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Pathologic Changes in Diabetes

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I. A MORPHOLOGIC COMPARISON OF THE PATHOLOGIC CHANGES WITHIN THE ISLANDS OF LANGERHANS IN EXPERIMENTAL AND HUMAN DIABETES

Carl A. Peterson

In 1922, Allen[1] stated that the establishment of the phenonenon of hydropic degeneration within the cells of the islands of Langerhans in the human diabetic would prove the essential identity of experimental and clinical diabetes. Though this phenomenon has yet to be proven-and all evidence indicates that it does not occur[2,3] - the concept of the essential identity of the two forms of diabetes remains of great practical importance.

Since the time of Allen's writings several new methods of producing experimental diabetes other than by partial pancreatectomy have been described: the administration of the hormones of the anterior pituitary gland and of the thyroid; the administration of the chemical, alloxan; and most recently, by the administration of large amounts of glucose. If one compares clinical diabetes with the diabetic state induced by these experimental methods on the basis of the resultant hyperglycemia, glucosuria, the development of ketone bodies, or the alterations of the nitrogen balance the two forms of diabetes will be found to be directly comparable. But if one makes a morphological comparison based on the alterations of the beta cell of the islands of Langerhans experimental and human diabetes will be found to be incomparable.

The justification for a morphological comparison cannot be denied when one considers the fact that the alterations of the beta cell in experimental diabetes offer the sole explanation for the development of the diabetic state. All the manifestation of experimental diabetes are a reflection of the state of the beta cells.

In establishing this morphological incomparability the various methods of experimental diabetes will be reviewed emphasizing primarily the alterations of the beta cells, the pathology of the pancreas in human diabetes will be outlined, and the facts obtained from this analysis will be tabulated.

Diabetes produced by Partial Pancreatectomy:

Allen,[1] in 1913, studied the pancreatic remnants in dogs made diabetic by the removal of nine-tenths of the pancreas. Using the Lane- Bensley[4] technique for selectively staining the cells of the islands of Langerhans Allen observed progressive loss of the specific granules of the beta cells as the diabetic state became apparent. This degranulation was followed by swelling of the beta cells and the appearance of non-stainable empty vacuoles within the cytoplasm of the cells. Allen interpreted this alteration as hydropic degeneration of the beta cell. Though the nucleus and cell membrane remained intact for a limited time after the cytoplasm had been completely replaced by vacuoles eventual rupture occurred and the cell disintegrated. The disappearance of the beta cells was not found to be associated with any discernible change in the alpha cells- they remained intact and retained their full complement of granules.

Homans[5] found identical changes in the beta cells of the cat rendered diabetic by partial pancreatectomy, but, in addition, made the important observation that the beta cells become partially degranulated in some cats in which not enough pancreas had been removed to produce a diabetic state - the first evidence that overstimulation of mild degree may produce changes in the beta cell without the coexistence of a diabetic state.

These investigators found that the rapidity of development and the severity of the induced diabetic state determined the degree of alteration of the beta

cells. In severe diabetes, produced by removal of more than 90% of the pancreas, the beta cells showed beginning vacuolization in 4-7 days, complete vacuolization in 30 days, and disappearance of the cells in 6-8 weeks.[1] Early in his work Allen postulated that these changes of the beta cells would be reversible and in 1923 Copp and Barclay[6] observed the recovery of the beta cells in animals treated with insulin before the stage of cytolysis had occurred.

These observations have been confirmed by many other investigators using both dogs and cats. In the rat Foglia[7] found that diabetes did not develop for 2 to 3 months after an adequate partial pancreatectomy, but that the changes in the beta cells during the diabetic state were identical to those described earlier by Allen and Homans.

Insulin Content: Haist and Best[8] have shown that when sufficient pancreas has been removed from a dog to render it diabetic, the insulin content falls progressively to very low values, but if not enough pancreas has been removed to produce diabetes the insulin content of the remnant remains within the normal range. Thus a direct relationship between the state of the beta cell and the insulin content of the pancreas has been established.

Mechanism: In diabetes produced by partial pancreatectomy the physiological mechanism producing the changes within the beta cells is the least difficult to interpret of all methods of experimental diabetes. The few remaining beta cells within the pancreatic remnant are stimulated (either by the hyperglycemia or the low level of blood insulin) to secrete to the point of exhaustion. The small remaining part is attempting to carry out the function of the whole organ. Proof of this exhaustion theory is the established fact that if the beta cells are relieved of overactivity by the injection of exogenous insulin, they recover from the exhausted state.[6] It is generally agreed that functional overstrain of the beta cells within the pancreatic remnant is the cause of the degranulation, hydropic degeneration, cytolysis and disintegration of the cell, and the production of the permanent diabetic state.

