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Genetic transmission of diabetes mellitus

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THE GENETIC TRANSMISSION OF DIABETES MELLITUS

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Introduction

The history of diabetes, not unlike the history of other diseases, begins with the discovery of some abnormality or group of symptoms and then empirical treatment of the symptoms or the abnormality without actual knowledge of the basic etiology. This thesis will review the chronological progress of scientific research and statistical summaries in an attempt to assess hereditary transmission in the etiology of diabetes mellitus.

Discussion

As early as 1917 Williams[1] tried to evaluate heredity, infection and diabetes mellitus. He noted a transmissible trend of arteriosclerosis and diabetes. In fact, he suggested that individuals with an arteriosclerotic family history should not marry into diabetic families, and that these people should be safeguarded against infections which induce or hasten the arteriosclerotic process.

In the 1920's an attempt was made to relate diabetes with hair, age, and body type. In a family of nine, Landis[2] found that four blonds were symptom free, whereas, five brunettes all had glycosuria. On the other hand, Barach[3] described the typical diabetic as a "Light complexioned person, with a scant covering of hair over the body, and the skin is abnormally smooth". John[4] found in studying 1,000 cases, the highest incidence was in the sixth and seventh decades.

Perhaps the greatest contribution during this decade was published in 1928 by Cammidge[5]. He found a family history of diabetes in 224 of 800 cases or 28%. In cross breeding between normal and hyperglycemic mice, he found that a natural high fasting blood sugar was recessive to a normal blood sugar. He also showed how a recessive characteristic might remain hidden for

many generations only to show up when the proper mating qualifications were met. If hybrid carriers were mated with true normals, all of the offspring had normal blood sugars. If these offspring were mated with true normals, the progeny were apparently normals; but, if the original offspring were mated to similar ancestry, the proportions would show recessive transmission.

Cammidge stated that if only a few generations were considered, it might appear to behave as dominant. It was his opinion, nevertheless, that there were many cases in which the character of a true mendelian dominant were plainly present and that there could be no doubt that some forms of glycosuria were transmitted in this way.

Cammidge felt that age might be a factor. In his experience the recessive type occurred most commonly before forty years, was grave from onset and hard to control, and tended to be self exterminating. He found the dominant type to be more common in elderly people, to usually be mild and persist for many years, and to interfere little with reproduction and longevity. He noted that the dominant type was the prevailing form of inheritance, because it was easy to follow statistically. Therefore, he maintained that if there was a history of heredity, it was a favor-

able sign, because then it meant dominance; and, thus, it would be less severe. Cammidge, as did Williams, discouraged the intermarriage between families where there was even a remote history of the disease.

In the 1930's a great wealth of material was published. In this decade there were many proponents for the recessive type of transmission. The heterogeniety of the disease became appreciated and attempts were made to eliminate the complicating factors. Some of the problems confronting the workers in the field were that persons died before the disease was recognized, that environment might be a factor in presenting diabetes, and that some diabetics remained undiscovered.

Wright[6] in 1931 maintained that the tendency to develop diabetes rested on two factors, hereditary (H or h) and acquired factors (AF or af), such as infection and obesity. He stated that diabetes was a product of the two factors, and that the same results were obtained whether the hereditary factor was large or small. Thus, H·af=D or h·AF=D. If both were large (H and AF), the disease would be inevitable; while if they were both small and present, or if one was absent; it might never be manifest during a lifetime.

Joslin[1] studied 2800 diabetics and found the frequency of a history of diabetes to be 15% in the hereditary group (parents, grandparents, uncles, aunts, and children) and 77% of familial occurrence (sibblings and cousins). He found evidence for recessive transmission in his material. He presented the following evidence:

If two diabetics marry, all of the children develop diabetes.

If a diabetic marries a non diabetic (with a diabetic family), one half of the children get diabetes.

If two non diabetics marry (but are hereditarily predisposed to diabetes), only one fourth of the children get diabetes.

If a diabetic marries a non diabetic (without a family history), none of the children develop diabetes.

Allan[8] found in 143 patients, 25% diabetic sibs. He maintained that if diabetes were inherited as a dominant trait, then it would be present in one or both parents 100% of the time; whereas, it actually was found in 10-15% of the parents (as seen in Joslin's statistics). He, thus, suggested that dominance should no longer be considered. However, Allan neglected incomplete penetrance.

Hansen[9] felt that diabetes was due to several re-

cessive factors and that if only a few of these were present, there would be orthoglycemic glycosuria; whereas, the presence of all would cause diabetes.

Macklin[10] published a summary of diabetes in twins and noted that it occurred more often in identical twins than in fraternal twins and that there was often little or no difference in the age of onset. He suggested recessive transmission.

In the years 1933 and 1934 Pincus, and White[11,12] published material advocating recessive transmission. Pincus and White found a family history in 22.94% of 523 diabetic families as compared with 10.46% for non diabetic control families. The odds were 19,300: 1 against such a difference having arisen by chance. However, they neglected to take ages into consideration. They, too, suggested that recessive be considered rather than dominant because the geneologies available indicated that the disease might skip one or more generations; and because if it were dominant, at least one parent in each mating would be diabetic or potentially diabetic. They noted in their study that when the assumption was made that diabetes developed in individuals homozygous for a recessive gene (mm), it could be demonstrated that the ratios of diabetic to non diabetic individuals among the siblings of the dia-

bectic patient, conformed with the consequent expectations provided it was assumed that potential diabetics, before they develop the disease, were subject to the ordinary chances of death.

