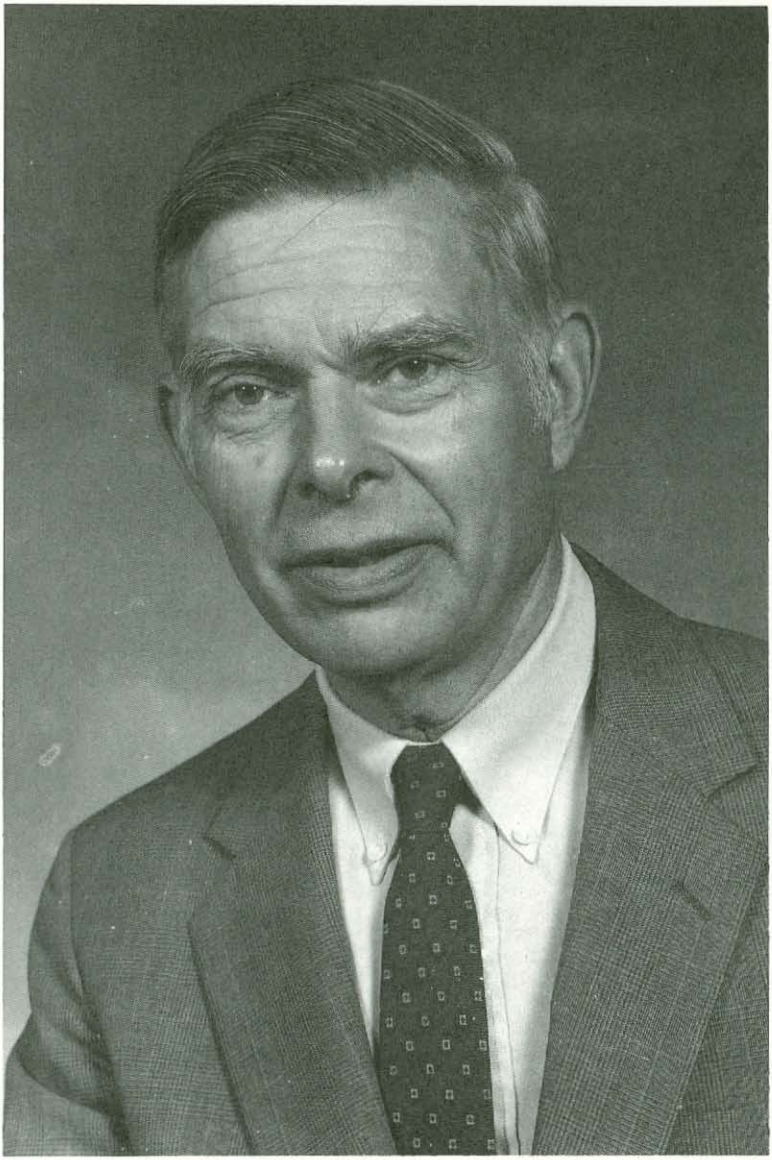
FREDERIC C. GOETZ
DOCTOR HONORIS CAUSA

Universitat Autònoma de Barcelona



UNIVERSITAT AUTÒNOMA DE BARCELONA

DOCTOR
HONORIS CAUSA
FREDERIC C. GOETZ

DISCURS LLEGIT A LA CERIMÒNIA
D'INVESTIDURA CELEBRADA
A L'AUDITORI DE LA FACULTAT
DE LLETRES D'AQUESTA UNIVERSITAT
EL DIA 22 DE NOVEMBRE DE L'ANY 1988

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PRESENTACIÓ DE FREDERIC C. GOETZ

PER

ALBERTO DE LEIVA

Excel·lentíssim i Magnífic Senyor Rector,
Digníssimes Autoritats,
Benvolguts col·legues,
Senyores i Senyors:

La Universitat Autònoma de Barcelona ha proposat que ens reuníssim avui aquí per a donar testimoni públic dels mèrits acadèmics de Frederick C. Goetz i de la col·laboració científica establerta entre el Departament de Medicina de la Universitat de Minnesota i el d'aquesta Universitat. En funció d'això, se li ofereix aquest Homenatge i se l'acull a la nostra comunitat en qualitat de Doctor Honoris Causa.

