EFFECTS OF ANTEROR PITUITARY EXTRACTS AND OF GROWTH HORMONE PREPARATIONS OF THE ISLETS of LANGERHANS and the PANCREAS

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Unlike endocrine glands which are under a pituitary tropic influence, the pancreatic islets do not atrophy within a period of several weeks following hypophysectomy.[11] Nevertheless there is good evidence that under certain circumstances extracts of the pituitary gland may exert stimulating effects on the islets of rats. Anselmino, Herold and Hoffman[1] first reported that an extract of the anterior pituitary gland administered to rats led to an increase in islet tissue. Using a different anterior pituitary extract, Richardson and Young[2] found that there was a large increase in the islet to acinar ratio in the pancreas. Marks and Young[3] later showed that repeated injections of an anterior pituitary extract led to an increase in the insulin content of the pancreas of the rat. Young[4] found that with repeated injections of a diabetogenic extract in dogs, the diabetes disappeared after a few days but reappeared when the dose was increased. The pancreases of these dogs showed proliferative changes in the islets and the author suggested that there was in the extract, in addition to the diabetogenic material, a more slowly acting pancreatropic factor which led to proliferation of the islet cells and increased insulin production. Proliferative changes in islets, acini and ducts of the pancreas in dogs injected with diabetogenic pituitary extracts were reported by Ham and Haist.[5] The influence of age on the effect of pituitary injections was pointed out by Mount,[6] who reported that a fresh saline extract of the anterior pituitary gland or a "Prolactin" solution tended to have a relative islet-increasing effect in mice 55 days old, but that this was largely absent in mice 95 days old. Krichesky[7] concluded that hypophysectomized rats showed an increase in islet tissue which was reduced again by the administration of pituitary extract. Adams and Ward[8] found similarly that the total number of islets increased in hypophysectomized newts and that administration of anterior pituitary extract tended to prevent the increase, though in normal animals the pituitary administration elevated the islet numbers. An apparent increase in islet volume and islet numbers may arise from the fact that there is a great reduction in the acinar tissue of the pancreas following hypophysectomy, this change leading to a large increase in the concentration of islet tissue in the pancreas. The effects of anterior pituitary extracts in hypophysectomized animals reported by Krichesky,[7] and Adams and Ward,[8] might conceivably result from a stimulating action of the extracts on the acinar tissue. However, in view of the

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reported effects of anterior pituitary extracts in intact rats, one might anicipate that such extracts would stimulate rather than depress the islets in hypophysectomized animals.

Since much of the information in the literature concerning the effects of anterior pituitary extracts on islet volume relates to intact animals, and the reported results of pituitary injections in hypophysectomized rats appear to be somewhat out of harmony with those obtained in the intact animals, it seemed desirable to investigate the influence of pituitary extracts on the total islet weights in intact and hypophysectomized rats. Following this, it was of interest also to investigate the effects of purified growth hormone preparations in intact and hypophysectomized animals.

MATERIALS AND METHODS

Intact male rats of the Wistar strain, and hypophysectomized and intact female and male rats of the Sprague-Dawley strain, were injected with crude saline extracts of the anterior pituitary gland prepared after the method of Schockaert.[9] In the first experiments the extract was prepared every third day from frozen glands. In the second experiment the extract was lyophilized and kept in the dried state. In the third experiment the extract was frozen quickly and preserved in the frozen state. A few tests were run also using a globulin fraction of the anterior pituitary gland provided through the kindness of Mr. D. W. Snair. Control animals were fed *ad libitum* except in the experiment with hypophysectomized rats when paired-fed controls were used in addition to the controls fed *ad libitum*. Test and control rats were sacrificed at the same times. Islet volumes were estimated by a slight modification of the method of Haist and Pugh.[10]

Three purified growth hormone preparations supplied through the courtesy of Armour and Company and one purified growth hormone preparation supplied through the courtesy of Frank W. Horner and Company were injected into hypophysectomized and intact rats of the Sprague-Dawley strain. A small amount of growth hormone preparation used for preliminary tests was supplied through the kindness of our colleague, Dr. J. Campbell. Control rats fed *ad libitum* were used for most of the experiments since the test animals ate more than the controls. In two series, the injected intact rats were paired-fed with the controls. In the series in which hypophysectomized animals were injected with anterior pituitary extracts or with growth hormone preparations, paired-fed controls were used also.

EXPERIMENTAL RESULTS

The effect of crude saline extracts of the anterior pituitary gland on the islet weight:

Table I shows the results of daily injections into intact male rats of freshly prepared crude saline extracts of the anterior pituitary gland and of reconstituted lyophilized saline extracts, in amounts equivalent to 2 gm. of the fresh gland, for periods of 22 to 50 days.