Pincus, White, and Joslin[9] summarized their sentiments in 1934. They felt that the evidence of inheritance of diabetes rested on three facts; The concurrence of diabetes in homologous twins, a greater incidence of diabetes in the relatives of a diabetic person than in a control population, and the demonstration that mendelian ratios are found in large series of case histories selected at random, and that these happen to be seen as mendelian recessive ratios.

Regarding twins, they found that nine of thirteen (70%) identical twins were both diabetic; whereas, only two of thirteen (16%) pairs of fraternal twins were both diabetic. Regarding mendelian ratios, they studied 800 diabetic families and found:

1. In carrier x carrier cross (Mm), 4% of the siblings were diabetic.
2. In diabetic (mm) x carrier cross (Mm), 10% of the siblings were diabetic.
3. In diabetic (mm) x diabetic (mm), 24% of the siblings were diabetic.

These results when compared to the 1:2:4: expected

ratios of truely simple mendelian recessive were very similiar.

Again in 1934 Pincus and White[14] attempted to establish these values by studying hyperglycemia in diabetic families. They found that in examining different types of matings (Mm x MM, Mm x mm, mm x mm) that the incidence of hyperglycemia suggested that such individuals might be taken as future diabetics since the ratios of them in these matings were approximately proportioned to the ratios of presumed unidentified genetically diabetic individuals called for by the mendelian hypothesis advanced to explain the inheritance of diabetes. They assumed that all diabetes would be apparent by ninty years of age.

Mm x Mm produced 6.8% diabetics.

Mm x mm produced 17.7% diabetics.

mm x mm produced 25% diabetics.

These ratios are 1:2.6:3.7 as compared to the expected 1:2:4: in recessive transmission.

Bortz[15] estimated that heredity was responsible for at least 25% of all cases of diabetes. He noted that Morgan[16] and his associates considered cytoplasmic inheritance and suggested that diseases in general, might be transmitted by way of cytoplasm rather than

the chromosomes.

Greisheimer and Goldsworthy[17] attempted to show the unreliability of oral glucose tolerance tests in predicting diabetes. Their tests consisted of 120 subjects who ate a balanced diet for one week prior to the test, fasted for twelve to fourteen hours before the test, had fasting blood sugars taken, took one gram of glucose per kilogram of body weight orally, and had specimens taken at one half, one, two, and three hour intervals and tested by the Shaffer-Somogyi method. They noted that no abnormalities appeared consistently in the glucose tolerance in subjects who had maternal diabetic relatives, paternal diabetic relatives, diabetic relatives in the two preceding generations or in those who had both maternal and paternal diabetic relatives.

Watson[18] in 1934 used twins to establish heredity as a factor in diabetes. He noted that in the general population that dizygotic twins were encountered three times as frequently as monozygotic twins. He reasoned that if environment were the principal cause of diabetes in twins that there would be no reason to suspect deviation from the natural 3:1 ratio with regard to dizygotic and monozygotic types. He pointed out, in fact, that the recorded observations had indicated that practically all diabetic twins were of the mono-

zygotic types. Out of the twenty-one diabetic twins on record (the sexes were the same in twenty cases), fifteen were evidently monozygotic and only one dizygotic. He concluded that the great majority of twin diabetics were of the monozygotic type and, therefore, the individual members of each set possessed an identical hereditary background, Mendelian recessive in some families and dominant in others.

In 1934 Cammidge[19] reiterated his opinion that the heretity of diabetes was dominant in older age groups and recessive in the younger set. However, he admitted that the dominant values might be excessive because of the short family history not allowing for the expression of recessive characteristics. He also noted that evidence for heredity was most frequently found in the early years of life, but suggested that these findings might have been because of better knowledge of the patient at an early age with other members of the family still alive and around to aid with the information.

Believing in recessive transmission Joslin[20] admonished that if a diabetic decided to marry he should choose a non diabetic in a non diabetic family, and then the children could expect to be free from the disease, although they too would be hereditary carriers and should avoid union with other such carriers.

Joslin along with Dublin and Marks[21] in 1937 stated that the hypothesis of dominance in the transmission of diabetes was untenable because on that hypothesis one would expect a far higher incidence of diabetics in the parents of diabetic children and in the children of diabetic parents than was actually recorded. They felt that the assumption of recessive inheritance was more logical as shown in studies by Pincus and White[22] who computed the number of children (brother and sisters of the patient) expected to be diabetic after allowing for the following:

1. The size of the family.
2. The fact that each family was chosen because one member had been identified as diabetic.
3. The age of onset of diabetes.
4. The fact that the expected numbers represented not actual diabetes, but persons capable of developing diabetes, and subject, therefore, to at least the usual mortality prior to the age at which diabetes would appear.

In their study Pincus and White found that in the group where both parents were presumably non diabetic, 64 out of 1495 siblings of the patients were diabetic as compared with 64.68 expected. In the

families classified as matings mm x Mm, there were 32 diabetic siblings out of 299, as compared with 32.43 expected.

Although they had attempted to circumvent errors in their computations, Pincus and White could not be sure that they had the correct designated matings. For example, some of the non diabetic parents, classified as Mm, might have been potentially diabetic, mm. Furthermore, this group included some who had died or would have died before diabetes had developed, and it also included living parents who might have subsequently developed the disease.

Maddox and Scott[23] studied 250 Austrialian diabetics and found a family history in 347. They found no support in their investigation for frequent propagation as a single dominant gene substitution. A cursory inspection of their pedigrees showed the distribution of affected individuals to be familial, or tending to occur most frequently as "sibs or collaterals" in alternate generations. They attributed this to transmission of a double dominant or transmission of two independent dominant genes on separate chromosomes since that mode of inheritance might closely resemble that of a single recessive gene substitution. Such a form of propagation, according to the authors, resulted in a

high proportion of affected offspring in the mating of one affected and one normal parent to such an extent that nearly every such union would produce one or more affected individuals.