Frederick C. Goetz va néixer fa 66 anys a Fond du Lac, Estat de Wisconsin, U.S.A. Tota la seva formació acadèmica va tenir lloc a la Universitat de Harvard, a Boston, Massachusetts, on aconseguiria, amb els màxims honors, el grau de Doctor en Medicina, el 1946. Fou Metge Resident del Departament de Medicina del Massachusetts General Hospital i Daymon Runyon Fellow del Departament d'Endocrinologia i Metabolisme, que aleshores dirigia el Professor George Thorn en el Peter Bent Brigham Hospital, també de Boston.

El 1955 es va incorporar al Departament de Medicina de la Universitat de Minessota, on ha romàs durant els darrers 33 anys, havent recorregut les etapes d'Instructor, Assistant i Associate Professor, i, des

de 1968, Professor of Medicine, a la Secció d'Endocrinologia i Metabolisme.

Així mateix, ha estat el seu càrrec la Direcció del Centre d'Investigació Clínica (Clinical Research Center) i de la Unitat de Diabetis.

L'activitat investigadora del Professor Goetz, recollida en més de 180 publicacions, cobreix diferents aspectes de Medicina Interna, Endocrinologia i Metabolisme, i preferentment de Diabetis Mellitus, tasca que se li ha reconegut internacionalment i per la qual ha rebut importants premis i distincions.

Frederick Goetz ha influït de manera notòria sobre múltiples idees, conceptes i actituds terapèutiques vigents enguany, que intentarem resumir de manera sinòptica, encara que probablement incompleta.

1) REGULACIÓ DEL METABOLISME HIDROCARBONAT
- Modificació de la insulinosecreció: influències d'edat i sexe.
- Funció endocrina pancreàtica i resistència insulínica a la diabetis mellitus tipus 2, no insulinodependent.
- Acció insulinosecretora i hiperglucemiant de diferents sucres, administrats aïlladament o en un àpat mixte, tant en animals d'experimentació com en persones sanes i pacients diabètics.

2) DIABETIS I EMBARÀS
- Modificacions de la insulinosecreció durant la gestació.
- Significat i valoració de la presència d'anticossos antiinsulina durant la gestació.
- Viabilitat fetal a gestants diabètiques amb ronyó trasplantat per nefropatia diabètica.

3) HIPOGLUCEMIANTS ORALS
- Eficàcia de la seva utilització clínica a curt i llarg termini amb seguiment prospectiu.

- Efectes adversos cardiovasculars.
  (Chairman, University Group Diabetes Program).

4) MICROANGIOPATIA DIABÈTICA
- Efectes terapèutics de la hipofisectomia sobre la retinopatia diabètica.
- Susceptibilitat genètica per a desenvolupar microangiopatia.
- Fases evolutives de la morfologia i funció glomerulars a la diabetis tipus 1, insulinodependent.
- Influències del control metabòlic i trasplantament pancreàtic.

5) NEFROPATIA DIABÈTICA
- Resultats clínics del trasplantament renal versus les diferents modalitats de diàlisi.
- Història natural de la microangiopatia diabètica desenvolupada «de novo» en el ronyó trasplantat.
- Efectes del trasplantament renal sobre el curs evolutiu de la retinopatia i neuropatia diabètiques i també sobre la malatia cardiovascular ateroscleròtica.

6) TRASPLANTAMENT PANCREÀTIC
- Resultats del trasplantament pancreàticduodenal a l'animal d'experimentació i del trasplantament de pàncreas complert, de fragments pancreàtics i d'illots en el pacient amb diabetis mellitus tipus 1, insulinodependent.
- Criteris de selecció de possibles candidats a trasplantament pancreàtic.
- Resultats del trasplantament pancreàtic sobre la regulació metabòlica i el curs evolutiu de la microangiopatia i de la neuropatia diabètiques.
- Descripció d'una nova forma clínica i experimental de diabetis insulinodependent: diabetis mellitus tipus 1 recidivant, per agressió de l'empelt pancreàtic.