It is evident from this table that the islet weight is increased as a result of the injections of these crude pituitary extracts ($p<.001$). However, the body weight also increased and the pancreas weight was elevated somewhat. Nevertheless, there is an increase in the islet weight per 100 gm. body weight ($p<.001$) and in the percentage of islet tissue in the pancreas ($p<.01$) showing that the increase in islet tissue is out of proportion to the increase in body weight or pancreas weight.

The effect of a globulin extract of the anterior pituitary gland:

Table 2 shows the results of the daily injections of a globulin fraction of the anterior pituitary gland, rich in growth factor, into male rats for periods of 14 to 48 days.

From this table it will be seen that the injection of a globulin extract of the anterior pituitary gland increases the weights of the islets of Langerhans above those of the control animals in each instance. However, the increase in body weight is also much greater than in the controls and as a result the islet weight per 100 gm. body weight is not much altered. These results are too few and the differences are not statistically signicant. Nevertheless the findings are suggestive.

The effects of the injection of anterior pituitary extract in hypophysectomized rats:

The effect on the islet weights of injecting a saline extract of the anterior pituitary gland daily for periods of 41 to 73 days into hypophysectomized female Sprague-Dawley rats is shown in Table 3. Islet weights in paired-fed intact uninjected rats, in hypophysectomized uninjected controls and in intact controls fed *ad libitum* are also shown.

From this it would appear that the injection of a crude saline extract of the anterior pituitary gland into hypophysectomized rats had caused the islets to increase in weight ($p<.01$). The values are similar to those in normal paired-fed uninjected controls. The percentage of islet tissue in the pancreas is similar to that in the hypophysectomized rats and higher than in the intact

TABLE I The effect of crude saline extracts of the anterior pituitary gland on the islet weights in intact male rats. Standard deviations are shown following the mean values.

Group	No. of rats	Mean Body weight Initial gm.	Mean Body weight Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 / pancreas wt.	Mean islet weight per 100 g. body weight mg.
1. Fresh APE 22-43 days.	5	183±51	271±71	0.970±0.220	11.7±2.8	1.22±0.24	4.4±0.82
2. Controls fed ad libitum.	4	168±48	233±50	0.753±0.182	7.0±1.6	0.93±0.03	3.0±0.32
3. Dried-reconstituted APE 42-50 days.	5	134±18	334±28	1.160±0.137	15.2±1.3	1.32±0.20	4.6±0.47
4. Controls fed ad libitum.	5	131±18	291±31	0.946±0.081	9.4±2.0	0.99±0.19	3.2±0.45
5. All APE injected.	10	159±45	302±61	1.065±0.200	13.4±2.8	1.27±0.21	4.5±0.63
6. All controls.	9	148±38	265±48	0.860±0.162	8.3±2.1	0.96±0.20	3.1±0.42
t values for 1 and 2 (by groups)				1.58	2.94**	2.37*	3.29**
t values for 3 and 4 (by groups)				3.0**	5.52***	2.7**	4.51**
t values for 5 and 6 (by groups)				2.43*	4.50***	3.27**	5.46***

* probably significant ($p<.05$) ** significant ($p<.01$) *** highly significant ($p<.001$)

Calculations of significance, including all animals, show that injections of crude anterior pituitary extracts increase the weight of the islets of Langerhans ($p<.001$), the percentage of islet tissue in the pancreas ($p<.01$), the islet weight per 100 g. body weight ($p<.001$) and probably the pancreas weight ($p<.05$).

TABLE II The effect of a globulin extract of the anterior pituitary gland injected into male rats.

Group	Duration Days	Body weight Initial gm.	Body weight Final gm.	Pancreas weight gm.	Islet weight mg.	Islet x 100 / pancreas wt.	Islet/100 g. body weight mg.
Injected 1 cc./day.	14	134	187	0.563	6.6	1.17	3.5
Control.	15	128	156	0.724	4.9	0.68	3.2
Injected 1 cc./day.	21	141	228	0.799	7.4	0.93	3.2
Control.	26	138	210	0.643	5.6	0.87	2.7
Injected 2.5 cc./day.	35	110	318	0.837	13.5	1.61	4.3
Control.	41	118	243	—	—	—	—
Injected 3.0 cc./day.	43	208	435	1.342	15.4	1.15	3.5
Control.	48	212	268	0.793	9.5	1.20	3.5

TABLE III The effect of crude anterior pituitary extract (APE) in hypophysectomized female rats (41-73 days). Standard deviations are shown following the mean values.