A study by Rudy and Keeler[24] showed a familial incidence four to six times as high in diabetic as in non diabetic patients. They noted that diabetes was more prominant among Jewish patients than in all other diabetic patients.

During the next decade, 1940's, some investigators developed the theory of possible sex linkage in the transmission of diabetes. In the meantime, recessiveness continued to be the most popular theory of transmission.

In 1941 Cole, Harned, and Keeler[25] studied the inheritance of glucose intolerance by crossing strains of rats. They crossed Y strain rats, in which 71% of the males and 58% of the females give diabetic-like glucose tolerance tests, with W strain rats, which showed no evidence of low tolerance. The crossing gave an F1 generation whose diabetic-like glucose tolerance was less than that of the Y stock in both incidence and severity. They also noted that the incidence of diabetic-like curves in the Y strain was the same from the mating of low tolerant Y males

with normal females, as from the mating of two low tolerant animals. They concluded that "The sire appears to exert a greater influence than the dam on the type of glucose tolerance of the offspring".

In the F2 generation from normal F1 animals, the incidence of decreased glucose tolerance in the males was only 14% and 0% in the females. Yet, four individuals showed a glucose tolerance greater than that of the W strain. The authors felt that the appearance of these hypertolerant F2 animals suggested new combinations of hypoglycemic factors. They concluded that the decreased glucose tolerance was not a simple recessive, but was probably the result of one principal gene plus modifiers, the principal gene tending to be incompletely recessive. The penctrance of this gene was believed to be less than 100% in homozygons combinations.

Penrose and Watson[26] also proposed sex linked transmission. In order to assume that heredity was of etiological importance so that secondary or modifying hereditary factors could be evaluated, they used only patients who were found to have at least one affected relative. They observed in studying brother and sister sibs that pairs of diabetic brothers and pairs of diabetic sisters occurred much more frequently than

brother-sister pairs. They felt that this effect was not due merely to the greater general incidence of diabetes among females.

Penrose and Watson offered three genetic explanations for the tendency of diabetes to affect females in one sib-ship and males in another:

(1) Partial sex linkage of the main genetical factor.

(2) There might be some examples of familial diabetes inherited in a fully sex-linked manner, which were comparatively rare but common enough to alter sib-pair frequences significantly.

(3) Secondary sex-linked factors might alter the age of onset or the degree of severity of a disease without being its main cause.

Neel[29] in 1947 presented a composit chart recording the results of various investigators regarding abnormal glucose tolerance curves in apparently normal relatives of diabetics. (Chart I)

Chart I

Investigator & Year	Relationship of Subjects To Diabetics	Type of Test	Number	Percent Abnormal	Control	Percent Abnormal
Sherrill 1921	Parents, sib, and children	glucose tolerance	38	55.3	28	39.3
John 1921	Family history of diabetes	glucose tolerance	104	55.7	287	25.8
Flaum and Schlesinger 1932	Diabetic parent or two or more relatives	glucose tolerance	32	72	—	—
Levit and Pessikova 1934	"Near relatives"	glucose tolerance	40	10	—	—
Pincus and White 1934	"Relatives"	FBS	76	14.5	76	0.0
	"Relatives"	glucose tolerance	95	20.0	49	2.0
Mackler and Fischer 1934	Sibs (mostly children)	glucose tolerance	30	0	—	—
Greisheimer and Goldsworthy 1934	"Relatives"	glucose tolerance	96	0	—	—
Pannhorst 1936	Children & grandchildren of low, conjugal diabetics	glucose tolerance	26	42.3	—	—
Steiner 1936	Parents, sibs, and children	glucose tolerance	258	11.3	—	—
Jonas 1937	"Relatives"	glucose tolerance	100	54	—	—

The results as summarized by Neel showed that a significant discrepancy existed between reports of investigators due to diverse standards as to what was abnormal, and to different modes of administering the test, poor controls, and no diet standardization. Nevertheless, there was much evidence for an increase of clinical and abnormal tolerance in relatives of diabetics. It was noted that only the results of Greisheimer and Goldsworthy were in contrast to the others. It should be noted that there are other diseases associated with abnormal glucose tolerance which could have affected these results.

Neel also reviewed Berg's[28] work on twin studies. Of thirty-six identical twin pairs (one being diabetic), both were diabetic in seventeen cases, and in thirteen cases one was diabetic while the other had an abnormal glucose tolerance. Of twenty-three pairs of fraternal twins, there were only two cases where both were diabetic and seven cases with one being diabetic and the other having abnormal tolerance. These findings are in agreement with those of Pincus and White.

In 1947 Burnstein and Patterson[29] published a study of two individuals who developed diabetes at the ages of 58 and 60 and their descendants. For twenty-five years these descendants regularly tested their urine

for sugar. No actual diabetic had been permitted to marry into the family, and none of the persons introduced by marriage gave a history of diabetes within recent generations. The results showed fifty-five diabetics among 161 direct descendants of the original marriage. The authors felt that the fact that the diabetes might be transmitted as a type Mendelian dominant was only suggestive.

In the third generation of this pedigree there were two sets of identical twins and in both instances each member of the pair became diabetic within a few weeks of each other. They concluded that this could be incomplete dominance or a recessive trait if those introduced by marriage were heterozygous.

