

## ENDOCRINE FUNCTION OF THE SURGICALLY REDUCED PANCREAS

By B. A. HOUSSAY, M.D., V. G. FOGLIA, M.D., AND F. S. SMYTH, M.D.

*(From the Institute of Physiology, Faculty of Medicine, Buenos Aires, Argentina)*

(Received for publication May 12, 1941)

The investigations of von Mering and Minkowski (1890) first demonstrated that it is possible to resect large portions of the pancreas without producing diabetes or glycosuria. Minkowski (1890, 1893) found that as little as one-quarter or one-fifth of the pancreas suffices to control glycosuria. Allen (1913) observed that diabetes follows very rarely when one-sixth or one-seventh of the pancreas remains; with an eighth of the pancreas remaining diabetes is mild; if only one-tenth remains the diabetes is pronounced, although in the experimental protocols there were cases without glycosuria in dogs in which only 2 to 3 gm. of pancreas remained. Both Minkowski and Hedon (1898) found that very small portions of the pancreas prevent diabetes, although it was easier to produce alimentary glycosuria in depancreatized than in normal animals.

Allen (1913) obtained similar results. He demonstrated also that a rich carbohydrate diet may alter the function of the remaining pancreatic tissue rendering it insufficient and producing diabetes progressively pronounced. Confirming these results, it was found many years ago in this laboratory that a large sugar intake (50 to 100 gm. daily), starting soon after the operation, determined the appearance of progressively pronounced diabetes in the great majority of dogs having 2 to 3 gm. of pancreas, but very rarely in those having 5 to 6 or more gm. of pancreas. It was observed also that only the total resection of the pancreas produces very pronounced diabetes with any certainty in healthy dogs that are properly fed. With subtotal resection it is not possible to predict what the immediate intensity of the diabetes will be. By leaving 0.9 to 1.6 gm. of pancreas after resection in dogs of 9.8 to 13.5 kilos a mild diabetes (diabetes of Sandmeyer) was obtained which progressed to fatal termination (Quian, 1932, 1933). Three dogs weighing 7.3, 7.3, and 10 kilos left with 2 to 3 gm. of pancreas and 6 dogs weighing 6.7 to 10 kilos left with 4 to 6 gm. of pancreas maintained normal glycemia after operation. In only one of them was there glycosuria and a slight degree of hyperglycemia (Houssay, Biasotti, and Rietti, 1932). It has subsequently been confirmed in a greater number of dogs that if 4 or more gm. of the gland remain, only exceptionally are hyperglycemia and glycosuria observed; with 3 gm. of pancreas, about 50 per cent of the animals maintain normal glycemia without glycosuria and the other 50 per cent have mild diabetes which is progressive and results in death in cachexia.

In the first days following subtotal resection of the pancreas glycosuria frequently is observed. It may be produced by traumatic alteration and postoperative degeneration of the pancreas and subsequently disappear or remain. If small doses of insulin

(5 to 10 units per day) are injected for a period of 8 to 10 days the animals recover more promptly than those not receiving it. With insulin treatment it is possible to have animals with the smaller amounts of pancreatic tissue free from glycosuria and diabetes.

Dogs with reduced pancreatic tissue are very sensitive to the diabetogenic action of extracts of the anterior hypophysis. They develop hyperglycemia with smaller doses than do normal dogs and if the injection of the anterior hypophysis is continued for a prolonged period they may become diabetic and die in cachexia in a few days or weeks even though the injections are suspended (Houssay, Biasotti, and Rietti, 1932; Houssay, Biasotti, Di Benedetto, and Rietti, 1932, 1933). These experiments were the first demonstration of permanent diabetes elicited by injection of extract of anterior hypophysis. This diabetes remained after discontinuing the injections of the extract. The results have been confirmed on the cat by Dohan and Lukens (1939) and Lukens and Dohan (1940) and in the rat by Long (1937, 1939).

Since 1932 we have observed that a return of normal glycemia may be induced in animals diabetic from injection of anterior hypophyseal extract if the hypophysis is resected or if insulin is injected. The use of insulin promotes healing of the histologic lesions of the pancreatic island in the cat according to Lukens and Dohan (1940). Hypophysectomized dogs weighing 8 to 10 kilos having about 4 gm. of pancreas are very sensitive to the action of the extract of anterior hypophysis although the glycemia returns rapidly to the normal level soon after suspending injections (Houssay and Biasotti, 1938; Houssay, 1939).