Group	No. of rats	Body weights Initial gm.	Body weights Final gm.	Pancreas weight gm.	Islet weight gm.	Islet x 100 / pancreas wt.	Islet wt. per 100 g. body wt. mg.
1. Hypox.	4	111±2	122±7	0.230±0.021	3.7±0.8	1.63±0.50	3.0±0.56
2. Hypox. injected with APE.	7	119±3	240±19	0.488±0.060	6.8±1.7	1.40±0.29	2.8±0.68
3. Paired-fed controls (for 2)	7	120±	216±24	0.860±0.120	7.4±2.4	0.85±0.18	3.4±0.99
4. Ad lib. controls.	4	132±9	291±8	1.070±0.059	9.9±1.2	0.93±0.11	3.4±0.43
t values for 1 and 2			11.9***	8.15***	3.48**	0.98	0.40
t values for 2 and 3 (compared by pairs)			4.2**	10.46***	0.88	5.86***	2.03
t values for 2 and 4			5.1***	15.6***	3.25**	3.06**	1.48
t values for 1 and 4			32.8***		8.53***	2.76*	1.14

*probably significant ($p<.05$); **significant ($p<.01$); ***highly significant ($p<.001$).

The calculations show that the injection of APE into hypophysectomized rats significantly increased the body weight above that of the uninjected hypophysectomized rats ($p<.001$) and above that of the paired-fed controls ($p<.01$) but that this weight was less than that of controls fed ad libitum. The pancreas weights were significantly increased by the injections of APE ($p<.001$) but the pancreas weights in the injected hypophysectomized animals were significantly less than in the paired-fed control group ($p<.001$) or the ad lib. control groups. The islet weight was significantly increased in the injected group ($p<.01$) but there was no significant difference in the islet weight between the hypophysectomized-injected rats and their paired-fed controls though the injected rats had less islet tissue than the controls fed ad libitum.

The islet x 100/pancreas ratio was not significantly different in the hypophysectomized and hypophysectomized-injected rats, but in the hypophysectomized-injected rats it was greater than in the paired-fed controls or control rats fed ad libitum. No significant differences in islet weight/100 g. body weight were shown.

control rats. The anterior pituitary extract did not restore the pancreas weights completely. The pancreases in the hypophysectomized-injected rats grew, but not as well as in the paired-fed controls even though the body weights in the hypophysectomized-injected groups were, in most instances, higher than in the intact controls. The differences in islet weight per 100 gm. body weight were not significant between hypophysectomized, hypophysectomized-injected and intact uninjected control groups.

This experiment indicates that a crude saline extract of the anterior pituitary gland can exhibit its stimulating effect on the islets in the absence of the pituitary. In the hypophysectomized animal the weight of the pancreas, as a whole, is not completely restored by such injections.

The results obtained with anterior pituitary extracts are shown in Figure 1.

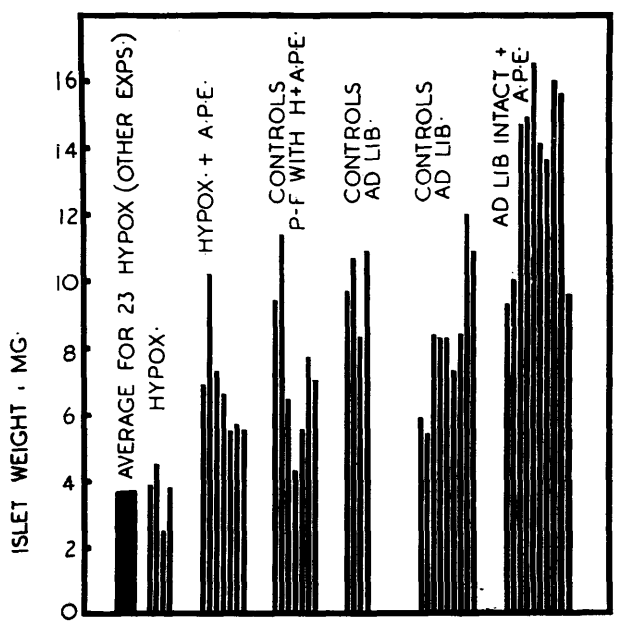

FIGURE 1 Collected islet weights for experiments in which crude saline extracts of the anterior pituitary gland (APE) were injected into hypophysectomized (Hypox) and intact rats. Values are also shown for control rats paired-fed with the hypophysectomized-injected rats and for control rats fed ad libitum.

The effect on the islet weights of injections of purified growth hormone preparations in hypophysectomized and intact rats.

In the experiments on the effects of growth hormone on the islets of Langerhans, hypophysectomized and intact male and female Sprague-Dawley rats were used.