Harris[30] in 1949 presented a number of interesting contemplations on the subject. He felt that if diabetes were a genetically homogeneous disease, then it must be assumed that all of the variation in the severity and age of onset was determined by enviornmental factors. However, if it was genetically heterogeneous, then it would be likely that much of its variation could be accounted for by heredity. A special instance of the latter situation would occur if, in fact, diabetes was not a single disease entity, but really several genetically distinct diseases.

Harris stated that when a disease was determined by a recessive gene, that there might be an increased frequency of the cousin marriages among the patients suffering from the disease. The rarer the disease, the higher would be the incidence of parental consanguinity. Furthermore, if there was an incidence of parental consanguinity which was significantly in excess of the level in the general population then that might indicate that one or more recessive genes were important. He felt that if in a disease, it was found that one type of case differed strikingly in the incidence of parental consanguinity from another type of case, that the two types of cases were determined by different gene combinations.

He studies 1241 patients and found that there was an increase in the rate of parental consanguinity in the form of diabetes coming on in childhood, adolescence and early adult life. However, no increase in the incidence of parental consanguinity was detected in those diabetics in which the disease developed in later life. He concluded that there must be some real genetical differences between the two groups of cases and that diabetes, therefore, could not be regarded as genetically homogeneous. This implied that one or more recessive genes were responsible for some, and perhaps

all, the cases of diabetes coming on in early life. The type occuring in mid and late life was very much commoner than the type developed in children and young adults. But, the absence of increased parental consanguinity did not preclude the possibility of recessive inheritance Harris claimed.

Although this evidence was in favor of the view that there were two diseases, Harris pointed out other evidence which suggested a more complex situation. It was not unusual to find that one or the other of the parents of a young diabetic was also diabetic, and generally when this was so, the parent suffered from the late onset, milder type of disease. This was in contrast with the hypothesis of two genetically distinct disorders, but might have been explained by assuming the milder late onset type of cases were heterozygous for the abnormal gene while the more severe, juvenile and young type of cases were homozygous.

Harris also made reference to sex linkage. He noted the varying manifestations of the disease in the two sexes in different families. First of all, there were proportionately more female than male diabetics in the general population. Harris found that if a series of female diabetics was considered, it was found that they had many more diabetic sisters than brothers. On

the other hand, among the close relatives of the male diabetics, the two sexes tended to be much more equally distributed. He summarized that in some families the disease mainly picked out females and in other families mainly males and that this occurred to a greater extent that if it were simply a random process.

Harris[31] proposed, yet, another, but later, hypothesis. He claimed that individuals who developed diabetes while young were more likely than non diabetics to die before they had passed through and completed the reproductive phase of their lives. And even if they did not die, they were less liable than the average member of the community to have living children. In other words, their effective fertility was disminished. Thus, it would have appeared that natural selection worked particularly against the juvenile and young adult diabetics, and one might have expected that the particular genes determining this type of disease should on the average be less well represented in the population in each succeeding generation. This dimunition did not exist, however; thus, Harris now maintained that it would seem that the particular gene or combination of genes which existed in the young diabetic was not, in fact, different than the genes which were found in late onset diabetes.

During the next twelve years many old concepts were discussed and modified. It was a very prolific period with many new investigators.

Again Harris[32], in 1950, proposed the hypothesis that many of the late onset mild cases could be regarded as heterozygous for a gene which in homozygous form gave rise to the early onset severe type of cases, where the severe diabetes occurred more often among those sibs of juvenile and young adult patients and would also account for an increase in parental consanguinity among the juvenile and young adult diabetics, but not among the late onset type. However, he noted that this could be based on common recessive autosomal modifying genes or to allelic modifiers.

Lincoln[33] in an attempt to report on what could happen when diabetics married presented a case of two married diabetics who had nine children. Two died of diabetes in childhood, the rest all developed obesity and all but one, about whom information was lacking, were known to have had abnormal glucose tolerance.

Thompson, Laakso, and Watson[34] in their study of 1380 diabetic patients found that the percentage of these patients with positive diabetic family histories varied inversely with the age of onset. As compared

with the total group, the onset age was latest for the diabetics with negative family histories, earlier for those with positive family histories and earliest for those with bilateral positive family histories of diabetes. The percentage of patients, each with a known positive family history of diabetes, fell from 79% in those with onset age zero to nine years to 26% in the group with onset age of 80-89 years. They concluded that diabetes behaved genetically as a "graded character". This opinion was in disagreement with the view that juvenile diabetics are homozygous and older diabetics heterozygous.

Barker, Cummons, and Shelton[35] proposed sex linked inheritance. They studied a family of eight persons including three boys and three girls. The father and the girls were of average height, had brown hair and brown eyes. The mother and the boys had blond hair, blue eyes, and their growth curves fell within the lowest 1% of normal range. The authors stated that "the mathematical analysis suggest that the growth rate and hair pigmentation are inherited in the same chromosome and that the growth retardation and blondness are inherited as recessive autosomal characterisitics with a homologous mother and a heterozygous father". It was discovered that the three boys had diabetes, while the

other members of the family showed no abnormal glucose tolerance. There was a history of diabetes on the father's side, but not in the mother's family. Using their own "genetic formula" the authors concluded that the chances were in favor of diabetes being a recessive sex linked characteristic with heterozygous parents, rather than a recessive autosomal characteristic with heterozygous parents.

In 1952 Steinberg and Wilder[36] entered their thoughts into the vast pool of concepts. They proceeded to refute some of the forementioned theories in their study of 1781 diabetic patients over a two year period at the Mayo Clinic. They stated that the relationship between the age of the patient and his affected parent at onset was spurious. They showed that the apparent tendency for diabetes to develop at an earlier age in successive generations (anticipation) was due to unvoidable errors in sampling and that, by chance alone, 65.3% of their cases would have had an earlier onset than their affected parents, whereas 70% of the pertinent family histories actually exhibited anticipation.

