	...	—	...	
29	...	64	...	1024	...	
30	...	70	...	—	...	
31	...	79	...	—	...	
Apr. 1	...	69	...	—	...	Wt. 9 st. $4\frac{1}{4}$ lbs.

Absence of abnormal thirst was a marked feature after the treatment had commenced.

Case III.—G. T., male, age 44. *Diabetes mellitus.* Record previous to commencement of treatment with islet substance is briefly as follows. Four years earlier the patient had business worries and drank to excess for a time, but broke it off. He became listless, easily tired, and drank large quantities of water. His urine was examined for the first time in July, 1901, and found to contain large quantities of sugar (4,800 grains in 24 hours). For a time he went on strict diet and the output of sugar ceased. It appeared occasionally afterwards and later became permanent. The patient tired of strict dieting and ate sugary and starchy foods. His weight remained fairly constant (about 11 stone) for the two years previous to the commencement of the experimental treatment in May, 1904. In the early part of that year he had an attack of congestion of the liver. At the beginning of treatment he was able to walk nearly two miles slowly, without feeling too fatigued. For a considerable period of time he was supplied with about $1\frac{1}{2}$ grams islets daily. The islets at first were boiled, acidified with weak acetic acid and filtered. The filtrate was taken three times daily, between meals. Subsequently, as will be seen, the islets were taken in the raw state. Urine and sugar estimations were made as frequently as possible, the full details of which are given below. In order to render the study of this record easier it is given in periods, each of which corresponds to some modification of the treatment.

(1). *Daily supply of $1\frac{1}{2}$ grams (gross wt.) boiled and proteid free islets.*

Date 1904.		Ounces Urine.		Grains Sugar.		Remarks.
May	3	...	225	...	6750	Temp. 97·8; Pulse, 90.
	4	...	210	...	4095	Temp., 98·4; Pulse, 86.
	5	...	204	...	4692	
	6	...	280	...	4900	Weight, 10 st. 9 lbs.
	7	...	250	...	5250	
	9	...	240	...	5520	
	11	...	225	...	6862	
	14	...	225	...	6525	
	15	...	220	...	6820	
	17	...	200	...	5200	Wt. 10 stone. 11 lbs.
	18	...	190	...	3610	
	20	...	205	...	2255	
	21	...	190	...	3325	
	25	...	195	...	3413	Wt. as before.
	28	...	190	...	2850	
June	1	...	195	...	3705	
	5	...	190	...	3325	Wt. as before.
	8	...	180	...	3510	
	12	...	190	...	2470	Wt. 10 st. $9\frac{1}{2}$ lbs.
	16	...	195	...	3413	
	20	...	190	...	3230	Wt. 10 st. 9 lbs.
	27	...	200	...	3500	

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Date 1904.	Ounces Urine.	Grains Sugar.	Remarks.
July 20	170	5950	...
23	140	3675	Wt. lost. 8 lbs.
26	165	3135	...
29	145	2900	...

The quantity of islets given was very small during this period. The sugar output shows a distinct falling off, so also the quantity of urine passed.

(2.) *Period of Five weeks during which no islet substance was taken.* (Sept. 1 to Oct. 8).

Date 1904.	Ounces Urine.	Grains Sugar.	Remarks.
Sept. 1	150	2850	...
8	160	4200	...
18	165	5445	Wt. as before.
25	155	5735	Patient feels well.
Oct. 3	—	—	Severe constipation; extreme weakness and exhaustion on the least effort.
8	115	2185	Exhaustion continues.

Probably exhaustion the factor here in the diminution of sugar, as this is frequently noted in diabetic cases.