Les relacions acadèmiques del nostre grup de treball amb el Professor Goetz es varen iniciar l'any 1974 arran de la meva incorporació al

seu equip en qualitat de Clinical and Research Fellow, que es perllongaria durant dos anys. Frederick Goetz acceptà el 1981 la invitació de la Unitat Docent de l'Hospital de Sant Pau i, en qualitat de Professor visitant, va tenir l'oportunitat de conèixer la nostra institució i, a partir d'aleshores, facilitar diferents programes d'intercanvi de personal i projectes conjunts de cooperació científica comptant sempre amb la decidida i generosa coparticipació de José Barbosa, anterior Fellow del Professor Goetz i actualment Professor of Medicine de la Universitat de Minnesota. D'aquesta manera, diferents Becaris del Programa de Formació del Personal Investigador, Fulbright Fellowship i Comité Conjunto Hispano-Norteamericano de Cooperación Científica y Técnica, han viajat a Minneàpoli per a estades de 6 mesos a un any. Així, ha estat possible la publicació conjunta d'un considerable nombre de publicacions internacionals i de comunicacions a Congressos. Esperem i desitgem que aquesta col·laboració perduri i sigui igualment profitosa.

L'actuació de Frederick Goetz durant el seu dilatat currículum acadèmic restarà sempre clarament diferenciada i reconeguda en l'ingent esforç desenvolupat per investigadors i clínics que ha influït tan decisivament en el benestar i el pronòstic de la malaltia diabètica durant aquesta centúria. El Professor Goetz és un home bondadós i afable, sempre atent i sol·lícit amb la seva família, col·laboradors i amics. La lleialtat i dedicació que professa als seus malalts es reflecteix en una actuació eficaç, intel·lectualment impecable i càlidament humana, i que pretenem il·lustrar, a manera de símil, amb el perfil del metge de «Ciencia y Caridad», obra realitzada per Picasso a Barcelona, el 1987.

És per tot això, Excel·lentíssim i Magnífic Senyor Rector, que sol·licito que el Professor Frederick C. Goetz sigui investit en el dia d'avui amb el grau de DOCTOR HONORIS CAUSA per la Universitat Autònoma de Barcelona, segons la proposta formulada en el seu dia per la Facultat de Medicina i el Departament de Medicina.

Moltes gràcies.

LA NATURALESA DE LA DIABETES MELLITUS EN L'HOME: CONTINUACIÓ DE L'EVOLUCIÓ DEL CONCEPTE ENDOCRINOLÒGIC

PER

FREDERICK C. GOETZ

És un gran privilegi per a mi rebre el grau Honoris Caus de la vostra distingida Universitat. No l'accepto únicament com un mèrit personal, sinó que també ho faig en nom de la meva Universitat, la de Minnesota, i de tots els qui estan treballant per solucionar una de les malalties més antigues, la diabetis mellitus.

La Universitat de Minnesota va ser fundada en el temps d'Abraham Lincoln, com a institució pública independent. Es mantenia gràcies a ajudes de terra que es dedicaven a financiar la Universitat. La nostra escola mèdica va ésser inaugurada el 1988 i precisament enguany es celebra el seu centenari.

Com a reconeixement al gran honor que m'estan oferint desitjaria compartir amb vostès part del treball que la nostra universitat està fent en el camp de la diabetis en l'ésser humà.

Aquest treball completa els detallats estudis bioquímics discutits anteriorment pel meu distinguit predecessor, el Dr. John Exton, el qual

es va dedicar a entendre els mecanismes d'acció de la insulina com a hormona.

Examinaré el concepte actual d'aquest desordre designat com «diabetes mellitus» i especialment les nostres idees canviants sobre com la insulina es relaciona amb la diabetis del pacient humà.

Per entendre l'estat actual de la diabetis humana, seria interessant examinar breument els canvis que s'han succeït al llarg dels anys, si tenim en compte que aquest és un trastorn familiar, vist alguna vegada com malaltia però que actualment considerem ser un grup de símptomes amb diferents causes, cada una de les qual amb un tractament diferent.