Insulin content and histopathological methods have been used to appraise the endocrine function of the pancreas but a more direct physiological measurement is preferable. The present studies were undertaken to test the functional capacity of the pancreas with various degrees of surgical reduction and under such strains as result from intravenous glucose and injection of anterior hypophyseal extract. Further observations of this function were obtained by the use of the temporary (Gayet) graft of the altered pancreas in animals with complete pancreatectomy.

### *Experimental Procedure*

We have made comparative studies of the function of the pancreas at rest and under conditions of strain in normal dogs, in dogs with the pancreas surgically reduced to about 10 gm., which is a reduction of approximately 50 per cent of normal, and in dogs with the pancreas reduced to about 4 gm., which represents a reduction to approximately 20 per cent of normal. In these animals some weeks after the healing of the operative wound determinations were made of: (1) glycemia before and after meals, (2) the hyperglycemic curve produced by intravenous administration of 1 gm. per kilo of glucose, (3) the diabetogenic dose of anterior lobe of the bovine hypophysis, and (4) the insulin secretion of pancreas grafted by vascular anastomosis in the cervical region of the pancreatectomized diabetic dogs.

*Methods.*—Dogs weighing 8.5 to 13 kilos were used; the great majority were 9 to 12 kilos and males. They were fed about 30 to 40 gm. per kilo of raw beef given in one meal at 2 p.m. every day. In the morning fasting blood for glucose determinations was taken from an incision on the edge of the ear. The Hagedorn-Jensen method for glucose determination was used after precipitation by the Somogyi method.

The tolerance to glucose was tested in non-anesthetized animals injected intravenously with 1 gm. of glucose per kilo of body weight in 33 per cent solution in

TABLE I

*Intravenous Injection of 1 Gm. of Dextrose per Kilo without Anesthesia: Time in Which the Glycemia Returned to 120 Mg. Per Cent*

Time of return.....	No. of animals				
	1 hr.	1½ hrs.	2 hrs.	3 hrs.	More than 3 hrs.
Normal dogs.....	9	1	1	—	—
Dogs with pancreas reduced to 10 gm.....	2	3	1	—	—
Dogs with pancreas reduced to 4 gm.....	4	—	1	4	1

TABLE II

*Dogs with Reduced Pancreas of 4 Gm.: Hyperglycemic Curves after the Injection by Intravenous Route of 1 Gm. of Glucose per Kilo of Body Weight*

Dog No.	Weight kg.	Days post-operative	Blood sugar					
			Before injection	15 min.	1 hr.	1½ hrs.	2 hrs.	3 hrs.
			mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent
5-5	12.0	16	106	299	120	103	99	96
5-6	12.0	16	81	287	190	170	140	108
5-4	10.0	20	84	252	116	101	—	97
6-1	11.0	20	101	258	181	154	123	93
6-2	9.5	20	83	284	195	154	139	97
5-2	7.0	20	107	335	211	180	151	122
5-0	8.5	24	117	306	194	146	137	110
7-2	5.0	54	113	282	115	90	83	81
7-3	10.0	32	92	233	110	96	87	83
7-5	6.3	29	110	313	207	138	119	98

distilled water. Samples of blood were taken before the injection of dextrose and 15 minutes, 1, 1½, 2, and 3 hours after. The animals received no food during the 19 hours before the injection and were kept fasting during the test.

Extract of the anterior hypophysis was injected intraperitoneally twice a day for 4 days. An extract of the anterior lobe of the bovine hypophysis in saline solution was used. The glands were frozen with carbon dioxide snow as soon as they were obtained shortly after the animals were slaughtered. The extracts were prepared at a temperature of 2–4°C. and were kept frozen until the moment of the injection in order to avoid a decrease in potency in the diabetogenic hormone.

Injections of equal doses of anterior hypophysis extract were given daily for 4

days and then were discontinued for from 3 to 10 days. If the glycemic level of 150 mg. per cent was not produced a larger dose was given the following week until the desired hyperglycemia was elicited. When the desired level was reached injections were discontinued for at least 10 days. The milligram dose per kilo per day injected

TABLE III

*Dogs with Reduced Pancreas of 10 Gm.: Hyperglycemic Curves after the Injection of 1 Gm. Glucose per Kilo of Body Weight by Intravenous Route*