Individaully paired-fed intact rats, intact rats fed *ad libitum* and hypophysectomized-uninjected rats were used as controls for the hypophysectomized-injected animals. Intact rats injected with the growth preparations were usually permitted to feed ad libitum but in some instances were paired-fed with the controls fed ad libitum. The injections were continued for a period of 21 to 28 days. The results of the injections of preparation 22 K R I (Armour and Company) are shown in Table 4. Injections of G-H preparation J-21609 R (Armour and Company) had the effects indicated in Table 5. The values obtained in the experiment using preparation C 3 E-J51 (Frank W. Horner Company) are presented in Table 6. Table 7 shows the effects of the injection of G-H preparation K 40805 R (Armour and Company). All results are combined in Table 8. Individual values are shown in Figure 2.

From the results it will be seen that the injections of each of the growth hormone preparations into hypophysectomized rats caused increases in islet weights above the levels in hypophysectomized uninjected animals. These increases were similar to the increases found in uninjected, intact control animals given the same amount of food. The combined results show that growth hormone preparations when injected into normal intact rats also occasioned significant increases in islet weights above the control values, though these increases were not great.

It is interesting to note too that injections of growth hormone preparations into hypophysectomized rats caused no increase in islet weight per 100 gm. body weight as compared to hypophysectomized-uninjected rats or paired-fed intact controls. However, as evidenced by the combined results, they did cause an increase in the islet weight per 100 gm. body weight when injected into intact rats. The pancreas weights, which were greatly reduced by removal of the pituitary gland, were increased by the injection of growth hormone preparations in the hypophysectomized animals but this increase did not restore the pancreas weights to the levels found in the intact paired-fed controls. No significant changes in pancreas weights were found to result from the injections of growth hormone preparations in intact rats. The high percentage of islet tissue found in hypophysectomized rats was reduced somewhat by the injections of growth hormone preparations but still remained higher than in intact rats.

The body weights of the hypophysectomized animals were increased by the injections of growth hormone preparations. The combined results showed that, in *intact* rats, the injections of growth hormone preparations led to no significant increases in body weight. In only one of the individual experiments was a probably significant increase obtained.

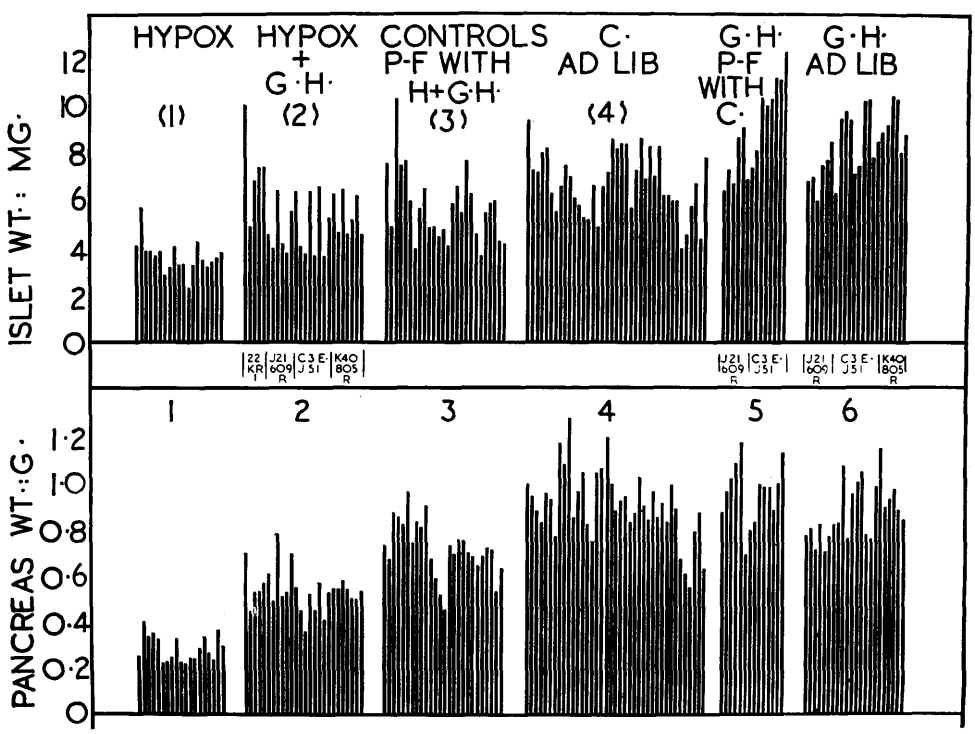

FIGURE 2 Individual islet weights and pancreas weights for experiments in which anterior pituitary growth hormone preparations were used. Hypox = hypophysectomized; G.H. = growth hormone preparations; C = control; P-F = paired-fed.