In accord with Harris, they noted that the frequency of diabetes among the sibs of patients with early onset was as great as that among the sibs with late on-

set. However, they recognized that this might occur because, if a young person was diagnosed as having diabetes, others at home would probably be examined. Thus, even mild diabetes would be detected. Also, there would be a better history when the knowledge of sibs was better as in young diabetics. Furthermore, there would be a similarity of environment between the patients and sibs when the patient was young.

In studying sex ratios they found no significant association between the sex of the patient and that of the affected parent nor between that of the patient and the affected sibs. However, they did find an excess of affected mothers. The frequency of females among the affected parents (59.5%) was significantly greater than among the patients. They stated that this might have been because of a higher effective fertility among female diabetics as contrasted to male diabetics.

Regarding dominance, they felt that the assumption of a single dominant gene with incomplete penetrance was not consistent with their findings. In their series diabetes was more than twice as frequent among the sibs when one parent was diabetic than when

neither was diabetic. They claimed that if a dominant gene with incomplete penetrance were the correct explanation, then the presence of overt diabetes in one parent would not be expected to increase the frequency of diabetes among the sibs.

Regarding Harris's theory that late onset mild diabetics were considered heterozygous for a gene which in homozygous form gave rise to the early onset severe types, or less than thirty years old, the authors made these comments: "Let us assume that when the onset is prior to thirty years, both of the parents should be heterozygous (assume that none are homozygous); when onset is after thirty years, it is possible that both parents are heterozygous, although usually only one will be. Now, if Harris was correct, the frequency of diabetes among the sibs of patients with onset prior to thirty years should be greater than among the sibs of patients with onset after thirty years of age, because, as pointed out, most of the patients with early onset are homozygous and come from matings in which both parents are heterozygous, while most patients with onset after thirty years are heterozygous and are derived from matings which are mostly

between a heterozygous and a normal. Furthermore, these frequencies should not be affected by the presence or absence of overt diabetes in one of the parents."

In their data, the frequency of diabetic sibs was the same (within statistical limits) regardless of the age of the patient at the onset, but in each age group the frequency of diabetic sibs was significantly greater when one parent was diabetic than when neither was diabetic. (Chart II)

Chart II

	Patients Age At Onset	All Sibs		Neither Parent Diabetic Sibs		One Parent Diabetic Sibs	
		Total	% diabetic	Total	% diabetic	Total	% diabetic
Harris	under 30	1019	4.1	971	3.5	48	18.8
	over 30	2773	4.1	2446	4.1	*327	10.7
Stein-berg & Wilder	under 30	828	6.0	736	5.0	92	14.1
	over 30	7456	6.0	5928	4.6	1528	11.2

Frequency of diabetes among sibs of patients with early and late onset.

Also in contrast to the findings of Harris, there was no strong evidence in their series to indicate a greater frequency of consanguineous marriages among the parents of patients with early onset of diabetes as compared to that which occurs among parents of those with late onset. As a matter of fact, they found a higher incidence of consanguineous marriages when the patients were over 30 years old than when they were under 30 years. Yet, there was still a possibility that there was an increase in consanguinity among the parents of diabetics in general. This would be consistent with a hypothesis which assumed that diabetes was due to a recessive gene.

Another requirement of recessiveness as pointed out by Pincus and White was that the ratio of frequencies of affected siblings derived from the three types of matings which yield recessive offspring be as 1:2:4. In the Steinberg and Wilder sample the ratio was 1:2:4:3.4. Still another requirement was that the age of onset not be influenced by the presence or absence of diabetes in the parents. In the Steinberg and Wilder series, the average ages of onset in the patients was essentially the same regardless of the presence or absence of diabetes in the parents.

Finally Steinberg and Wilder devised a test to de-

rive numerical expectations, and examined the closeness of the fit of these expectations to the actual observed data. The test was based on the following: (Chart III)

1) Assume that diabetics are homozygous recessive.
2) Allow p to equal the frequency of the gene leading to diabetes,
3) Allow q to equal the frequency of the genes normal allele.

Chart III

Mating	Frequency	Frequency of Recessives in Total Population	Population of Recessives Arising from given Mating
Neither diabetic	$4p^2q^2$	p^2q^2	q^2
One parent diabetic	$4p^3q$	$2p^3q$	$2pq$
Both diabetic	p^4	p^4	p^2

Expected frequencies of matings yielding diabetics, proportion of diabetics in total population of offspring, and proportion of diabetics from each mating.

The results as charted:

Mating	Steinberg & Wilder		Pincus & White		Allan	
	Expected	Observed	Expected	Observed	Expected	Observed
Neither diabetic	1588.6	1589	440.6	440	122.8	124
One parent diabetic	370.8	370	78.8	80	19.4	17
Both diabetic	21.6	22	3.6	3	0.8	2

Matings yielding diabetic offspring-comparing expected frequencies with observed.

To summarize, Steinberg and Wilder did not believe in genetic heterogeneity or sex linked tendencies. They did believe in a simple recessive gene, but did not believe that all cases of diabetes were due to a simple recessive gene as there was evidence that in an occassional pedigree the disease was due to a dominant gene. They felt that the variability of diabetes might be due to genetic modifiers.