Diabetes produced by the Injection of Anterohypophyseal Extract (A.P.E.):

In 1937, Young[9] first produced permanent diabetes in dogs by giving a series of daily injections of A.P.E in appropriate doses. The morphologic changes within the islands were first reported upon by Richardson and Young[10] in 1938. These reports were later confirmed and augmented by Richardson[11] and Ham and Haist.[12] These investigators found that the changes produced by A.P.E. closely parallelled those previously described by Allan and Homans in the partially depancreatized animal.

Progressive degranulation of the beta cells followed the daily injections of A.P.E. becoming complete within 7 days. Hydropic degeneration followed the degranulation if the injections were continued. This, in turn, was followed by disintegration of the cells and shrinkage of the islands due to the disappearance of the beta cells.

These changes were found to be reversible if the injections of A.P.E. were discontinued before beta cell cytolysis had begun. Three days after cessation of the injections in an animal in which the beta cells had been totally degranulated, Ham and Haist[12] observed partial regranulation. No recovery of the beta cells or reversal of the diabetic state is possible once the stage of beta cell cytolysis has been reached.

A species difference in response to injections of A.P.E. should be noted. In cats, Lukens and Dohan[13] found it necessary to remove one-half to three-fourths of the pancreas prior to injections of A.P.E. in order to render the animal permanently diabetic; in rats, a hyperplasia of the island tissue follows injections of A.P.E. (Richardson and Young[10]); in rabbits, the insular tissue doubles in amount (Ogilvie[14]); and in the

puppy dog the islands hypertrophy in response to the injections.

Insular Content" Best, Campbell and Haist[15] have shown that there is a progressive reduction in the insulin content of the pancreas as injections of A.P.E. are continued in the experimental animal. If the daily injections are limited to 7 in number and the animal is allowed to recover, the insulin content of the pancreas progressively increases as the beta cells recover. If the injections are continued beyond 7 days the insulin content is reduced to extremely low values. Again, in this instance the direct correlation of the changes in the beta cell with the insulin content of the pancreas is very striking.

Mechanism: The physiological mechanisms producing the diabetic state and the alterations of the beta cell in this method of experimental diabetes are not completely understood. There is general agreement that one important factor in this instance is the production of a hyperglycemia by the injected hormone. Ham and Haist[12] originally believed that this induced hyperglycemia formed the basis for the development of the diabetic state in these animals treated with A.P.E through a mechanism of exhaustion of the beta cells. However, more recent evidence makes this theory untenable. Houssay[16] has shown that if the same degree of hyperglycemia as is obtained by the injections of A.P.E. is maintained in a dog by frequent injections of glucose that animal will not become diabetic nor exhibit the pancreatic changes characteristic of diabetes. Further, he has also shown that in an animal given four daily injections of A.P.E. there is complete suppression of insulin secretion by the pancreas. From this evidence Houssay concludes that there are two factors responsible for the production of the diabetic state induced by injections of A.P.E.: an extrapancreatic factor - the hyperglycemia, and an intrinsic pancreatic factor- a toxic reaction of the hormone of the anterior pituitary on the beta cells resulting in a suppression of insulin secretion.

The experiments of Anderson and Long[17] furnish corroboratory evidence for this theory. In perfusing pancreases with various substances, these authors found that when purified growth hormone of the anterior pituitary was added to their perfusing solution the formation of insulin by the pancreas was completely inhibited. Glucose alone in the perfusing solution promoted the formation of insulin.

Based on this evidence of Houssay and Anderson and Long the conclusion is obtained that the physiological mechanisms producing the diabetic state in animals treated with A.P.E. are a combination of exhaustion of the beta cells plus a toxic factor which directly influences the secretion of insulin by the pancreas.

Diabetes produced by Thyroid Extract:

If a partial pancreatectomy in an experimental animal is followed by the administration of thyroid extract for a few weeks a permanent diabetic state will develop in an animal that would otherwise recover completely (DeFinis and Houssay[18]). The beta cells show progressive changes following the administration of thyroid: Degranulation, hydropic degeneration, pyknosis and cytolysis. The end result is a disappearance of the beta cells and shrinkage of the islands.

These changes are reversible if the thyroid administration is stopped before cytolysis of the beta cells occurs and the animal will return from a diabetic state to normal metabolism as the beta cells recover.

Insulin Content: Fraenkel-Conrat and associates[19] have shown that the insulin content of the pancreas in hypophysectomized rats treated with thyroxin was reduced to one-half that of the controls. Though the effect of thyroid on the insulin content is well illustrated in this experiment, it should be noted that these were not diabetic animals on which the determinations were made.

Mechanism: Houssay[16] considers the mechanism of production of diabetes in thyroid administration to be a combination of the same two factors as in A.P.E. administration- an exhaustion and a toxic factor. He found that the administration of thyroid produced a hyperglycemia in an experimental animal but he also demonstrated that a complete suppression of secretion of insulin by the pancreas occurs- the same result as in A.P.E. administration.