CONCLUSIONS

The experiments reported here support the conclusion that daily injections of crude saline extracts of the anterior pituitary gland stimulate the islets to grow in intact rats. This confirms the work of other investigators previously mentioned. In hypophysectomized rats the crude saline extracts also caused the islet weights to increase. This is contrary to the previously mentioned reports concerning the effects of pituitary extracts in hypophysectomized animals.

The injection of several different growth hormone preparations also caused an increase in islet weights in hypophysectomized and in intact rats. In the intact rats, the increase was significant but not large. With both the crude anterior pituitary extracts and the growth hormone preparations the increases in islet weights in the hypophysectomized rats were similar to those obtained in intact control rats receiving the same caloric intake. The islet weights per 100 gm. of body weight were not increased by the injections of the anterior pituitary extracts or growth hormone preparations in the hypophysectomized rats. The observed increases in islet weights in the hypophysectomized animals may thus conceivably result from the increased food consumption in the injected hypophysectomized rats, the increase in body weights, and the effect this has on insulin requirements. In the intact animal, both the anterior pituitary extracts and the growth hormone preparations stimulate the growth of the islets to a greater extent than the growth of the body, and not only is the islet weight increased but the islet weight per 100 gm. of body weight is elevated also. Some additional factor, absent in the hypophysectomized animal, would appear to be operating in the intact rat.

Another interesting observation relates to the pancreas as a whole. The great reduction in pancreas weight resulting from the removal of the pituitary gland has been reported before from this laboratory[11] and also by Griffiths[12] and by Koster.[13] It is important to note that while the body weight in the hypophysectomized rats injected with anterior pituitary extract or growth hormone may be significantly grater than in the intact paired-fed controls, the pancreas weight is significantly less than in the control rats. The pancreas is not completely restored by the growth hormone or pituitary injections. This was reported also by Griffiths[12] using a crude anterior pituitary extract. Some further factor not present in the growth hormone preparations appears to be required. Either this factor is absent in the crude extract also, or the animal has become resistant to the necessary factors present in the extract. Because the pancreas weight is not restored completely the percentage of islet tissue in the pancreases of hypophysectomized-injected rats remains higher than in the intact controls.

Though there is a stimulating effect of certain anterior pituitary extracts and principles on the islets, this does not mean that there is a pituitary pancreatropic effect in the same sense as there are thyrotropic, gonadotropic and adrenocorticotropic effects. Atrophy of the pancreatic islets does not occur to any great extent within a period of several weeks following removal of the pituitary gland.[11] Hence the anterior pituitary is not required for maintenance of the islets, though normally the islets fail to grow in its absence.

The means by which the pituitary stimulates growth of the islets of Langerhans in intact and hypophysectomized rats has not been clearly demonstrated as yet. Some of the functions of the anterior pituitary gland are antagonistic to those of the endocrine pancreas and when certain of the products of the anterior pituitary are present in excess, more insulin is required or signs of diabetes are observed. This may be demonstrated in sensitive adult dogs or in partially depancreatized animals of several species. These diabetogenic effects can be prevented by giving insulin. In the *intact rat* the diabetogenic pituitary preparations do not produce diabetes, possibly because the islets in the rat can sufficiently increase their insulin supply. It has been shown in this paper that the islet weight in the rat is increased by injections of saline extracts of the anterior pituitary gland and by injections of growth hormone preparations, both of which are diabetogenic in sensitive adult dogs. The islet increase in the rat may thus be a compensatory response to an increased requirement for insulin. No convincing evidence of a direct stimulating action of anterior pituitary preparations on the pancreatic islets has been obtained However, the pituitary extracts and preparations have effects outside the pancreas which could increase the need for endogenous insulin. The manner in which this increased requirement is transmitted to the pancreas, whether through an increase in blood sugar level, or a reduction in blood insulin level or through the liberation of some other chemical intermediary is not known.

SUMMARY

The weight of the islets of Langerhans in the pancreas was increased by daily injections of a crude saline extract of the anterior pituitary gland, and also by

TABLE IV The effect of 1 mg.: rat: day of growth hormone preparation 22 KR (Armour) on the weight of the islets of Langerhans.