Thompson and Watson[37] showed in their study that diabetes was present in 415 (8.96%) of 4631 sibs of diabetic parents. When neither parent was diabetic, 7.69% ~~69%~~ of the sibs were diabetic, and when one parent was diabetic, 15.30% of the sibs were diabetic. These were in a 1:1.99 ratio which approximated closely with the 1:2 ratio expected on the basis of recessive inheritance. Furthermore, it was noted as with Steinberg and Wilder, that diabetes appeared with approximately equal frequency in the sibs, regardless of onset age of the propositi. Also, there was no apparent tendency for diabetes to affect chiefly males in some pedigrees and chiefly females in others.

Bartels[38] in 1953 thought that the difference in time of manifestation of diabetes between the generations might

be due in part to common recessive autosomal modifying genes and that the different varieties of diabetes were due to an allelic series of genes.

In 1954 Fajans and Conn[39] attempted to predict diabetes by using cortisone stimulation prior to the standard oral glucose tolerance test. They distinguished diabetics by a one hour level of greater than 160mg% and a two hour level of greater than 120mg%. With cortisone stimulation unsuspected diabetes was found in at least 19% of 152 relatives of diabetic patients; whereas, only one of 50 control subjects demonstrated a diabetic glucose tolerance test. Furthermore, of 75 non diabetic relatives of diabetics 24% showed marked loss of carbohydrate tolerance during the cortisone-glucose tolerance test. Only one of the 37 controls showed the same loss.

During the same year Allan[40] noted that the study of diabetes in twins seemed to favor the belief that the inheritance of this disorder was transmitted by a recessive gene following Mendelian Law. He pointed out that in three major series both twin-mates of the uniovular type were affected in 62.2%, and 11.9% of the binovular variety. He stated that almost without exception in uniovular twins, both members were said to suffer after the age of 43years as shown in Berg's study.

Conn[41] repeated the cortisone primed glucose tolerance

tests in 1958 and found that in 259 subjects (non diabetic relatives of known diabetics) 25% reacted positively as opposed to 3% in the control group. Each glucose tolerance test had been preceded for at least three days by a diet maintenance containing 300 grams of carbohydrate per day.

Perhaps some of the most convincing work in the field of inheritance and diabetes was produced by Joslin and White[32] in 1959. They demonstrated that the evidence in favor of the theory that the potentiality for developing diabetes was inherited rested primarily on five facts:

1. The concordant occurrence of diabetes in similar twin mates.
2. The statistically greater frequency of diabetes in close blood relatives of diabetics than in those of control populations.
3. The demonstration of Mendelian ratios of the recessive type in large series of cases selected at random.
4. The demonstration of expected ratios in presumely latent cases.
5. The fact that the incidence of diabetes in the genealogies of diabetes behaves as a recessive trait.

Regarding diabetes in twins, they studied 33 similar

and 63 dissimilar tiwns. Of the 33 sets, 16 (48.5%) had diabetes and only 2 (3.2%) of the 63 had diabetes. On the other hand, 10% of the dissimilar twin parents were diabetic and only 5% of the similar twin parents were diabetic. They pointed out that Hildegard Then Berg[9] found that 65% of 46 similar twins had diabetes and only 22% of 87 dissimilar twins had diabetes. After the age of 43, all of the similar twins were concordant with diabetes.

Joslin and White then compared the incidence of diabetes among 4434 parents and siblings of diabetics and 1290 parents and siblings of non diabetics. The incidence in the diabetic population was 6.7% as compared with 1.23% in the control population. They noted that Ford and Glenn[4] in 1951 studied 1741 cases and found an incidence five times greater than in the control population.

Next Joslin and White reviewed the material which demonstrated Mendelian ratios of the recessive type. They felt that dominance could not be clearly demonstrated because of the tendencies of diabetes to skip generations and because of the low incidence of diabetes among the parents of patients. They used the term "pseudo-dominance" as suggested by the occasional occurrence of diabetes in three successive generations. In fact, in their series they recognized diabetes twice in four successive generations. The authors presented their Mendelian recessive

statistics as done by Pincus and White in the 1930's. They described three types of matings:

1. Mm•Mm ---------- MM; 2Mm:mm
2. Mm•mm ---------- Mm:mm
3. mm•mm ---------- mm

They stated that the above ratios would be altered by family size, age of onset, chance of dying before the age of development of diabetes, the changing status of the population, and inaccuracy of diagnosis. Then, the expectation of diabetes appearing among the siblings was calculated on the average number of children per family and it was determined that the expected number of siblings in the totally homozygous marriage (mm) remained 100%, became 40% in the heterozygous-homozygous marriage (Mm mm), and became 16% in the heterozygous-heterozygous marriage (Mm Mm). This calculated proportion became 1:2.5:6.1 in contrast to the theoretical 1:2:4. ratio. In obsering 2309 cases the actual ratio was 1:2:5. or very similar to the Mendelian recessive pattern.

By using hyperglycemia they next attempted to demonstrate the mendelian recessive ratio in latent diabetics. First, it was assumed that hyperglycemic individuals represented future diabetics. Then in studying blood sugars in the apparently normal siblings of the forementioned marriages, ratios of 1:2.6:3.7 were found in comparing to the theoretical 1:2:4 proportion, thus, again approximat-

ing the recessive values.

Finally, a review of geneologies of diabetes was made to show an incidence of diabetes behaving like a mendelian recessive trait. Of 18,493 members of diabetic families (304 geneologies) as studied in the Joslin Clinic, 9.75 were diabetic (5.3%). Of 6,042 (110 geneologies) studied by Ernst Hanhart[45], 74 were diabetic (1.2%). One should have expected much higher values for a dominant trait. That the heredity of the diabetic trait was simple recessive was substantiated in the findings that the incidence of diabetes in the siblings of the diabetic population rose to 27.3%.