(3.) *Filtered extract of islet substance in Normal Saline, given hypodermically.*

Date 1904.	Ounces Urine.	Grains Sugar.	Remarks.
Oct. 9	110	2090	Dose—one-tenth gram.
10	120	3150	Dose slightly increased; Constipation, nausea, and great inertia, as on Oct. 3rd.
11	—	3150	Dose as on 10th.
12	115	3020	Dose—one-fifth gram. For the first time his circulation was disturbed; his evening pulse 104.
13	—	—	Morning pulse, 92; no injection; in evening patient felt better than for several days before.
14	120	2520	Two injections of one-fifth gram; pulse 88.
15	115	3450	No injection; pulse 88.
16	115	3020	No injection; pulse 80; feeling stronger.

This was purely experimental. The amount of reaction caused by the hypodermic injection, accompanied as it was with no improvement such as we appeared to get by other methods of administration, caused us to abandon this mode of treatment.

(4.) *Daily supply of 1½ grams boiled unfiltered islet substance, in three doses, two hours after food.*

Date 1904		Ounces Urine.		Grains Sugar.		Remarks.
Oct. 17	...	160	...	2090	...	Pulse 90.
19	...	120	...	2040	...	Pulse 80.
21	...	115	...	1955	...	
23	...	115	...	2415	...	Pulse 88.
25	...	125	...	1875	...	Wt. 10 st. 11 lbs. Stomach and bowels satisfactory. Thirst is never now a distressing symptom ; patient feels well.
28	...	130	...	2730	...	
30	...	125	...	2125	...	
Nov. 1	...	120	...	2040	...	
3	...	125	...	2625	...	
6	...	120	...	2400	...	Sleeping and eating well ; stronger, no depression.
8	...	130	...	2730	...	
10	...	125	...	2500	...	Wt. 10 st. 11 lbs.
12	...	130	...	2340	...	Note on diet.—Patient taking one slice white bread to tea, one large or two small potatoes at dinner, and occasionally oatmeal porridge for supper.
14	...	135	...	2295	...	
16	...	140	...	2660	...	
19	...	130	...	2470	...	
21	...	135	...	2565	...	
23	...	140	...	2660	...	
25	...	125	...	2125	...	
Dec. 2	...	135	...	2565	...	
8	...	115	...	1955	...	Extremely well ; standing cold weather well.
11	...	130	...	2470	...	
13	...	—	...	—	...	Supply of islets stopped

In spite of the additional carbohydrate in diet the diminished quantity of sugar is maintained during this period.

(5.) *Brief period without supplies of islets.*

Date 1904.		Ounces Urine.		Grains Sugar.		Remarks.
Dec. 15	...	135	...	2835	...	No islets since 13th.
18	...	140	...	3220	...	
20	...	—	...	—	...	General health good. It is noteworthy that both the tests for sugar this week show a higher figure than was reached during the whole of the previous month, as is shown above.

(6.) *Period during which patient received islets raw, macerated in Normal Saline. It was found impossible to maintain a daily supply, although a much larger quantity was consumed than at any previous time. Unless otherwise stated below, the day's supply when given was about 4 grams fresh islets.*