However, in this instance, the work of Anderson and Long[17] provides contradictory evidence. These authors noted no supression of insulin secretion by the pancreas when thyroxin was added to the perfusing solution.

Thus, though it is evident that a second factor in addition to the extrapancreatic factor of hyperglycemia is necessary to explain the development of the diabetic state after thyroid administration, the nature of this intrinsic factor is unknown.

Diabetes produced by Alloxan:

In 1937, Jacobs[20] reported that intravenous administration of alloxan in rabbits produced a transitory elevation of blood sugar followed by a period of hypoglycemia and death. No histologic studies were made. In 1943, Dunn and associates[21] reported that alloxan caused selective necrosis of the cells of the islands of Langerhans, and in the same year a number of authors reported the establishment of a permanent diabetic state following the administration of alloxan in various experimental animals.[22-27]

The beta cell changes were identical in all species of animals. Hughes and associates[28] reported slight but perceptible changes in the beta cells within five minutes after the injection of alloxan; within 10-15 minutes a definite partial degranulation of the beta cells was noted; by the end of one hour shrinkage of the cells had occurred; pyknosis of the nuclei soon followed and by five hours, or later, disintegration and disappearance of the beta cells had resulted. Twenty-four hours after the injection the islands showed pale staining granular debris and an occasional necrotic cell.

The alpha cells are not altered by the injection of alloxan, and after the debris of the necrotic beta cells has been removed (3 to 5 days) the islands often consist almost entirely of alpha cells. The changes produced by alloxan are not reversible- the animal cannot recover from the diabetic state.

Insulin Content: Goldner and Gomori[29] have shown that the insulin content of the pancreas of dogs with alloxan diabetes is extremely low. Ridout and Wrenshall[30] have reported that in the rat the insulin content of the pancreas was reduced to 1/10 of normal 48 hours after the injection of alloxan. Again in this instance the insulin content correlates very closely with the state of the beta cells.

Mechanism: "Alloxan diabetes is due solely to a toxic action which is intense and immediate," Houssay[31]. This quotation expresses the consenses of investigators in the field. All avidence indicates that the injection of alloxan causes a non-specific hyperglycemia, probably by direct action upon the liver (Houssay), followed by a period of hypoglycemia which is due to the outpouring of insulin from the dying beta cells killed by a direct selective action of alloxan. This hypothesis has been indirectly confirmed by Ridout, Ham, and Wrenshall[32] who have shown that the insulin content of the pancreas during the various cycles in the induction stage of alloxan diabetes is not markedly reduced until the period of hypoglycemia at which time it is reduced to very low values.

Until very recently it has been generally believed that alloxan acted on an all or or none basis, i.e., if the animal did not become diabetic following alloxan administration it was believed the chemical was neutralized and no harmful effects were obtained. However, Molander and Kirschbaum[33,34] have recently shown that

sub-diabetic doses of alloxan will alter the glucose tolerance of experimental animals even though they do not become diabetic, and secondly, that if such an animal which has been given sub-diabetic doses of alloxan is also given thyroid it will become permanently diabetic. Though neither agent alone in these experiments will produce a diabetic state the summation of their influences upon the beta cells will result in permanent diabetes.

Diabetes produced by the Injection of Glucose:

Lukens and Dohan[35,36], in 1947, produced "persistent diabetes" in one normal and several partially depancreatized cats by the administration of large amounts of glucose by intraperitoneal injections at 8 hour intervals. The partially depancreatized cats became diabetic in from two to four weeks; the normal cat required injections for 39 days. It was assumed that the persistent hyperglycemia induced by the glucose injections was the cause of the development of the diabetic state.

In discussing the pathological changes within the pancreases of these animals the authors state that the earliest abnormality observed was the degranulation of the beta cells. Hydropic degeneration of the cells followed in all cases. In one case the authors describe atrophy of the islands and decrease in the number of beta cells- indirect evidence for beta cell cytolysis. The remaining beta cells were described as hydropic.

Thus it would appear that glucose in large amounts acted just as other experimental methods for the production of diabetes- it exercised a specific action upon the beta cells resulting in degranulation, hydropic degeneration, and incomplete cytolysis. But this incomplete cytolysis is extremely important. It results in a residual of beta cells which, even though they may be hydropic, are very significant. Animals with hydropic beta cells spontaneously recover from diabetes if injections of A.P.E. or thyroid are discontinued at that stage, and, further, the hydropic beta cells in the pancreatic remnant of a partially depancreatized diabetic animal will completely recover if exogenous insulin is supplied to the animal. Thus from the evidence one would predict that the animals in the experiments of Lukens and Dohan would likewise recover. This is precisely what occurred. The one animal which lived long enough, and coincidentally the same animal in which the atrophied islands were described, recovered spontaneously from its diabetic state. This fact again forcefully emphasizes the conclusion that to produce permanent experimental diabetes the beta cells must be destroyed.