Em refereixo al concepte de febre entès com una malaltia. Segons «la vértola», sembla ser que la «la febre» constituïa la segona causa d'admissió a l'Hospital General de la Santa Creu des dels seus començaments, cap a finals del segle XIV.

Dos-cents anys més tard, Luis Mercado de Valladolid, metge de Felip II, va donar suport a les idees que, en el segle dotze, van proposar sobre la febre Gale, Avicena i especialment Averroes de Córdoba. La febre és una malaltia que es manifiesta per la pell vermella, el pols ràpid i una sensació de fred i calor. Ell sostenia, a *«De febrium essentia»,* que el concepte de «calor natural» era la causa de la febre.

La història del coneixement de les causes reals de la febre, tal i com les coneixem, és fascinant i excitant. Està fermament basada en observacions de laboratori en micro-organismes, que van ser més detallats i especificats en el segle passat. Pel temps de l'apertura del Nou Hospital de la Santa Creu i Sant Pau a començaments del segle XX, la febre va ser reconeguda com una síndrome causada per un elevat nombre d'agents infecciosos-tifus, malària, febre tifoidea, etc. i també per causes no infeccioses.

Les observacions en el laboratori i l'experimentació controlada continuen fornint la base pel tractament de la síndrome «febre».

La història del nostre coneixement de la diabetis mellitus és tan excitant com la història de les malalties infeccioses i la febre, encara que aquesta és una historia cent anys més antiga. La diabetis és també un transtorn bastant vell i ja va ser observat a l'antic Egipte. Probablement estigui descrit en el «Papirus Ebers», que data del 1800 A. C. Inclús ara es considera una malaltia aïllada, caracteritzada per un augment de concentració de glucosa a la sang. Quan el nivell de glucosa de la sang és especialment alt, es donen símptomes de set i augment del volum d'orina.

Al llarg dels últims deu anys s'ha comprovat que, com la febre, la diabetis no és una malaltia aïllada. Per mitjà de diferents mecanismes, aquestes causes produeixen el mateix efecte, un persistent augment del nivell de glucosa a la sang.

Fins al descobriment de l'aïllament de l'hormona proteica insulina, no es va entendre que la diabetis era més aviat una síndrome que no pas una malaltia aïllada. El signe principal està definit com una observació de laboratori (augment de glucosa a la sang) però el principi és invariable.

La primera suggerència que apunta cap a l'existència de més d'un tipus de diabetis va ser expressada per Harold Himsworth a Londres, pels voltants dels anys 30. Després d'utilitzar un test estàndard on s'hi mesurava el sucre del pacient que reaccionava a una injecció d'insulina, va dividir els seus malalts en dos grups: aquells que eren sensibles a la insulina i els que no ho eren. Aquest concepte dels dos tipus de diabetis va ser elaborat en els posteriors pròxims 25 anys, mentre s'ideaven nous mètodes per mesurar la insulina en els teixits i fluids del cos. Amb la introducció, els anys seixanta, d'una ràdio-immunoassaig extremada-

ment sensible, va quedar clar que els pacients que reaccionaven a les injeccions d'insulina animal estaven mancats, parcialment o totalment, d'insulina en el plasma.

Pels volts del 1980, es va acordar que aquest tipus de diabetis anomenada «juvenil», però designada com «Tipus 1» s'associava a fenòmens característicament immunològics i que aquests s'associaven, també a una destrucció permanent de les cèl·lules beta dels illots de Langerhans del pàncreas, que són els que produiexen la insulina.

Quin fenomen fou el primer i per què, és una qüestió que no està gens clara.

L'any 1984, a partir d'observacions fetes a malalts que rebien transplantaments pancreàtics com a tractament per a la seva diabetis, va donar-se un avançat i revelador apropament al problema.

Aquest procediment fou desenvolupat per primera vegada a la Universitat de Minnesota per Richard Lillehei i altres, i va ser modificat per David Sutherland. En una sèrie de cinc trasplantaments de tipus especial —en els que els donants sans eren bessons monocigòtics de receptors amb diabetis insulinodependent de llarga durada— es va observar que els empelts funcionaven perfectament i «guarien» la diabetis tot eliminant la necessitat diària d'injeccions d'insulina, sense haver de prendre cap altre medicament immunosupressor.