Date 1904.		Ounces Urine.		Grains Sugar.		Remarks.
Dec. 23	...	—	...	—	...	4 grams taken.
24	...	135	...	2160	...	None.
25	...	135	...	3105	...	None.
26	...	130	...	2470	...	None.
27	...	120	...	3120	...	4 grams taken.
28	...	120	...	2160	...	4 grams taken.
29	...	120	...	2280	...	4 grams taken.
30	...	115	...	1840	...	4 grams taken.
31	...	125	...	2125	...	4 grams taken.
Jan. 1	...	130	...	2080	...	4 grams taken.
2	...	130	...	2340	...	4 grams taken.
3	...	125	...	1875	...	None taken.
4	...	125	...	2000	...	None taken.
5	...	120	...	2520	...	4 grams taken.
6	...	130	...	2600	...	4 grams taken.
7	...	120	...	2280	...	4 grams taken; Wt. 10 st. 10 lbs.
8	...	130	...	2210	...	4 grams taken; Patient out every good day, feels strong, no weakness in legs.
9	...	135	...	2295	...	None taken.
10	...	120	...	1680	...	None taken.
11	...	135	...	2295	...	1½ grams taken.
12	...	115	...	2300	...	4 grams taken.
13	...	130	...	1950	...	4 grams taken.
14	...	120	...	1920	...	4 grams taken.
15	...	130	...	1950	...	4 grams taken.
17	...	125	...	2250	...	4 grams taken.
20	...	130	...	2600	...	5½ grams in 3 days.
23	...	135	...	2700	...	2½ grams on 21st, 1½ grams on 23rd.
26	...	130	...	1430	...	4 grams on 24th, 2½ grams on 25th, 1½ grams on 26th.
28	...	120	...	1680	...	2½ grams on 27th, none on 28th.
31	...	125	...	2125	...	None on 29th and 30th, 4 grams on 31st.
Feb. 2	...	115	...	1955	...	4 grams on 1st, 1½ grams on 2nd.
4	...	120	...	2160	...	4 grams on 4th, 4 grams on 3rd.
7	...	125	...	1625	...	8 grams between 5th and 7th.
9	...	115	...	1955	...	8th and 9th, 4 grams in all.
11	...	115	...	1495	...	4 grams on 10th, 2½ grams on 11th; Wt. 10 st. 10½ lbs.
14	...	120	...	2040	...	None on 12th, 4 grams on 13th, 1 gram on 14th.

Date 1904.		Gunces Urine.		Grains Sugar.		Remarks.
Feb. 16	...	130	...	2210	...	15th and 16th, 8 grams in all.
18	...	125	...	2125	...	17th and 18th, 8 grams in all.
21	...	115	...	1783	...	3 grams on 19th.
23	...	130	...	2080	...	None on 20th, 21st and 22nd; 1½ grams on 23rd.
25	...	140	...	1820	...	4 grams each on 24th and 25th.
28	...	135	...	2228	...	26th, 27th and 28th, 4 grams each day.
Mar. 2	...	125	...	2125	...	None; 2½ grams on 1st.
4	...	135	...	2295	...	4 grams on 3rd, 4 grams on 4th.

During all this period the diminution in sugar is well maintained, as well as weight, but it was soon apparent that we had come to the limit of reduction so far as this case was concerned.

(7.) *Period of nine days without supplies of islets.*

Date 1904.		Ounces Urine.		Grains Sugar.		Remarks.
Mar. 7	...	135	...	2295	...	Last supply on 4th.
9	...	145	...	2248	...	
11	...	145	...	2610	...	
13	...	—	...	—	...	No test; on 14th, sugar 3150 grains.

There was no apparent recovery from this point.

(8.) *Same as period 6, but towards the end the supplies were considerably reduced.*

Date 1904.		Ounces Urine.		Grains Sugar.		Remarks.
Mar 14	...	150	...	3150	...	4 grams taken each day from 14th to 18th.
16	...	150	...	2850	...	
18	...	135	...	2835	...	
21	...	145	...	3045	...	None taken for the five days, 19th to 23rd.
23	...	150	...	2550	...	
25	...	145	...	2610	...	For nine days, 24th to April 1st, the average supply per day was 2 grams.
27	...	135	...	2565	...	
30	...	140	...	2660	...	
April 1	...	130	...	2600	...	
3	...	145	...	2610	...	4 grams on 2nd.
6	...	120	...	2280	...	None on 3rd, 4th, 5th, 4 grams on 6th, 4 grams on 7th, after which no further supplies were given. Wt. on 4th, 10 st. 7 lbs.
8	...	120	...	2040	...	

Further Notes.—About the 23rd March the patient felt only fairly well, and was languid. He does not appear to have, at any subsequent time, been quite so well as usual, and on the 10th April he was sick and vomiting during the night, with stomach pains. On the morning of the 11th he was better, but again took ill during the night. On the morning of the 12th coma, and death at 6-30 p.m.