Insulin Content: Best, Haist, and Ridout have found that high carbohydrate diets do not greatly effect the insulin content of the pancreas. However, no determinations have been made upon animals in which large enough amounts of glucose have been administered by injection to alter the morphology of the beta cells. From previous evidence, one could safely predict that the insulin content would be lowered in pancreases where the beta cells had become degranulated or hydropic due to the action of glucose.

Mechanism: The mechanism in this instance is obviously a matter of excessive functional demand upon the beta cells leading to exhaustion. However, the problem has not been finally settled whether the hyperglycemia or the low blood level of insulin is the primary stimulus for secretion.

Changes in the Beta Cells in other Experimental Conditions (Non-diabetic):

Effect of Glucose Injections: Because of the important clinical implications of the work of Lukens and Dohan and because of the need for further clarification of the effects of glucose a number of recent experiments are reported.

After demonstrating that the beta cells of the rats pancreas can be degranu-

lated in a very short interval of time by a single large dose of glucose injected into the left ventricle of the heart (Peterson[37]) it was presumed that repeated injections might alter the morphology of the beta cell further and that an increasing intolerance to glucose would develop. However, the reverse was found to be true. The longer the injections were continued the greater became the tolerance for a given amount of glucose[38]. Other recent experiments have suggested the answer to this perplexing problem. Haist[39] has demonstrated recently that the island volume of the rat's pancreas can be doubled in one week if the animal is given continuous injections of glucose. Houssay[40] has also shown that if in a rat, which has been 95% depancreatized, daily large intraperitoneal injections of glucose are administered the usually expected diabetes can be prevented from developing. Similar animals not treated with glucose will invariably become diabetic within two months after the pancreatectomy. This unexpected result can be explained by assuming that the daily injections of glucose cause a proliferation of the island tissue- just as Haist demonstrated. Though the quoted experiments would seem contradictory to the work of Lukens and Dohan, the species difference of the animals used in the experiments must not be overlooked. It must be remembered that A.P.E. also produces a proliferation of the island tissue in the rat, but diabetes follows its administration in the dog.

However, Barron and State[41] gave large doses of glucose to dogs and were not able to demonstrate the development of hydropic changes within the cells, but the duration of their experiments did not approach that of Lukens and Dohan.

Mechanism: Exhaustion of the beta cells due to oversecretion undoubtedly explains the degranulation of the cells after glucose administration.

Effect of Starvation: Rats given only water will show complete degranulation of the beta cells within two weeks (Barron[42]). The cells show no sign of hydropic degeneration.

Effect of Fat Diet: Rats fed an exclusively fat diet, lard or olive oil, were found to have completely degranulated beta cells in 10 days[42]. No hydropic changes were noted. Further observations have shown that though the beta cells eventually recover completely it requires from two to four weeks[38].

Effect of Daily Insulin Injections: Marked degranulation of the beta cells developed in two weeks following daily injections of protamine zinc insulin subcutaneously in rats. Though the injections were continued for two months in some instances no hydropic degeneration or beta cell alterations other than the degranulation were noted. Complete recovery of the beta cells followed the degranulation but required a length of time directly proportionate to the duration of the daily injections. During the degranulated state the animals showed a marked reduction in glucose tolerance[38].

Insulin Content: Best, Haist, and Ridout[43] have shown that the insulin content of the pancreas in starved, fat fed, or insulin injected animals is markedly reduced within two weeks. Again, the correlation of the reduced insulin content and the degranulated beta cells is noteworthy.

Mechanism: Haist[44] attributes the reduction of the insulin content of the pancreas in these experimental procedures to a "resting" of the pancreas. In all three experimental conditions the animals need for insulin is greatly reduced: the starved and fat-fed animals receive no carbohydrate in the diet and therefore require less endogenous insulin; the animals given daily injections of exogenous insulin receive more than is required for the metabolism of their dietary carbohydrates and thus, in this instance also the need for endogenous insulin is markedly diminished.

Thus another mechanism is established which will result in the degranulation of the beta cells- a resting phenomenon.

And the establishment of this physiological mechanism brings us to the position of ascribing two diametrically opposed mechanisms for the development of a single alteration of the beta cell- degranulation. Exhaustion or resting produce morphologically indistinguishable beta cells- degranulated cells. However, one resultant difference from the two physiological mechanisms should be emphasized: in resting cells the alterations never go beyond the stage of degranulation; in exhausted cells the degranulation is frequently followed by hydropic changes and, in the extreme case, by cytolysis. This difference may be important in applying this information to the field of human diabetes.