Amb els trasplantaments d'òrgans usuals, el receptor ha de prendre contínuament dosis diàries d'aquestes poderoses drogues (ciclosporina, azatioprina i un corticosteroide).

Malauradament, aquest gratificant resultat només durava al voltant d'un mes, després del qual s'esdevenia una altra vegada una marcada

hiperglicèmia, a més de la desaparició de la insulina i del C-peptide del plasma sanguini i de l'orina.

Per poder entendre el que estava passant va ésser necesari obtenir teixit biopsiat dels emplets pancreàtics. Alguns malalts van autoritzar que els fessin la biòpsia, possibilitant, així, la investigació directa, abans irrealitzable, del desenvolupament del dany dels illots pancreàtics. El que es va revelar va ser un atac altament específic sobre la cèl·lula beta productora d'insulina, sense cap evidència de rebuig generalitzat de teixit, que hom esperava en transplantaments de bessó a bessó, ni tampoc en qualsevol de les altres conegudes cèl·lules endocrines dels illots que produeixen glucagon i altres hormones.

Va ser possible d'identificar els agents d'atac com a limfòcits de la sèrie T, concretament les T8 citotòxiques, que sembla que són els agents de diverses menes de malalties autoimmunitàries, tals com la tiroiditis limfocitària. Aquest ressorgiment del procés que presumiblement havia destruït prèviament els illots dels pàncreas dels bessons diabètics succeïa inclús tan tard com disset anys després de l'aparició de la diabetis. Sense cap dubte, aquest fet indicava una llarga memòria immunològica en el sistema immunològic cel·lular.

Aquestes observacions han ajudat a refermar la teoria que sosté que la diabetis deficient d'insulina Tipus 1 és, des del seu origen, un procés immunològic auto-destructiu. Aquest procés condueix eventualment a una pèrdua total d'insulina, que ha de ser constantment subministrada per mantenir el malalt viu; però pot ser previngut per un mitjà apropiat de supressió del dany immunològic de les cèl·lules dels illots al començament del procés.

El tipus més común de diabetis, que s'anomena «adulta» o del Tipus 2, havia estat caracterizat, mentrestant, per la seva associació amb quantitats mesurables d'insulina en el plasma. Aquests pacients poden so-

breviure i inclús trobar-se relativament bé sense injeccions diàries d'insulina, malgrat que el nivell de glucosa de la sang pugui ser alt. Aquestes persones són diabètiques no insulin-dependents.

Hi ha molta incertesa pel que fa al grau de dany cel·lular dels illots en aquests casos: pateixen una fallada parcial de les cèl·lules que conduiria eventualment a una pèrdua total d'insulina si els pacients poden ser seguits durant suficient temps? O tenen illots robustes i sanes que mai no s'exhauriran, sigui quin sigui el temps durant el qual sigui elevat el sucre de la sang?

En el primer cas es pot observar la diabetis adulta com una forma parcial del Tipus 1, possiblement un aspecte subtil del dany de les cèl·lules beta. En el darrer cas, el problema bàsic es trobaria fora del pàncreas.

Aquesta controvèrsia s'estudia en una població natural definida més que no pas en un grup de subjectes que estan en un hospital o en una clínica universitària, on artefactes deguts a l'autoselecció són inevitables.

El nostre grup de recerca ha tingut molta sort perquè ha pogut estudiar els residents d'un petit poble de la nostra regió, que té al voltant de 5.000 habitants, adequada per al nostre estudi. També la producció d'insulina: messurar el peptide-C relacionat amb la insulina en una mostra d'orina recollida durant 4 hores (està ja establert que la insulina i el C-peptide són alliberades en quantitats equi-molars a mesura que la insulina és segregrada pels illots pancreàtics), degut a la considerablement més útil secreció d'insulina que la mesura d'insulina per si mateixa.