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 pancreas	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox.	2F 2M	4	112	109±17	0.341±0.062	4.4±0.8	1.46±0.23	4.1±0.5
2. Hypox.+ GH prep. 22KR 1 (Armour)	2F 3M	5	104	182±25	0.556±0.092	7.4±1.8	1.31±0.13	4.0±0.5
3. Controls P-F with (2).	2F 3M	5	104	176±22	0.789±0.088	7.6±1.9	0.99±0.17	4.3±0.6
4. Controls fed ad lib.	3F 3M	6	108	213±33	0.920±0.058	7.7±1.1	0.84±0.11	3.7±0.7
t values for 1 and 2 (by groups)				4.90**	3.99**	2.92*	1.25	0.27
t values for 2 and 3 (by pairs)				0.19	4.21†	0.27	4.92**	0.92
t values for 2 and 4 (by groups)				1.71	8.06***	0.42	6.75***	0.78

*probably significant ($p<.05$), **significant ($p<.01$), †significant ($p<.02$), ***highly significant ($p<.001$)

Calculation of the t values shows that the hypophysectomized animals injected with growth hormone preparation 22KR 1 (Armour) had significantly higher body weights and pancreas weights ($p<.01$) and probably significantly higher islet weights ($p<.05$) than hypophysectomized uninjected rats. The body weights and islet weights in the injected rats did not differ significantly from those in intact control animals receiving the same caloric intake, but the pancreas weights were significantly higher in the control group ($p<.02$). Injections of this growth hormone preparation did not completely restore the pancreas weights or percentage of islet tissue in the pancreas.

TABLE V The effect of growth hormone preparation J-21609 R (Armour) on the weight of the islets of Langerhans. Mean values are followed by the standard deviation.

hypox=hypophysectomized

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean $\frac{\text{islet x 100}}{\text{pancreas}}$	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox+ GB prep. J-21609 R (Armour)	3F 3M	6	109	184±16	0.602±0.117	4.8±1.0	0.81±0.08	2.6±0.7
2. Controls P-F with (1)	3F 3M	6	109	165±24	0.819±0.011	5.3±0.91	0.67±0.14	3.3±0.7
3. Controls fed ad lib.	4F 3M	7	112	201±48	0.982±0.151	6.3±1.3	0.66±0.16	3.2±0.6
4. Intact inj. GH prep. J-21609 R P-F with (5)	3F 3M	6	119	211±35	0.966±0.167	7.5±1.2	0.79±0.11	3.6±0.3
5. Controls fed ad lib. Sacrificed with (4)	3F 3M	6	116	208±34	0.964±0.242	6.4±0.8	0.69±0.12	3.1±0.4
6. Intact+ GH prep. J-21609 R. Fed ad lib.	3F 3M	6	120	200±21	0.763±0.050	7.3±0.9	0.95±0.11	3.6±0.3
7. Controls fed ad lib. Sacrificed with (6)	3F 3M	6	120	168±23	0.685±0.121	5.2±1.1	0.77±0.09	3.1±0.5
t values for 1 and 2 (by pairs)				1.74	3.18*	1.05	2.87*	1.57
t values for 1 and 3 (by groups)				0.83	4.98***	2.35*	2.18*	1.56
t values for 4 and 5 (by pairs)				0.26	0.03	2.20*	2.33	2.09
t values for 6 and 7 (by groups)				2.46*	1.46	3.57**	3.09†	2.14

*$p<.05$, **$p<.01$, ***$p<.001$. †$p<.02$

Calculations of the t values indicate that the body weights and islet weights in hypophysectomized rats injected with this growth hormone preparation do not differ significantly from the values in paired-fed intact rats. The pancreas weights and percentage

of islet tissue in the hypophysectomized rats are not restored completely by the injection of this growth hormone preparation. Its injection into intact rats led to a significant increase in islet tissue in animals fed ad libitum ($p<.01$) and to a probably significant increase ($p<.05$) in intact animals paired-fed with controls which were fed ad libitum. The injected animals which were paired-fed with the controls showed final body weights similar to the controls, whereas when the injected animals were fed ad libitum a probably significant increase in body weight was observed ($p<.05$). In the latter, also, a significant increase in the percentage of islet tissue in the pancreas was noted ($p<.01$)

TABLE VI The effect of growth hormone preparation, C3E-J51 (Frank W. Horner Co.), on the weight of the islets of Langerhans. Standard deviations are shown following the mean values.