Dog No.	Weight kg.	Days post-operative	Blood sugar					
			Before injection	15 min.	1 hr.	1½ hrs.	2 hrs.	3 hrs.
			mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent
5	9.0	9	95	236	171	86	84	86
1-8	7.5	36	95	253	153	103	98	75
1-6	11.0	47	82	253	100	85	82	75
1-4	8.2	50	98	240	110	87	82	85
4	8.0	59	99	258	157	132	117	92
2	9.0	61	99	236	137	115	97	—

TABLE IV

*Normal Control Dogs: Hyperglycemic Curves after Intravenous Injection of 1 Gm. Glucose per Kilo of Body Weight*

Dog No.	Weight kg.	Blood sugar					
		Before injection	15 min.	1 hr.	1½ hrs.	2 hrs.	3 hrs.
		mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent
1	9.0	83	274	62	56	61	64
2	13.0	77	357	179	143	93	67
3	8.0	80	131	80	85	78	99
4	7.5	71	156	75	83	75	80
5	10.0	76	163	91	91	87	81
6	6.0	82	211	108	86	84	77
7	12.0	91	163	94	84	96	87
8	9.0	80	200	95	86	80	89
9	8.5	94	200	100	87	94	100
1-0	10.5	118	230	182	100	86	94
1-1	10.5	100	238	84	88	80	94

during these 4 days in each experiment was 20, 40, 80, 100, 150, 250, 500, 1000, 1500, or more until a positive effect was obtained.

The capacity to secrete insulin as determined by the effect on diabetic hyperglycemia was studied by grafting the pancreas in the neck of dogs 20 hours after pancreatectomy. This technique has been used by Gayet and Guillaumie (1927, 1928), by Gayet (1933), and by Houssay, Lewis, and Foglia (1928, 1929).

The extirpation of the pancreas was performed aseptically in dogs anesthetized with