En els darrers tres anys hem pogut completar aquesta primera fase del nostre estudi en els residents de Wadena, a Minnesota. Hem mesurat el grau de secreció del C-peptide en una mostra a l'atzar de 430 adults saludables residents al poble i els hem agrupat d'acord amb l'edat i el sexe. També hem estudiat 85 dels 110 coneguts metges diabètics de la

comunitat. Tota aquesta gent ha estat examinada dues vegades, amb una dosi de 75 gr. de glucosa en un dia i amb un líquid de 700 K-calories barrejat amb el menjar un altre dia. Els resultats dels dos exàmens es correspon molt bé dins dels subjectes individuals.

En la mostra feta a l'atzar dels 430 adults saludables (cap d'ells conegut com a diabètic), hi havia un extens assortit d'excreció del peptide-C. Però no hi havia cap diferència entre els tres grups d'edat del nostre estudi: entre 20 i 39 anys, entre 40 i 59 anys i de 60 anys en amunt. Vam estudiar algunes persones més grans de 90 anys i vam trobar que excretien força peptide-C. Hi havia alguna associació entre obesitat i excreció del C-peptide, però això no era gaire important en la gent gran, que sol ser generosa en reserves d'insulina i de peptide-C. No hi havia cap diferència entre homes i dones. Es van trobar més de 20 nous casos de diabetis reconeguda pel test de tolerància de glucosa, però tots ells mostraven abundant peptide-C.

Pràcticament tots els 85 metges diagnosticats com a diabètics ho eren del tipus «origen adult», segons criteri clínic. Va resultar de gran interès el fet de trobar que tots, excepte cinc del tipus «origen adult», mostraven la mateixa quantitat d'excreció de peptide-C que els subjectes agrupats per edats de la nostra feta a l'atzar d'adults saludables.

Aquest estudi continuarà de manera prospectiva. En aquest moments, les condicions preliminars dels nostres primers estudis horizontals són: primer, que la funció de la cel·lula beta preservada per la secreció d'insulina normalment no disminueix amb l'edat; segon, que la típica diabetis de l'adult o Tipus 2 no està associada amb la fallada progresiva de la cèl·lula beta (malgrat que algunes anormalitats en la velocitat de la resposta de la insulina han estat clarament mostrades per altres).

És ara, l'any 1988, quan estem començant a pensar en les conseqüències pràctiques d'aquesta realització, que hi ha almenys dos tipus de dia-

betis. Hem de recordar que fa un segle la medicina tant sols reconeixia l'existència de diverses infeccions que causaven febre. Van caldre cinquanta anys més per trobar tractaments específics basats en coneixements microbiològics. Pel que fa a la diabetis, podem esperar guarir o prevenir el Tipus 1 amb un tractament basat en immunologia —una vacuna específica o antisèrum per protegir la cèl·lula beta, per exemple, no seria inimaginable—. És aquest el camp en el que el Professor de Leiva i el seu col·lega, el Professor Barbosa, estan treballant activament.

Per a la diabetis del Tipus 2, la comprensió ha d'arribar d'augmentar el coneixement bioquímic de com la insulina actua en els teixits extrapancreàtics. És possible que en el futur definim altres sub-tipus de diabetis causats per la resistència de la insulina en diversos òrgans «diabetis del fetge», «diabetis muscular», etc. El desenvolupament de tractaments purament específics arribarà, estic segur, quan aquest coneixement s'hagi guanyat.

L'explosió del coneixement de la diabetis durant tota la meva vida ha estat profundament impressionant per a mi. Per això és un gran honor compartir les contribucions que les nostres dues universitats han fet en aquest coneixement i continuaran fent durant els pròxims anys.

THE NATURE OF HUMAN DIABETES MELLITUS: CONTINUING EVOLUTION OF AN ENDOCRINOLOGIC CONCEPT

It is a high privilege for me to receive a degree, *Honoris Causa,* from your distinguished university. I am proud to accept it on behalf of may home University of Minnesota, and for all those working to solve the problem of one of the most ancient of human diseases, diabetes mellitus.

The University of Minnesota was founded at about the time of President Abraham Lincoln, as a public, independent institution. Its support was provided by grants of land dedicated to support the University. Our medical school was opened in 1888 and is celebrating its 100th anniversary this year.