Human Diabetes:

Degranulation of the beta cells is found to be complete in 25% of cases of human diabetes, and partial, but definite enough to warrant a diagnosis, in an additional 35% of the cases (Bell[45]). Thus 60% of the cases of human diabetes can be diagnosed from the pathological changes within the beta cells of the islands of Langerhans if a special staining method such as Gomori's[46] stain is used. But, equally important, 40% of the cases show no alteration from the normal pancreas using these same methods of study.

Hydropic degeneration of the beta cells does not occur in human diabetes. In the early part of the twentieth century investigators believed that hydropic degeneration invariably occurred in human diabetes (Weichselbaum[47]). Allen[48], in 1922 stated, "Hydropic degeneration is demonstrable in the human pancreas whenever diabetic symptoms have been sufficiently intense and prolonged, but is ordinarily missed in the mildest cases." However, in 1930 Warren[49] demonstrated changes which simulated hydropic degeneration in pancreases removed later than three hours portmortem and he further demonstrated that these alterations were totally lacking in pancreases removed within one hour postmortem. He also demonstrated the production of hydropic changes in the cells of the islands by leaving a pancreas at room temperature for four hours before fixation. Bell[50] believes that hydropic changes within the cells of the islands are due either to postmortem changes or inadequate fixation. In any case, to demonstrate hydropic changes within the islands and to ascribe these changes to diabetes one would be obliged to demonstrate normal appearing alpha cells. In all the descriptions of hydropic islands this important fact has been omitted. Further, insulin therapy has not altered the morphology of the beta cells in this respect. In a recent review of the cases of diabetes in the pre-insulin era on file in the Department of Pathology I was unable to demonstrate any significant morphological alterations from those of the insulin era.

Cytolysis of the beta cells has not been deomonstrated in human diabetes. But in some cases they may be replaced or displaced by hyaline material deposited intercellularly within the islands of Langerhans.

This hyalinization of the islands, a degenerative change, is a frequent finding in human diabetes- about 50% of diabetics (Bell[51]). Opie[52] was the first author to report the occurrence of this material within the islands of Langerhans and coincidentally thereby established the relation of the islands to diabetes. (Ten years earlier vonMering and Minkowski[53] had established the relation of the pancreas to the clinical condition of diabetes). Opie believed the lesion he described to be specific for diabetes. This opinion is still widely accepted[51]. Bell[51] has found that this hyalinization of the islands is primarily found in diabetics in the older age groups and that there is a marked correlation with other ageing changes such as arteriosclerosis. This hyaline material is not formed by the islet cells but is deposited intercellularly.

In experimental diabetes, a few instances of hyaline deposits within the islands have been reported[11], but it is rarely seen. However, in spontaneous diabetes in animals it is not infrequently

seen. I have studied one such case in a 10 year old dog.

In summary, the specific changes within the islands of Langerhans in human diabetes are degranulation of the beta cells in about 60% of the cases and varying degrees of hyaline deposition within the islands in about 50%. Frequently, especially in older diabetics, the combination of partially hyaline islands with degranulated beta cells is seen. Hydropic degeneration and beta cell cytolysis do not occur in human diabetes.

Insulin Content: Scott and Fisher[54] have shown that the average insulin content of the diabetic pancreas is 0.4 units insulin per gram of tissue while the average of the normal pancreas is 1.7 units of insulin per gram. However, the diabetic values varied from 0.03 u/gm. to 1.9 u/gm. while the normal values varied from 0.6 u/gm. to 3/8 u/gm. Thus it is obvious that the values of some diabetics lie well within the normal range and the values of some normal pancreases lie within the diabetic range. This variation is unquestionably significant even though the measurement of insulin content is a biologic assay. The authors of the report found this variation difficult to explain, but from the work of Bell[45] in which he demonstrated that 40% of the diabetic pancreases have fully granulated beta cells one would expect that many diabetics would have pancreases with insulin contents well within the normal range. Though the number of cases reported by Scott and Fisher is small a further direct correlation of the degree of granulation of the beta cells with the insulin is obvious if one divides the data into age groups.

Age Group	Avg.Insulin Content of Pancreas (Scott and Fisher)	Avg. degree of Granulation of Beta Cells (Bell)
1-30 yrs.	.07 u/gm.	0 to 1
30-60 yrs.	.45 u/gm.	1 to 2
60- over	.544 u/gm.	2 to 3*

* 3 = fully granulated

Thus again, a direct correlation of the insulin content and the state of the beta cells can be made in the field of human diabetes.

Mechanism: The physiologic mechanism of human diabetes is unknown. None of the mechanisms applicable to experimental diabetes with the possible exception of one, the resting phenomenon, can be applied. The evidence for this conclusion is derived from a morphologic comparison of the two forms of diabetes as outlined on next page.