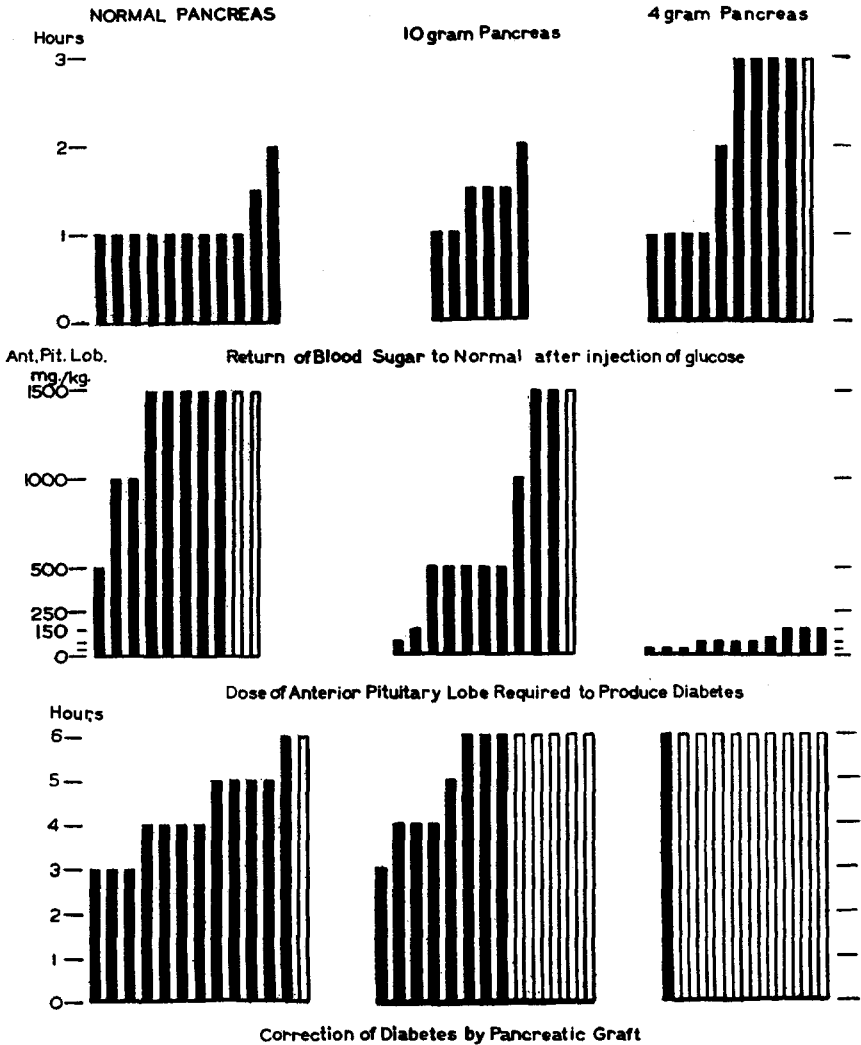


FIG. 1. Each column corresponds to one experiment in a different animal. First row: In black: time in hours for the return of blood sugar to 1.20 per cent or lower after the intravenous injection of 1 gm. of glucose per kilo. In white: glycemia not falling to 1.20 per cent. Second row: In black: daily intraperitoneal dose of alkaline extract of fresh bovine anterior pituitary gland per kilo per day for 4 days, which raised the blood sugar to 1.50 per cent or more. In white: this degree of hyperglycemia was not produced. Third row: Pancreatic graft in neck. In black: time in hours necessary for the fall of diabetic hyperglycemia to 1.20 per cent or less. In white: cases in which hyperglycemia did not fall to this level in 6 hours.

ether. In order to leave only 4 gm. of the pancreas, the free end or duodenal tail was resected, and of this 4 gm. were weighed and the size of this sample served as a gauge for the amount of pancreas to be left intact. A ligature was placed in the side of the gland adhering to the duodenal wall and the splenic end was resected. Starting near the pylorus, the pancreas was extirpated until there remained only a mass of tissue around the main pancreatic duct of Santorini of a size equal to the 4 gm. portion previously weighed.

To leave *in situ* about 10 gm. of pancreas, the free duodenal and the splenic end were resected and the pancreatic tissue beside the duodenum was left untouched. The weight of the remaining portion varied from 8.5 to 11.5 gm. as calculated by subtracting the weight of the amount resected from the average weight of the pancreas of several dogs of similar body weight. Alizón Garcia and Lewis (1933) have

TABLE V

*Rise of Glycemia Caused by Action of Extract of Fresh Anterior Lobe of Bovine Hypophysis by Intraperitoneal Route during 4 Successive Days in 2 Dogs with Pancreas Reduced to 10 Gm.*

Anterior lobe daily	Dog 2-6					Dog 5-4				
	Blood sugar					Blood sugar				
	Days after injection					Days after injection				
	Before	1	2	3	4	Before	1	2	3	4
<i>mg. per kg.</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>	<i>mg. per cent</i>
40	84	80	82	78	101	97	90	84	105	89
80	80	114	127	123	144	78	94	91	96	83
150	74	105	102	128	151	70	83	78	91	89
250	111	114	123	181	177	62	76	88	99	79
500	—	—	—	—	—	74	84	82	94	103
1000	—	—	—	—	—	69	87	83	93	141
1500	—	—	—	—	—	78	88	107	122	114
2000	—	—	—	—	—	82	102	93	112	211
Sensitive to 150 mg. per kg. daily						Sensitive to 2000 mg. per kg. daily				

made determinations on 193 dogs to establish the ratio between body weight and the weight of the pancreas. In a high percentage of dogs of 7.5 to 10 kilos the pancreas weighed 16 to 20 gm.

*Glycemia before and after Meals.*—The glycemia was determined in the morning after a fasting period of 18 hours, the animals being accustomed to the laboratory and quiet. In these cases the mean fasting blood sugar in dogs with 4 gm. of pancreas was 89 mg. per cent; in those with 10 gm. it was 91 mg. per cent; and in normal dogs 90 mg. per cent. In some dogs the blood sugar was determined before, during, and after a meal consisting of 35 gm. of raw beef per kilo of body weight. The variations observed in the glycemetic curve were substantially identical in the three groups of animals.

*Glycemetic Curve after Injection of Glucose.*—Although the three groups of animals had glycemia within the normal levels, the intravenous injection of 1 gm. of glucose

per kilo of body weight produced a condition of strain on the pancreas and revealed that some of the animals with reduced pancreas had a more prolonged hyperglycemia than the normal animals. The glycemia returned to a level of 120 mg. per cent in an hour in 9 out of 11 normal dogs; in  $1\frac{1}{2}$  to 2 hours in 4 out of 6 dogs with 10 gm. of pancreas; and in 3 or more hours in 5 out of 10 dogs with 4 gm. of pancreas (Tables I to IV, and Fig. 1).