In discussing the linkage of genes, Joslin and White felt that no positive evidence of sex linkage had been demonstrated. They explained that the fact that one or more factor pairs might be involved in diabetic heredity was suggested by the high incidence of obesity, of congenital defects, and possibly such degenerative lesions as cataracts and atheroselenosis.

It was felt that the high frequency of the recessive gene or genes producing diabetes suggested strong forces of positive selection. Joslin and White noted that in 1955 Steinberg[44] estimated the frequency of q to equal 0.224 (by taking q^2, the incidence of diabetes both diagnosed and undiagnosed, at about 0.05 and penetrance at 20% in order to produce a disease incidence of about 1% in the

United States during this decade). It was felt that this frequency was far higher than could be explained by any known mutation rate. Steinberg's calculations revealed the following chances of developing diabetes in the siblings.

1. both parents diabetic 100%
2. one parent diabetic, other family grandparent plus aunt or uncle diabetic 85%
3. one parent diabetic, other family grandparent or aunt or uncle diabetic 60%
4. one parent diabetic, other family first cousin diabetic 40%
5. one parent or both grandparents diabetic 22%
6. one grandparent diabetic 14%
7. one first cousin diabetic 9%

Joslin and White felt that a suggestion of the strong selective forces was offered by the overrapid growth of diabetic children and adolescents in height, weight, and metacarpal development, sexual maturity and even intelligence. They cited from the work of Mills[47], Post, and White[49] who spoke of procreative advantage. They felt that if persons with the homozygous diabetes producing genotype reached sexual maturity at significantly earlier ages than others that it would suggest a higher "adaptive valve" of the genotype and would therefore offer a tentative explanation of the extraordinarily high frequency of the provocative gene or genes.

Grunnet[49] felt that a majority of cases of diabetes were hereditarily conditioned and a lesser percentage were acquired (exogenically conditioned). He felt that a part of the mild cases of diabetes in elderly individuals were probably exogenically conditioned. However, the majority of all cases of diabetes were regarded as one group of primary pancreatogenic diabetes, presumably inherited ressively.

Steinberg[50] in 1959 reiterated earlier work and pointed out that there was a greater frequency of concordance among monozygous twins, but that the concordance was not complete. Thus, he felt that post natal environmental factors were important in determining the occurrence of frank diabetes. He restated the sentiment that the familial incidence of diabetes might be explained by assuming that the susceptibility to diabetes was due to homozygosity for a recessive gene. On the other hand, the heterogeneity of the disease would lead geneticists to suspect that more than one genetic mechanism was involved in the susceptibility.. Steinberg felt that Grunnet's theory of endogenously and exogenously conditioned diabetes was unanalyzed genetically.

Balfour[51], like wise, noted that although Pincus and White first concluded in 1933 that diabetes was probably determined by recessiveness, this did not explain the great variations in both age of onset and clinical severity. He suggested that the degree of penetrance might reduce the

incidence of the clinical disease in those who were genetically susceptible. Balfour suggested that diabetes might be a collection of disorders all caused by enzyme deficiencies of glucose metabolism. Thus, the clinical expression would depend on inheritance through multiple genes.

In 1960 West[52] performed standard glucose and steroid primed glucose tolerance tests in subjects whose parents were both diabetic. The average age was 37 years. He found impaired tolerance in 29% and felt that this was in keeping with Steinberg's theory that the genetic susceptibility in this group approached 100% since diabetes was more likely to appear in the later decades.

Clarke[53] offered two explanations regarding the heterogeneous manifestations of diabetes. The first, incomplete penetrance, where some individuals that were genetically liable to the disease did not get it. He suggested that sometimes other genes or an environmental factor were necessary before the major effects of a major gene could be manifest. The second was multifactorial inheritance. In this case he felt that the severest type of diabetes had the complete set of genes influencing the character.

In 1961 Steinberg[54] noted that while all the major studies indicated homozygous recessivenss with diabetes, there was no evidence that susceptibility in every case

was due to homozygous for the same gene. He suggested that the method most likely to distinguish between the alternatives of a single locus versus two or more loci was to follow the offspring of families in which both parents were diabetic. Then if only one locus was concerned, all of the children would be liable to diabetes, and at least one child in each family would be diabetic. However, if two or more loci were involved, there would be many families with no diabetic children; and the observed frequency of diabetic children would be significantly lower than the computed number.

Pickens, Chase, and Jackson[55] reported discordance in a pair of identical twins. The non diabetic twin developed a questionably abnormal glucose tolerance test twenty-one months before he also became glycosuric.

This study ends with a presentation by Post[56] in 1962 to establish the hypothesis that all diabetics were homozygous, for a recessive gene at a single locus. In keeping with Steinberg's suggestion, Post believed that a study of the offspring of two diabetic patients permitted a more direct test of the single locus recessive hypothesis. If, however, the offspring were not homozygous for a single gene, this would indicate either a second, or at least more than one recessive diabetes permissive gene, each at a different locus, or complimentary alleles.

Post maintained that the reason some homozygous recessives become diabetic early and the majority remain non diabetic prior to the oldest ages included the chance inheritance of other genes, such as might be called modifying genes, as well as the vagaries of environmental influences such as diet, exercise, pregnancy, and early death. It was to be assumed that all potential diabetics in the oldest age group had by that time become frank diabetics.

Post felt that if the age of each offspring of a number of conjugal diabetic mating was known, that the probability of each one being a frank diabetic at the time of the study could be estimated assuming first, the hypothesis of a single gene at a single locus and secondly, that if there were only a few observed cases from the matings that these could be attributed to either additional loci, or might be due to low penetrance of a single gene. Then the estimated number of diabetics could be compared with the number of observed diabetics.