Morphologic Comparison of Experimental and Human Diabetes

In the tabulation experimental diabetes has been divided into three groups, the non-diabetic experiments which produce alterations of the beta cell, the diabetes of a temporary type, and the permanent diabetes- the meta-diabetes of Houssay[16]. Upon dividing experimental diabetes into these groups it becomes obvious that the beta cell changes within each group are identical: In the non-diabetic experiments- degranulation only; in temporary diabetes- degranulation and hydropic degeneration; and in permanent or meta-diabetes the beta cells have been destroyed. The only possible exception to this scheme is the glucose diabetes, but as previously emphasized the results of the experiments themsleves place this form of diabetes in the temporary classification. One is also able by this means to make a valid comparison between the two classes of permanent diabetes- experimental and clinical.

From the tabulation several facts become obvious.

1. Permanent experimental diabetes and human diabetes (permanent) are morphologically incomparable: In experimental diabetes every method results in total destruction of the beta cells and, indeed, this is essential for the diabetic state to become permanent; in human diabetes

MORPHOLOGIC COMPARISON OF EXPERIMENTAL AND HUMAN DIABETES

Experiment	Beta Granulation	Beta Cells	Insulin Content	Probable Mechanism
Non-Diabetic:				
Fasting			Reduced	Resting
Fat-feeding	Reduced	Degranulation only	Reduced	Resting
Insulin inj.			Reduced	Resting
Glucose I.V.			?	Exhaustion
Temp. Diabetic:				
Hypophyseal (A.P.E.) Thyroid	Reduced	Degranulation Hydropic Degen.	Reduced	Exhaustion + toxic
Perm. Diabetic:				
Meta-pancreatic				Exhaustion
Meta-hypoph.	0	Necrotic Disappear	Reduced	Exhaustion + toxic
Meta-thyroid				Exhaustion + toxic
Meta-alloxan				Toxic
Meta-glucose?	Reduced	Degranulation Hydropic degen. Cytolysis ?	?	Exhaustion
Human Diabetes	Normal- 40% Reduced-35% 0 -25%	Degranulation only No hydrop. degen. No cytolysis*	$\frac{1}{4}$ of normal	?

The beta cells are invariably intact.

2. Human diabetes compares morphologically only with the group of non-diabetic experiments in which the beta cells become degranulated and in particular only with that part of the group in which the resting phenomenon explains the alteration of the beta cells. In this group no further alterations of the beta cell than the degranulation have been noted- a comparable situation to human diabetes.

3. 40% of the cases of human diabetes in which the beta cells show no alteration from the normal are completely incomparable with any form of experimental diabetes.

Discussion

Before any conclusions can be drawn from the data on the accompanying tabulation several facts must be considered. First, the morphological studies reported herein are limited to alterations visible by regular and special staining methods only. Studies of enzymatic systems or histochemical alterations may in the future offer further bases of comparison of experimental and clinical diabetes. Second, a rather acute process, experimental diabetes, is being compared with a slowly developing chronic process, human diabetes. However, this difference in the length of time required for the development of the diabetic state cannot explain the fundamental difference in the two forms of diabetes- the total absence of beta cells in the one case and the normal number in the other case. Third, since all cases of human diabetes are at present treated with insulin, one is comparing treated human diabetes with untreated experimental diabetes. But again, from the fundamental difference in the two types of diabetes arises the answer to this objection. Permanent diabetes of the experimental type which is characterized by the destruction of the beta cells can obviously show no response to insulin in cells which are not present- the beta cells. However, in the study of human diabetes the objection may be valid. Though the pancreases of the pre-insulin era show no morphological difference from those of the insulin era with regular staining procedures, adequate studies with special staining methods for granulation of the beta cells have not been made. It is not unlikely that such a study would show a different distribution of the degranulated pancreases from those of the insulin era. Fourth, a high percentage of human diabetic cases, about 50%, show degenerative changes which are extremely rare in the field of experimental diabetes. However, in analyzing this objection it becomes obvious that the 50% of the cases of human diabetes which do not show degenerative changes, mostly the younger diabetics, form a large group for adequate morphological studies and for comparison with experimental diabetes.

What conclusions, then, can be derived from this data? First, the beta granules are undoubtedly a form of insulin. One is led to this conclusion from the close correlation of the insulin content of the pancreas with the state of the beta cells in all forms of diabetes, experimental and human. Second, permanent experimental diabetes is invariably dependent upon the destruction of the beta cells by one means or another; human diabetes exists invariably in the presence of intact beta cells. Third, nothing in the field of experimental diabetes is comparable to the 40% of the cases of human diabetes in which completely normal beta cells are present. Fourth, in animals, prolonged high degrees of hyperglycemia lead to degranulation and hydropic degeneration of the beta cells; in human diabetes, prolonged periods of hyperglycemia lead to degranulation of the beta cells (probably) but never to hydropic degeneration. Fifth, the physiological mechanisms applied to the field of experimental diabetes to explain the morphological alterations of the beta cells are not applicable in the field of human diabetes. Since all the mechanisms applied to the field of experimental diabetes explain the destruction of the beta cell it is obvious that they cannot be applied to the field of human diabetes where the beta cells are intact. The "resting" mechanism, discussed above, may however by this same definition, be applied to the field of human diabetes. No present evidence indicates that a resting cell shows any further alteration than degranulation- a situation comparable to human diabetes. However, though animals with beta cells degranulated by resting do show altered glucose tolerances none of these animals are diabetic.