*Diabetogenic Doses of Extract of Anterior Hypophysis.*—A 20 per cent saline or alkaline extract of anterior lobe of fresh raw hypophysis was injected intraperitoneally. The daily dose was administered in two injections, one in the morning and the other in the afternoon for 4 successive days. When the glycemia determined in the morning and 18 to 20 hours after the last ingestion of food reached a level of 150 mg. per cent or higher, the result was considered positive. The factors that may alter the results are: the potency of the extract, the diet, and the sensitivity of the animal. The glycemia does not increase if the animal does not eat. When the daily dose was ineffective a larger dose was injected the following week and if this dose was also ineffective a still larger dose was tried until that dose was found which produced the required degree of hyperglycemia (150 mg. per cent) (Table V).

#### RESULTS

In Table VI and Fig. 1, the results obtained are summarized. 70 per cent of normal dogs gave positive results with 1500 mg. of fresh anterior lobe of the hypophysis per kilo per day; the maximum glycemia observed was of 3.22 per cent, the average 1.78 per cent. With 1000 mg. per kilo per day there were 53 per cent positive results and with 500 mg. per kilo per day only 14 per cent were positive. Seven out of 12 animals with about 10 gm. of residual pancreas were more sensitive to the extract of the hypophysis; there was hyperglycemia higher than 1.5 per cent in 5 with daily doses of 500 mg. per kilo, in one with 150 mg., and in one with 80 mg. In the last 2 animals, the pancreas showed a marked insufficiency in its capacity to resist the action of pituitary extract. In 5 animals, however, the resistance was similar to that of control animals with a normal pancreas.

In dogs with 4 gm. of pancreas a great sensitivity to the diabetogenic action of the hypophysis was observed. Positive results were observed in all the animals with doses of 40 to 150 mg. per kilo per day, in other words with doses 10 to 25 times smaller than those that produced positive results in about 50 per cent of the control animals in 4 days.

In addition to the animals mentioned in Table VI, there were 9 hypophysectomized dogs with 4 gm. of pancreas. For these the dose of anterior hypophysis extract required to produce glycemic levels higher than 1.5 per cent (frequently higher than 2 per cent and in a few instances reaching 3 per cent) was 20 to 40 mg. per day and kilo.

In the great majority of the injected animals examination of the liver revealed a fatty appearance regardless of the status of glycemia. A resistance to the action of insulin induced by extracts of anterior hypophysis first noted in 1933

in dogs in this Institute has been repeatedly observed since that time. This action has been found in animals with or without hyperglycemia and in dogs with reduced pancreas.

The sensitivity of the dogs to the action of the extract of hypophysis was fairly constant but in a few cases it did increase or diminish slowly. For example dog 7-5 with 4 gm. of pancreas showed the same sensitivity to 80 mg. of extract per kilo of body weight in determinations made on August 19 and October 21, and dog 7-3 gave a positive result with 250 mg. of extract on September 2 and also a positive result with 80 mg. on October 21.

TABLE VI

*Daily Dose of Fresh Anterior Lobe of Bovine Hypophysis in Mg. per Kilo That Caused Increase of Glycemia to 150 Mg. Per Cent within 4 Days*

Control dogs	Mg. per kg. of weight								
	40	80	100	150	250	500	1000	1500	2000
Total No. of dogs.....						21	38	74	
No. with glycemia exceeding 150 mg. per cent.....						3	20	54	
Percentage of animals with glycemia exceeding 150 mg. per cent.....						14	53	70	
Dogs with 8 to 10 gm. pancreas with glycemia level higher than 150 mg. per cent.....		1		1		5	1	2	1*
Dogs with 4 gm. pancreas with glycemia level higher than 150 mg. per cent.....	3	4	1	3					

\* The glycemia level did not reach 150 mg. per cent even with doses of 2500 mg. of anterior lobe.

#### *Secretion of Insulin.*—

The duodenum-pancreas was grafted in the neck of chloralosed diabetic dogs, pancreatectomized 24 hours before. By means of Payr's cannulas, the carotid artery of the receptor was anastomosed to the celiac artery of the duodenum-pancreas and the jugular vein to the portal vein of the graft. The temperature of the irrigated graft was maintained at about 38°C. by a thermostatic control. All results obtained from experiments in which there was a faulty circulation through the graft or visible abnormalities of the pancreas or cyanosis or death of the receptor dog, were discarded. With the pancreas of about 10 gm. the graft was perfused for 6 to 8 hours and with that of 4 gm. the graft was perfused for 8 to 10 hours.