I wish to respond to the great honor you are showing me by sharing with you some of the work performed at our University in the field of greatest interest to me, diabetes mellitus in the human being. This work in many ways complements the detailed biochemical studies discussed here earlier by my distinguished predecessor, Dr. John Exton, who has devoted himself to understanding the mechanisms of action of insulin as a hormone. I will examine the present concept of the disorder designa-

ted as «diabetes mellitus» and in particular our changing ideas of how insulin relates to the expression of diabetes in the human patient.

To make clear the present state of understanding of human diabetes, it is attractive to examine briefly the changes over many years in the way we regard another familiar disorder, which also was once regarded as a «disease» but which we now consider to be a set of symptoms (a syndrome) which has many different causes and for which the proper treatment varies a great deal according to the specific cause.

I refer to the concept of *fever* as a disease. Along with «la vèrtola», it has been noted that «*la febre*» constituted the two principa causes for admission to the Hospital General de la Santa Creu from its beginning epoch at the end of the 14th century.

Two hundred years later, Luiz Mercado of Valladolid, physician to king Philip II, still held essentially the same views of fever which had been proposed by Galen, by Avicenna, and especialy by Averroes of Córdoba in the 12th century: fever is a disease manifested by «flushed skin, quickened pulse, and a sense of hot and cold periods». He supported the concept of «natural heat» as the cause of fever, in his treatise *De febrium essentia.*

The story of the dawn of knowledge concerning the true causes of fever, as we now recognize them, is fascinating and exciting. It is firmly based on laboratory observations on micro-organisms which became increasingly detailed and specific in the 19th century. By the time of the opening of the 20th century, fever was recognized as a syndrome which can be caused by a great number of different specific infections-typhus, malaria, typhoid, etc, etc- and by non-infectious causes as well.

Laboratory observations and controlled experimentation continue to provide the basis for the treatment of the syndrome «fever».

The story of our understanding of diabetes mellitus is just as exciting as the story of infectious diseases and fever-but it is a story which has lagged at least 100 years behind the other. Diabetes is also a very old disorder and was probably recognized in ancient Egypt. It is probably described in the Ebers papyrus from 1800 B. C. Even today it is generally regarded as a single disease, characterized by an increased concentration of the sugar glucose in the blood, with characteristic symptoms of thirst and increased urine volume when the blood glucose level is especially high.

Within the last ten years, however, it has become increasingly clear that, like fever, diabetes is not a single disease. By quite distinct mechanims, different causes may produce the same effect, a persistent increase in the blood glucose level.

It was not until the discovery and isolation of the protein hormone insulin-and until it became possible to measure insulin and related substances in body fluids-that substantial progress was made in understanding that diabetes is best regarded as a syndrome, and not as a single disease. With respect to diabetes, the principal «symptom» of the syndrome is now defined as a laboratory observation (high blood glucose), but the principle is unchanged.

The first clear suggestion that there might be more than one kind of diabetes came from Harold Himsworth in London, in the 1930's. Using a standardized test in which the diabetic patient's blood sugar response to an injection of insulin was measured, he divided his patients into insulin-sensitive and insulin-insensitive types of diabetes. This concept of two types of diabetes was steadily elaborated in the next 25 years, as better methods of measuring insulin in tissues and body fluids were devised. With the giant step of introduction of a highly sensitive radioimmunoassay in the 1960's, it became apparent that patients responsive to small injections of animal insulin also were *deficient or totally lacking in* measurable (endogenous) plasma insulin.

By 1980 it was generaly agreed that this form of diabetes —once called «juvenile» but currently designated simply as «Type 1»— was associated with characteristic immunological phenomena, and that these also were associated with permanent destruction of the insulin-producing cells (beta cells) in the islets of Langerhans in the pancreas. What came first, and why, was not at all clear.