In summary, his procedure estimated the number of diabetics among offspring of conjugal parents as being the sum of the probabilities that a hypothetical homozygote of the same sex would have been a manifest diabetic at his or her particular age.

He demonstrated chi-square tests of goodness of fit between the number of diabetics expected under the sin-

gle locus hypothesis and the numbers observed in Dr. West's sample and the Department of Human Genetic's[57] sample. In both samples the numbers expected were slightly exceeded by those observed. Alterations were made regarding the death rates of potential diabetics. In Post's data of 161 offspring, the number of diabetics expected was 8.7 against thirteen observed. The differences were not considered of statistical significance. Since no observed number was less than expected, but in every case more, it was concluded that most, if not all, of the present onset age data came from families whose diabetes was genetically controlled at a single locus. However, multiple loci could not be excluded.

Finally, Post also assumed that the numbers of unmanifest potential diabetics diminished progressively through life until virtually none were left in the oldest age group in which a few diagnoses were still made and a few diabetics were still to be found. This assumption was suggested in his study by the progressive tapering off of onset frequencies beyond middle age before disappearing completely in the oldest age groups.

Conclusion

In following the progression of concepts in the heredity of diabetes, it can be seen that the basic theory presently held is primarily that of recessiveness, but dominance is still being considered.

Roberts[51] presents the following as criteria in simple recessive inheritance:

1. The great majority of affected persons are the offspring of parents who are normal to all outward appearances.
2. There is a familial incidence, that is, sibships frequently occur in which more than one child is affected. Taking a pool of a large number of sibships, it is possible by suitable methods to discover the proportions of normals to affected is really 3:1.
3. If the abnormality is rare, an undue proportion of related marriages is found amongst the parents of affected persons; the rarer the defect, the higher the proportion of consanguineous marriages.
4. Affected persons who marry normals have normal offspring only, in the great majority of cases.
5. When affected persons married to normals do have affected children (or when they have hap-

pened to marry heterozygotes), the proportion of normals to affected is 1:1.

6. There is an increased rate of consanguineous marriages amongst the unions of affected and normals which do yield affected offspring.
7. Affected persons who marry affected persons have affected offspring only provided that both owe their abnormality to the same gene.

Roberts presents the following as criteria in dominant inheritance:

1. Every affected person has an affected parent, for the gene must have come from one or the other, unless there should be a chance mutation.
2. Affected persons married to normals have, on the average, affected and normal offspring in equal proportions.
3. The normal children of affected persons, when they in turn marry normals, have only normal offspring. This also applies to their further descendants.

In examining Robert's criteria for recessiveness, it was noted that normal parents can have affected offspring. Of course, this can occur when two heterozygotes mate. Likewise, heterozygotic matings can produce 1:3 ratios or 25% affected as theorized by many

in this thesis. Furthermore, a possible increase in consanguinity was suggested by both Harris and Steinberg. Finally, the fact that affected persons who marry normals have only normals, and the fact that affected persons have only affected offsprings was also pointed out by the proponents of recessive inheritance in this paper. Descrepancies in these values occur when one considers phenotype or clinical normals rather than genotype normals, which, of course, is impossible.

It would seem that as perfectly as an explanation of recessiveness fits Robert's criteria, so does an explanation of dominance not fit his criteria. For example, every affected person does not have an affected parent, and the condition is too prevalent to be based on mutation. Furthermore, incomplete penetrance might explain a lesser percentage of affected offspring than parents, but probably would not account for a consistantly greater number of affected offspring than affected parent as seen by Steinberg and Wilder and others. Likewise the expected ratios seen in this thesis are in accord with recessive transmission, not dominance. Thus, affected persons married to normals do not have, on the average, affected and normal offspring in equal proportions unless the clinically normal individual is, in fact, heterozygous recessive.

Summary

In this paper an attempt has been made to review the etiology of diabetes based on inheritance and present it in such a manner that one can see how sentiments progressed to present day concepts. The most recent articles in the subject, for the most part, propose recessive inheritance with modifications such as modifying genes, environmental factors, and multiple loci. In comparing the material presented in this paper with criteria given by Robert's, it can be seen that diabetes probably is transmitted by recessive genes.

Addendum

A genetic study is presently under way at the University of Nebraska College of Medicine on a family from Valentine, Nebraska. Certain members of this family demonstrate hypogonadism, dwarfism, and diabetes mellitus. The results are not yet completed, but certain patterns seem to be taking form as one is able to analyze data obtained from histories of diabetes and as a result of oral glucose tolerance tests performed by Dr. M. J. Henn, Dr. Henry Lynch, myself, and other members of a genetic team at the medical school.

The proband, an individual who serves as the basis for a genetic study, is a sixteen year old white male who demonstrates hypogonadism, dwarfism, and diabetes mellitus. Of twenty-eight relatives tested, six or about 21% have diabetes. Diabetes is present in two generations of offspring from the union of a diabetic mother and a non diabetic father. However, the proband's father has a sister with diabetes. Thus, he would most likely be heterozygous.

With a heterozygous-homozygous mating, one would expect diabetes in half the cases. There are only three known cases of diabetes among the eighteen first generation offspring, but this might be expected since a

a majority are still in early adult life; and also, there are a few who have not yet been tested.

Although this study is not concluded, one can observe a hereditary transmission of diabetes. The possibility of recessive transmission exists, but probably will not be recognizable until completion of the tests. The final results of this study will be published at a later date.

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