The grafted pancreas regulates the glycemia, replacing the function of the pancreas *in situ*. The glycemia is maintained within the normal levels and insulin is secreted according to the humoral stimulation and the glycemie level. It prevents or corrects the diabetic hyperglycemia. For example, in a dog



pancreatectomized 20 hours before, the grafting of a duodenum-pancreas produces a rapid decrease of the glycemia, reaching the normal level in 3 to 5 hours

TABLE VII

*Graft of Pancreas to Carotid and Jugular of Dogs Made Diabetic by Pancreatectomy 24 Hours Previously: Number of Cases in Which the Glycemia of the Receptor Returned to a Level of 120 Mg. Per Cent or Lower in a Given Number of Hours*

Pancreas grafted	Decrease in hrs.				No decrease in 6 or more hrs.	Summary		
	3	4	5	6		Total No. of animals	Decrease in 3-5 hrs.	Decrease in 6 or more hrs.
Total and normal.....	3	4	4	1	1	13	11	2
Reduced to 8-10 gm.....	1	3	1	3	5	13	5	8
Reduced to 4 gm.....	—	—	—	1	9*	10	0	10

\* Two dogs had decrease in 7 hours, remaining 7 had no decrease during the 8 to 10 hours under observation.

TABLE VIII

*Graft of Duodeno-Pancreas of Normal Dogs to the Neck of Dogs Pancreatectomized 24 Hours before*

Dog No.	Weight receptor dog kg.	Blood sugar at end of given hrs.											Weight of donor dog kg.
		Before	½	1	1½	2	3	4	5	6	7	8	
		mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	
1	—	294	268	246	210	184	119	98	95	104	107	118	7.0
2	—	242	213	210	202	188	121	105	82	77	78	71	8.0
3	—	202	185	165	156	124	119	100	111	101	—	—	7.2
4	13.5	257	265	257	257	225	162	126	119	100	—	—	14.0
5	13.0	352	296	277	239	226	188	127	105	100	—	—	12.0
6	12.5	280	221	260	217	—	187	160	138	108	—	—	11.3
7	15.5	239	220	205	198	211	205	185	168	159	—	—	14.0
8	12.0	227	197	179	172	136	—	124	97	97	—	—	16.5
9	12.0	258	224	222	201	192	142	129	98	89	—	—	12.0
1-0	16.0	213	180	176	187	173	149	109	100	87	—	—	12.5
1-1	13.0	231	216	199	155	126	132	98	95	91	—	—	11.5
1-2	11.0	202	209	195	166	135	109	93	90	82	—	—	10.0
1-3	9.0	217	227	239	227	198	125	118	113	119	—	—	12.3

without surpassing it (Tables VII and VIII). For further information see Houssay (1937).

The average speed in the fall of the glycemia of the receptor pancreatectomized dog gives an indication of the amount of insulin secreted in the time unit. Gayet (1928, 1933) has observed that the fall of the glycemia is more

TABLE IX

*Graft of Duodeno-Pancreas of Dogs with Reduced Pancreas by Pancreatectomy to 10 Gm. in the Neck of Dogs Pancreatectomized 20 Hours before*

Donor					Receptor															
Dog No.	Weight kg.	Day after operation	Glycemia per cent	Weight of pancreas gm.	Dog No.	Weight kg.	Blood sugar after given hrs.													
							Be- fore	½	1	1½	2	3	4	5	6	7	8			
							mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent
—	6.1	58	178	—	1	12.5	187	—	170	140	145	104	90	83	74					
5	9.0	26	100	12.9	2	14.5	271	236	236	236	162	130	116	112	—					
8	7.0	20	100	10.0	3	12.0	194	176	189	172	180	180	134	134	91					
9	10.0	18	94	14.7	4	17.0	458	462	484	466	458	440	440	378	376					
1-0	11.0	18	96	17.0	5	16.0	298	306	256	256	222	147	131	124	124					
1-7	10.5	20	92	12.5	6	17.0	247	245	235	207	187	167	138	122	99					
1-1	10.7	35	88	14.0	7	20.0	220	223	207	217	189	175	140	121	102					
2-0	7.0	20	102	—	8	17.0	294	266	244	214	208	164	120	101	84					
1-8	8.5	84	103	16.4	1-0	9.5	278	254	235	201	197	141	106	85	80	78	80			
2-3	8.3	74	94	8.2	1-2	13.0	283	265	257	222	207	176	136	110	104	91	91			
5-4	8.4	55	88	9.4	1-3	14.0	266	244	235	231	218	201	147	134	129	136	129			
1-9	8.5	111	98	15.0	1-4	13.5	358	340	337	326	310	247	239	207	207	198	194			
1-6	11.0	116	90	—	1-1	11.0	274	241	220	208	214	235	250	241	226	—	—			