What are the mechanisms, then, of human diabetes? The answer to this question is at present unknown and any discussion of it would of necessity be speculative. There are, however, a few facts from the field of experimental diabetes and a few recent experiments that may be worthy of consideration. If one considers the pancreas alone in

relation to human diabetes three possibilities exist: first, insulin is not being formed in adequate amounts by the beta cells (degranulated resting cells?); second, normally formed insulin is not released from the pancreas in adequate amounts (fully granulated pancreases?); or third, normally formed and normally delivered insulin is neutralized or excessively metabolised after reaching the general circulation (degranulated beta cells due to mild overstimulation?). But the story of human diabetes cannot be completely explained solely upon a pancreatic deficiency, for pathologic studies have shown that even in diabetics very well controlled with exogenous insulin the arteriosclerotic changes are greatly accentuated over those changes found in non-diabetics in the same age group. The nature of this non-pancreatic factor is unknown.

Briefly, three groups of animal experiments give some evidence for physiological mechanisms that would fit with the speculative theories presented above. Houssay and Martinez[55] have recently demonstrated intense vasospastic phenomena within the pancreas of the dog initiated by clamping the renal or splenic pedicles. The resultant vasospasm is so complete that india ink injected into the aorta of the animal is withheld almost completely from the pancreas and alloxan in these animals will not produce diabetes for it is withheld from the pancreas until neutralized. We have observed similar findings in the rat. In separate works Lotspeich[56] has produced evidence that one action of insulin is the promotion of synthesis of muscle protein from amino acids in the blood, and Johlin[57] has shown that by excessive administration of the amino acid glycine, the requirement for insulin in rabbits can be reduced by one-half. From these two experiments it would appear that insulin utilized for the synthesis of amino acids may be freed by the administration in large amounts of one of the essential amino acids and would be available for carbohydrate metabolism.

Summary

In experimental diabetes produced by partial pancreatectomy and by the injection of the hormones of the anterior pituitary and the thyroid gland progressive alterations of the beta cells occur-degranulation, hydropic degeneration, cytolysis, and disappearance of the cells; in diabetes produced by administration of alloxan necrosis of the beta cells follows in a few hours after the injection. In all forms of permanent experimental diabetes the beta cells are invariably destroyed.

In experimental diabetes of the temporary type, in which the animals recover spontaneously, beta cells are invariably present though they may be severely hydropic. Diabetes produced by the injection of glucose is of this type.

In human diabetes beta cells are invariably present in the islands of Langerhans. In 40% of the cases they show no alterations from the normal cell; in 35% of the cases they are partially degranulated; and in 25% of the cases the beta cells are completely degranulated.

The very close correlation of the degree of granulation of the beta cells with the insulin content of the pancreas indicates that the granules are probably some form of insulin.

Since human diabetes and experimental diabetes are morphologically incomparable the physiologic mechanisms applied to explain the development of the diabetic state in the experimental animal cannot be directly applied to human diabetes. Human diabetes is probably not solely pancreatic in origin and the physiological mechanisms responsible for its production are unknown.

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II. MEDICAL SCHOOL NEWS

Coming Events

December 9 - Annual meeting of the Minnesota Medical Foundation, Campus Club, Coffman Memorial Union, 6:30 p.m.

December 16-17 - Continuation Course in Obstetrics for General Physicians.

* * *

Faculty News

Dr. Wesley Spink gave the Gehrmann Lectures for 1949 at the University of Illinois College of Medicine on November 30 and December 1. "Epidemiology and Pathogenesis of Brucellosis" and "Diagnosis, Treatment and Prevention of Human Brucellosis" were the subjects for the two lectures which Dr. Spink delivered.

On December 7, 1949, Dr. Spink will also give the Alpha Omega Alpha lecture at Ohio State University. The subject at that time will be, "Investigations on the Diagnosis and Treatment of Brucellosis".

* * *

Annual Meeting of the Minnesota Medical Foundation

All Patron, Life, and Annual members of the Minnesota Medical Foundation are invited to attend the annual meeting of the Foundation on Friday, December 9. Dinner will be served at 6:30 p.m. in the diningroom of the Campus Club in the Coffman Memorial Union.