Case IV.—J. L., age 50—*Diabetes mellitus.*—The following statement indicates the progress of the patient for the period during which he was under observation and treatment :—

Urine per 24 hours. (7 days' average)		Grains sugar per 24 hours. (7 days' average.)		Remarks.
177	...	2675	...	Diet ordy., no carbohydrate. Temp. 97·2 to 98·3, lost 5½ lbs. in wt.
141	...	3513	...	20 m. liq. morph. t.d., lost 1 lb. in wt.
124	...	3987	...	20 m. liq. morph. every 6 hrs., gained 2 lbs. in wt.
151	...	4574	...	Morph. every 6 hrs., lost 1 lb. in wt.
137	...	3612	...	40 m. liq. morph., 2 drachms cod liver oil nightly, lost 5 lbs. in wt.

For the seven days prior to the commencement of the treatment with islet substance the figures are :—

Ounces Urine.	Average.	Grains Sugar.	Average.	Remarks.
145	135	3480	3516	Diet as before. No Drugs ; lost 4 lbs.
156		3432		
170		3910		
110		1980		
156		5304		
114		3420		
96		2784		

The following are the corresponding figures for the period during which the patient remained under treatment *with islet substance* ; boiled extract was given, but only small quantities were available at the time.

Ounces Urine.	Average.	Grains Sugar.	Average.	Remarks.
134	126	3484	3367	No drugs and no alteration in diet ; gained ½ lb.
148		3848		
165		4125		
119		2975		
80		2240		
104		3120		
134		3752		
140	99	4060	2765	
94		2444		
64		1792		

Patient, at this stage, left the hospital, declining to remain longer under treatment.

This case shows the effect of the usually adopted method of treatment ; it may be noted that very great fluctuation in the amount of sugar, even on successive days, are common features of these cases, *e.g.*, one day 1980 grains and the next 5304 grains. While the patient is taking islets these fluctuations are much less marked, and a general trend in a downward direction was noted so long as the patient could be induced to stay in hospital.

Case V.—W. M., female, age 59—*Glycosuria*.—The following is the record of this case while the patient was under treatment:—

(a) *Prior to treatment with islet substance.*

1904.	Ounces Urine.	Average.	Grains Sugar.	Average.	Remarks.
Jan. 30	... 60	64	960	743	During this period the patient lost 3½ lbs.; Diet: antidiabetic.
31	... 66		990		
Feb. 1	... 80		1120		
2	... 60		920		
3	... 57		684		
4	... 54	55	432	402	Temp.: nothing specially noteworthy; Pulse: 68 to 96.
5	... 74		296		
6	... 51		306		
7	... 68		476		
8	... 50		400		
9	... 40		240		
10	... 54		432		
11	... 80		640		
12	... 40		320		

(b) *Period of treatment with islets.*

13	...	55	49	440	127	At end of this period, patient had gained ½ lbs.
14	...	52		312		
15	...	46		46		
16	...	52		52		
17	...	40		40		
18	...	52	48	—	None	Temp.: as before; Pulse: much steadier, 68 to 82; Diet ordinary during this period.
19	...	48		—		
20	...	45		—		
21	...	49		—		
22	...	46		—		
23	...	47		—	None	
24	...	52		—		
25	...	50		—		
26	...	50		—		

Six weeks later patient reported 'well.'

This case had none of the symptoms usually associated with *Diabetes mellitus*, save the glycosuria. Special diet was evidently proving satisfactory up to the time the islets were started, though there was a distinct loss of weight. The disappearance of the sugar is more markedly rapid after islet treatment came into effect.

In concluding this series we take the opportunity of stating that the cases were not entirely under our care, but that permission to give the treatment and make observations was kindly given by Professor Finlay and Dr. Edmond, Physicians at the Aberdeen Royal Infirmary ; Dr. W. R. Pirie, Aberdeen Dispensary ; and Dr. Lilius Thomson, Edinburgh ; and for whose courtesy we desire to express our thanks. We also beg to acknowledge with thanks grants from the Carnegie Trustees, with which our expenses were defrayed.