TABLE X

*Graft of Duodeno-Pancreas of Dogs with Reduced Pancreas by Subtotal Resection to 4 Gm. in the Neck of Dogs Pancreatectomized 20 Hours before*

Donor					Receptor																
Dog No.	Weight kg.	Days post- operative	Glycemia per cent	Weight of pancreas gm.	Dog No.	Weight kg.	Blood sugar after given hrs.														
							Be- fore	½	1	1½	2	3	4	5	6	7	8	9	10		
							mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent	mg. per cent
5-2	8.0	53	100	7.7	1	23.0	193	179	200	137	130	130	134	123	112	114					
6-1	7.0	32	116	7.7	2	10.0	264	258	256	266	248	235	202	204	188	182	166				
5-0	8.0	58	112	8.0	3	14.0	272	242	227	220	229	227	223	191	166	176	171				
5-6	13.0	17	81	12.0	4	13.0	278	252	262	242	212	177	155	136	126	114	95				
6-4	4.5	31	138	5.2	5	13.0	287	275	247	238	236	224	192	169	148	166	166	148	148		
6-6	7.5	30	93	—	6	23.0	293	245	225	213	211	215	211	185	178	161	165	156	156		
7-5	10.0	54	96	—	7	22.0	310	261	205	195	196	205	169	153	147	152	154	150	123		
7-0	10.0	26	94	8.3	8	9.5	281	289	257	245	240	291	167	172	224	194	172	180	158		
6-2	9.0	59	96	—	9	18.0	148	146	144	142	144	146	149	144	149	144	132	140	126		
7-1	5.5	26	102	7.0	1-0	13.5	254	252	256	256	244	206	200	160	133	119	102	105	95		

rapid when the grafted pancreas comes from a heavier dog than the receptor and is slower when the ratio is reversed. A graft of reduced pancreas (3.58 to 9.8 gm.) in the neck of pancreatectomized dogs was observed to produce a less rapid return to normal glycemia. Reduction of the pancreas for graft was made immediately before transplant.

In our experiments, we compared the secretion of insulin of the whole pancreas and of the pancreas reduced to 10 and to 4 gm. by surgical operation carried out weeks or months before (Tables IX and X).

Grafting of the pancreas reduced the normal level of the glycemia in diabetic dogs within 5 hours in 11 out of 13 when the total gland was grafted, in 5 out of 13 when the graft had 10 gm. of pancreas, and in none when the graft had only 4 gm. of pancreas. The fall to the normal glycemia was not reached in a period of 5 hours in 2 out of 13 when the total pancreas was grafted, in 8 out of 13 with 10 gm. of pancreas, and in 10 with 4 gm. (Tables VII to X). Therefore, normal secretion of insulin occurred in only 5 of the 13 with a pancreas of 10 gm. (Tables VII and IX), and in none with a pancreas of 4 gm. (Tables VII and X).

In the diabetic dogs in which glycemia did not fall to the limit of 120 mg. per cent or below there was a very slow but gradual decrease in the blood sugar which showed that the graft of reduced pancreas irrigated with diabetic blood secreted insulin although in smaller amounts than the total pancreas did. It is possible that even the reduced pancreas might have been able to reduce the degree of intensity of the diabetes if the experiment had been carried on for a longer period of time.

#### DISCUSSION

The pancreas reduced to 10 or 4 gm. is capable of maintaining glycemia within normal levels in basic conditions or after a meal of meat, but under conditions of strain it is usually unable to react with the same speed and efficiency as the total pancreas does.

Thus in dogs with a pancreas reduced to 10 gm., which represents a half of the normal weight, there was in several cases a slight prolongation of the hyperglycemic curve produced by intravenous injection of 1 gm. of glucose per kilo. However, in some animals with pancreas reduced to 10 or 4 gm., the time of return to normal of the blood sugar was the same as in the normal controls. In the dogs with a pancreas reduced to 4 gm. ( $\frac{1}{4}$  to  $\frac{1}{5}$  of the normal weight) there was in half of the animals a longer prolongation of the curve.

The diabetogenic action of anterior lobe of fresh bovine hypophysis was observed in more than 50 per cent of the normal dogs injected intraperitoneally with a daily dose of 1000 mg. per kilo during a period of 4 days; with a daily dose of 500 mg. per kilo in dogs with 10 gm. of pancreatic tissue; and with a daily dose of 40 to 150 mg. in the dogs having only 4 gm. of pancreas.