Dr. Donald J. Cowling, President Emeritus of Carleton College and Chairman of the Governor's Commission for the Mayo Memorial, will be the guest speaker. During the brief business meeting the activities of the Foundation for the past year will be reviewed, and reports of the progress made thus far in the Jennings C. Litzenberg Memorial Fund and in the E. T. Bell Fund will be presented.

Reservations for the dinner should be made as soon as possible by phoning or writing Dr. G. N. Aagaard, University of Minnesota Hospitals.

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New Minnesota Medical Found. Members

Austin Clinic, Austin.
C. A. Olson, M.D., Baldwin Clinic, Baldwin, Wisconsin.
C. M. Adkins, M.D., Thief River Falls.
K. L. Nelson, M D., Clara City.
C. E. Watz, M.D., 1515 Edgcumbe Road.
Benedik Nelby, M.D., Blooming Prairie.
D. P. Gibson, M.D., 8550 Oakland Ave., Detroit, Michigan.
Donald L. Kegaries, M.D., Box 1832, Rapid City, South Dakota.
A. D. Rydland, M.D., 5350 Oliver, S.
George T. Ayres, M.D., 2241 N. Laurel, Phoenix, Arizona.
Robert Earl, M.D., 350 St. Peter St.
Malvin J. Nydahl, M.D., 400 LaSalle Building.
D. L. Tilderquist, M.D., 626 Medical Arts Building.
William P. Ryerde, M.D., Lake City.
L. R. Critchfield, M.D., 1517 St. Clair St. Paul.
J. E. Holt, M.D., 372 St. Peter St., St. Paul.
Walter J. Marcley, M.D., 5110 Wentworth
L. G. Smith, Montevideo.
Peter S. Rudie, M.D., 2001 Lakeview Dr. Duluth.
Charles Sheard, M.D., Mayo Clinic, Rochester.
R. F. Pierson, M.D., Slayton.
Donald E. Otten, M.D., 530 Eugene Medical Center, Eugene, Oregon.
H. P. Linner, M.D., 333 Medical Arts Building.
George G. Ulmer, 400-418 So. 6th St.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

December 4 - December 10, 1949

No. 267

Sunday, December 4

9:00 - 10:00 Surgery Grand Rounds; Station 22, U. H.

10:30 - 11:00 Surgical Conference; Hepatic Function in Patients with Carcinoma; Donald Shahon; M-109, U. H.

Monday, December 5

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Seminar; Routine for Cerebral Palsy; Miss Ruth Hamilton; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; X-rays and Cytochemistry; David Glick; 214 M. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; Collagen Changes in the Skin in Lupus Erythematosus; R. W. Goltz; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Classroom, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U.H.

4:00 - Public Health Seminar; Subject to be announced; 113 Medical Science.

4:00 - Pediatric Seminar; Infectious Mononucleosis; Albert Ellinger; 6th Fl. W., Child Psychiatry, U. H.

4:00 - Medical-Surgical Conference; Albert Miller; Main Conference Room, Bldg. I, Veterans Hospital.

5:00 - 5:50 Clinical-Medical-Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy, O. J. Baggenstoss and Staffs; M-109, U. H.

Tuesday, December 6

8:15 - 9:00 Roentgenology-Surgical-Pathological Conference; Craig Freeman and L. G. Rigler; M-109, U. H.

8:30 - 10:20 Surgery Conference; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell; Veterans Hospital.

12:30 - Pediatric-Surgery Rounds; Sta. I, Minneapolis General Hospital; Drs. Stoesser, Wyatt, Chisholm, McNelson and Dennis.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:00 - 2:30 X-ray Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:00 - 5:00 Physiology-Surgery Conference; Experimental Attempts to Regulate Coronary Blood Flow; Drs. Jensen and J. R. Bobb; Eustis Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by University Hospital Staff; Todd Amphitheater, U. H.

Wednesday, December 7

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans, Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker, Veterans Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson, and Staffs; Todd Amphitheater, U. H.

12:00 - 1:00 Radio-Isotope Seminar; 113 Medical Sciences.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; Veterans Hospital, Main Conference Room, Bldg. 1.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; E-101, U. H.

Thursday, December 8

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Classroom, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; Studies on ACTC; T. F. Setterquist; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Classroom, Minneapolis General Hospital.

4:15 - 5:00 Bacteriology and Immunology Seminar; The Virus Papilloma-to-Carcinoma Sequence; J. T. Syverton; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

Friday, December 9

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:45 - 12:50 University of Minnesota Hospitals General Staff Meeting; Tetanus; Jolyon Tucker and Gene Lasater; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U. H.

4:00 - 5:00 Electrocardiographic Conference; George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

Saturday, December 10

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; M-109, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Small Classroom, Minneapolis General Hospital.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 11:30 Surgery-Roentgenology Conference; ToddiAmphitheater, U. H.

9:00 - 11:30 Neurology Conference; Vascular Diseases; Veterans Hospital.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.