hypox=hypophysectomized

Group	Sex	Number of rats	Mean body weights Initial gm.	Final gm.	Mean pancreas weight gm.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet weight (mg.) per 100 g. body weight
1. Hypox	4F 5M	9	92	103±10	0.257±0.045	3.4±0.5	1.33±0.23	3.3±0.7
2. Controls P-F with (1)	4F 5M	9	91	103±23	0.546±0.060	4.1±0.7	0.78±0.18	4.4±0.16
3. Hypox+ GH (Horner's)	5F 3M	8	91	152±24	0.478±0.073	4.9±1.5	1.00±0.17	3.2±0.89
4. Controls P-F with (3)	5F 3M	8	90	142±20	0.646±0.114	5.7±1.2	0.88±0.10	4.0±0.70
5. Controls fed ad lib.	5F 3M	8	97	216±17	0.901±0.062	7.7±1.0	0.85±0.09	3.6±0.48
6. Intact+ GH prep. (Horner's) P-F with (5)	5F 3M	8	97	218±17	0.948±0.108	10.1±1.6	1.06±0.10	4.7±0.9
7. Intact+ GH prep. (Horner's) fed ad lib.	5F 5M	10	96	219±15	0.891±0.126	8.6±1.4	0.98±0.22	3.9±0.54
t values between 1 and 2 (by pairs)					0.306	8.93***	3.09†	5.82***	2.82*
t values between 1 and 3 (by groups)					5.72***	7.62***	2.85†	3.35**	0.31
t values between 3 and 4 (by pairs)					2.27	4.74**	1.14	1.33	1.63
t values between 5 and 7 (by groups)					0.32	0.07	1.65	1.58	1.57
t values between 3 and 5 (by groups)					6.31***	12.46***	4.38***	2.21*	1.01
t values between 5 and 6 (by pairs)					0.35	0.94	3.25†	3.73**	3.08†

*** $p<.001$ ** $p<.01$ † $p<.02$ * $p<.05$

Calculations of the t values for 1 and 2 show that in hypophysectomized rats the pancreas weights ($p<.001$), islet weights ($p<.02$) and islet/100 g. body weight ($p.<.05$) were less than in paired-fed controls, while the percentage of islet tissue in the pancreas was greater ($p<.001$). Administration of growth hormone preparation to hypophysectomized rats caused a significant increase in body weight ($p<.001$), pancreas weight ($p<.001$) and islet weight ($p<.02$) and a significant decrease in the percentage of islet tissue in the pancreas ($p<.01$). The hypophysectomized-injected rats compared to paired-fed controls had significantly smaller pancreases but the differences were not significant for body weight, islet weight, islet weight per 100 g. body weight or percentage of islet tissue in the pancreas. Intact animals injected with GH preparation and paired-fed with controls (5 and 6) showed an increase in islet tissue ($p<.02$) islet weight per 100 g. body weight ($p<.02$) and percentage of islet tissue in the pancreas ($p<.01$), though the rats injected with GH preparation and fed ad libitum showed no significant changes.

daily injections of growth hormone preparations, in hypophysectomized and in intact rats. In the hypophysectomized rats this increase was proportional to the increase in body weight, whereas in the intact rats it was relatively greater.

The pancreas weight, greatly reduced following hypophysectomy, was partially though not completely restored by the administration of growth hormone preparations or of crude saline extracts of the anterior pituitary gland.

The percentage of islet tissue in the pancreas, greatly increased by hypophysectomy, was reduced somewhat by daily injections of growth hormone preparations or of crude saline extract of the anterior pituitary gland, but the percentage of islet tissue in the pancreas of the hypophysectomized-injected animals remained higher than in control rats.

The growth hormone preparations and crude pituitary extracts occasioned an increase in body weight in the hoypophysectomized rats but the effect on body growth was less evident in intact rats.

The results were discussed and the possibilities of indirect or direct effects of the anterior pituitary preparation on the islets of Langerhans were considered.

TABLE VII The effect of growth hormone preparation K 40805 R (Armour) on the weights of the islets of Langerhans.

hypox=hypophysectomized

Group	Sex	No. of rats	Mean body weights Initial g.	Final g.	Mean pancreas weight g.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet wt. (mg.) per 100 g. body weight
1. Hypox	3F 3M	6	99	115±4	0.302±0.046	3.7±0.37	1.24±0.20	3.2±0.31
2. Hypox + GH prep. (K 40805 R, Armour)	3F 4M	7	106	195±24	0.535±0.027	5.5±0.87	1.02±0.16	2.8±0.48
3. Controls P-F with (2)	3F 4M	7	106	157±26	0.655±0.065	4.9±0.92	0.75±0.10	3.1±0.67
4. Controls fed ad lib.	3F 3M	6	105	225±32	0.905±0.061	7.0±1.1	0.78±0.11	3.1±0.2
5. Intact + GH prep. (K 40805 R, Armour)	3F 3M	6	108	243±33	0.944±0.011	9.3±0.9	0.99±0.13	3.9±0.4
t values for 1 and 2 (by groups)				8.06***	11.39***	4.67***	2.13	1.56
t values for 2 and 3 (by pairs)				5.74**	5.37**	1.23	4.62**	1.23
t values for 2 and 4 (by groups)				1.94	14.65***	2.95†	3.05†	1.50
t values for 4 and 5 (by groups)				0.95	0.76	3.83**	3.04†	4.60***