Partial pancreatectomy does not reduce the concentration of insulin per gram in the pancreatic tissue that is left, provided the extirpation is not large enough to produce diabetes, in which case there is a decrease in the concentration of insulin (Haist and Best, 1940).

By grafting the pancreas in the neck of a pancreatectomized dog it can be demonstrated by the stimulation produced by diabetic hyperglycemia that the pancreas reduced to 10 gm. secretes less insulin than the total pancreas and that of 4 gm. still less.

The functional capacity of the reduced pancreas does not always depend on the weight of the pancreatic tissue left, for in some cases the pancreas reduced to 10 gm. had a normal functional capacity whereas in a few other cases the functional capacity was reduced to that of the 4 gm. pancreas.

The function of reduced pancreas in some animals changed progressively, increasing or decreasing according to the changes in the islands of Langerhans (Porto).

#### CONCLUSIONS

The pancreas reduced to 4 or 10 gm. weeks or months previously by partial resection, is able to maintain a normal glycemc level in dogs of about 10 kilos in good condition. When the pancreas is reduced to 4 gm. the capacity for secreting insulin under certain conditions of strain is diminished whereas a pancreas reduced to 10 gm. may have a normal or decreased capacity. This decreased functional capacity is shown: (1) by a longer hyperglycemic curve after the intravenous injection of 1 gm. of glucose per kilo; (2) by the requirement of smaller doses of extract of anterior hypophysis to produce diabetes; and (3) by the longer time required to correct the diabetic hyperglycemia if reduced pancreas is grafted in the neck of pancreatectomized animals. The time to recover is in inverse ratio to the weight of the transplanted pancreatic tissue.

#### BIBLIOGRAPHY

- Alizón Garcia, J., and Lewis, J. T., *Rev. Soc. argent. biol.*, 1933, **9**, 179.  
 Allen, F. M., Studies concerning glycosuria and diabetes, Cambridge, Harvard University Press, 1913.  
 Dohan, F. C., and Lukens, F. D. W., *Am. J. Physiol.*, 1939, **126**, 478.  
 Gayet, R., Le fonctionnement endocrinien du pancréas et sa régulation sans le concours du système nerveux, Paris, Masson et Cie, 1928; Titres et travaux scientifiques, Paris, Masson et Cie, 1933.  
 Gayet, R., and Guillaumie, M., *Compt. rend. Soc. biol.*, 1927, **97**, 1613; 1928, **98**, 676.  
 Haist, R. E., and Best, C. H., *Science*, 1940, **91**, 410.  
 Hedon, E., Diabète pancréatique, Travaux de physiologie, O. Doin, Paris, 1898.  
 Houssay, B. A., *Am. J. Med. Sc.*, 1937, **193**, 581; *Ergebn. Vitamin- u. Hormonforsch.*, 1939, **2**, 297.  
 Houssay, B. A., and Biasotti, A., *Rev. Soc. argent. biol.*, 1938, **14**, 297; *Compt. rend. Soc. biol.*, 1938, **129**, 1259.

- Houssay, B. A., Biasotti, A., Di Benedetto, E., and Rietti, C. T., *Rev. Soc. argent. biol.*, 1932, **8**, 563; *Compt. rend. Soc. biol.*, 1933, **112**, 494.
- Houssay, B. A., Biasotti, A., and Rietti, C. T., *Bol. Acad. méd. Buenos Aires*, 1932, 171; *Rev. Soc. argent. biol.*, 1932, **8**, 469; *Compt. rend. Soc. biol.*, 1932, **111**, 479.
- Houssay, B. A., Lewis, J. T., and Foglia, V. G., *Rev. Soc. argent. biol.*, 1928, **4**, 859; *Compt. rend. Soc. biol.*, 1929, **100**, 140, 142, 144.
- Long, C. N. H., *Harvey Lectures*, 1937, **32**, 194; *Tr. College Physn. Philadelphia*, 1939, **7**, series 4, 21.
- Lukens, F. D. W., and Dohan, F. C., *Science*, 1940, **92**, 222.
- Porto, unpublished observations.
- Quian, R. H., *Rev. Soc. argent. biol.*, 1932, **8**, 437; *Compt. rend. Soc. biol.*, 1932, **111**, 469; *Rev. odontol.*, 1933, **21**, 257.