† $p<.02$ ** $p<.01$ *** $p<.001$

Calculations of t values show that injections of growth hormone preparation K 40805 R (Armour) led to a highly significant increase in body weight, pancreas weight and islet weight in the hypophysectomized rat ($p<.001$). The final body weights in the hypophysectomized-injected animals were significantly greater than in paired-fed controls ($p<.01$), but the pancreas weights were significantly less than in the paired-fed controls ($p<.01$) and the islet weights were not significantly different. The high percentage of islet tissue in the pancreas of hypophysectomized rats is not restored to normal by the injections ($p<.01$). The pancreas weights ($p<.001$) and islet weights ($p<.02$) in the hypophysectomized-injected animals were less than in control rats fed ad libitum, but the percentage of islet tissue in the pancreas was higher ($p<.02$). Injections of this growth hormone preparation into the intact animal occasioned a significant increase in islet weight ($p<.01$) and percentage of islet tissue in the pancreas ($p<.02$) and a highly significant increase in islet weight per 100 g. body weight as compared to controls fed ad libitum.

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TABLE VIII Summary table of mean values for islet weight, including all growth hormone preparations and both sexes. Mean values are followed by standard deviations.

hypox=hypophysectomized

Group	Number of rats	Mean body weights Initial g.	Final g.	Mean pancreas weight g.	Mean islet weight mg.	Mean islet x 100 / pancreas	Mean islet weight (mg.) per 100 g. body weight
1. Hypox	19	98	108±11	0.289±0.057	3.7±0.7	1.33±0.22	3.4±0.6
2. Hypox + GH	26	102	177±27	0.537±0.089	5.5±1.6	1.02±0.21	3.1±0.8
3. Intact P-F with hypox + GH	26	101	158±25	0.716±0.120	5.8±1.5	0.82±0.17	3.7±0.8
4. Intact + GH fed ad lib.	22	106	220±27	0.873±0.124	8.4±1.4	0.98±0.16	3.9±0.4
5. Intact fed ad lib.	39	109	206±35	0.896±0.155	6.8±1.3	0.77±0.13	3.3±0.6
6. Intact ad lib. controls for 7.	14	105	213±25	0.928±0.160	7.1±1.1	0.78±0.13	3.4±0.5
7. Intact PF with 6 and inj. with GH	14	106	215±25	0.956±0.131	9.0±1.9	0.94±0.17	4.2±0.9
t values for 1 and 2 (by groups)			10.32***	10.61***	4.66***	4.73***	1.38
t values for 2 and 3 (by pairs)			3.02**	7.79***	0.81	5.38***	2.74†
t values for 4 and 5 (by groups)			1.65	0.58	4.64***	5.46***	3.94***
t values for 2 and 5 (by groups)			3.55***	10.64***	3.55***	5.98***	1.19
t values for 6 and 7 (by pairs)			0.48	0.64	3.75**	4.15**	3.53**

* $p<.05$ † $p<.02$ ** $p<.01$ *** $p<.001$

The combined results show that the administration of growth hormone preparations in hypophysectomized rats led to increases in body weight, pancreas weight and islet weight which were highly significant ($p<.001$). The percentage of islet tissue in the pancreas of hypophysectomized rats was reduced by the growth hormone administration ($p<.001$). While the body growth was greater in the hypophysectomized-injected rats than in the paired-fed controls ($p<.01$), the pancreas weights were less ($p<.001$) and the islet weights did not show a significant difference. The islet weight per 100 g. body weight was less in the injected than in the control groups ($p<.02$). The percentage of islet tissue in the pancreases of the hypophysectomized animals was not completely restored by the injection of growth hormone preparations. In the intact rats the injections of growth hormone preparations caused no significant increases in body weight or pancreas weight, but the islet weight, percentage of islet tissue in the pancreas and islet weight per 100 g. body weight were significantly increased.

A Definition of Health

Health, like age, is relative. There are degrees of health just as there are degrees of illness, or intelligence, or equanimity, or beauty. Health is an abstraction or ideal. Perfect health is probably unattainable, though it may be approached. Unfortunately, the antiquated, negativistic definition of health as "that state of existing in he absence of disease" is still to be found in some medical dictionaries. Let us redefine health as having quantitative attributes and perfect health as that state of being in which all the functional capacities of the organism have maximum reserves. Optimum health is affected by age. The adolescent or young adult may have maximum cardiac and muscular vigor, but the intellect has not as yet developed to its peak. By the time intelligence and emotional homeostatis are fully developed, somatic depreciations will have reduced other functional capacities to below optimum levels.

The relativity of health is particularly significant in dealing with mature persons. Normal is a vague and misleading term. The commonest connotation is that "normal" is nearly synonymous with "average". Average health certainly does not imply optimum. Thus, normal health and optimum health are frequently widely divergent.

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