An unanticipated and very reveling insight into the problem arose in 1984 from observations on patients receiving a pancreas transplant for relief of insulin-deficient diabetes. This procedure was first developed at the University of Minnesota by Richard Lillehei and others and was extensively modified by David Sutherland. In a series of 5 transplants of a very special type —in which the living healthy donors were the identical, monozygotic twins of recipients with long-standing insulin-deficient diabetes— it was found that the grafts could function perfectly, completely reversing the diabetes and eliminating the need for daily insulin injections— without the need for any immunosuppresive medicine. With the usual organ transplants, the recipients must continuosly take daily doses of these powerful drugs (cyclosporin, azathioprin, and a corticosteroid).

Unfortunately, this gratifying result lasted for only about one month. Then marked hyperglycemia returned, together with disappearance of insulin and the insulin-related C-peptide from blood plasma and urine.

To understand what was happening, it was necessary to secure biopsy tissue from the pancreatic grafts. This the patients permitted, allowing a previously unobtainable look at the development of damage to the pancreatic islets. What revealed was a highly specific attack on the insulin-producing beta cells only. There was no evidence whatsoever of generalized tissue rejection (which was not to be expected in twin-to-twin transplants) nor even of any of the other known endocrine cells in the islet (which produc glucagon and otther hormones). It was possible to identify

the attacking agents conclusively as lymphocyte of the T-cell series, specifically the T8 or cytotoxic «Killer» cells which had been suspected of being the agents in several forms of auto-immune, self-destructive diseases such as lymphocytic thyroiditis. This reenactment of the process which presumably had previously destroyed the islets of the diabetic twins' own pancreases occurred as long as 17 years after the original onset of diabetes.

Unmistakeably, this indicated a surprisingly long immunologic memory in the cellular immune system.

These observation have given firm support for the concept that Type 1 insulin-deficient diabetes is, at its origin, an immunologic self-damaging process. This process leads eventually to total loss of insulin, which then must be constantly supplied to keep the patient alive. It might be *prevented* however, by and appropriate means of suppresing or interrupting the immunologic damage to the islet cells at the very beginning of the process.

The much more common form of diabetes commonly caled «adult» or Type 2 diabetes han been found, meanwhile, to be often associated with measurable amounts of insulin in plasma. Such patients can survive and even feel relatively well without daily insulin injections, even though the blood glucose level may be high. These are non-insulin-dependent diabetic persons.

There has been much uncertainty, however, about the degree of islet cell damage in such cases: are they simply suffering from a partial failure of islet cells, which would eventually lead to total insulin loss if the patients could be followed long enough? —or do they have essentially healthy, robust islet cells which are unlikely to be exhausted no matter how long the blood sugar is high? In the former case, adult diabetes might be regarded simply as a partial form of Type 1 diabetes, possibly

with a more subtle form of betacell damage. In the latter case, the basic problem would necessarily lie outside the pancreas.

This controversial question is best studied in a defined, natural population, rather than in the groups of subjects who are found in a hospital or university clinic, where bias due to self-selection is inevitable.

Our research group has been fortunate in the opportunity to study the residents of a small town in our region. With about 5,000 inhabitants, it is just the right size for our research. Also, it has been possible to establish a convenient and simple method for estimating insulin production by measuring the insulin-related C-peptide in a sample of urine collected over 4 hours. It is well established that insulin and C-peptide are released in equi-molar quantities as insulin is secreted by the pancreatic islets. Because of its considerably slower removal rate from the plasma, however, C-peptide gives a more useful measure of insulin secretion rate than the measurement of insulin itself.

In the last 3 years we have been able to complete the first phase of our study of the residents of Wadena, in Minnesota. We have measured the secretion rate of C-peptide in a random sample of 430 healthy adults living within the town, stratified according to age and gender. We have also studied 85 of the 110 known, physician/diagnosed diabetic persons in the commmunity. The subjects have been tested twice, with an oral dose of 75 gm of glucose on one day and a liquid 700 kilo-calorie mixed meal on another day. The results with the 2 different tests agree well within individual subjects.

In the random sample of 430 healthy adults (none of whom was previously known to be diabetic), there was a wide range of C-peptide excretion. However, there was no difference among the thre age groups under study: age 20 to 39, 40 to 59, or 60 and older. We studied several persons over 90 years old and found them to be excreting abundant

C-peptide! There was some assocation between obesity and C-peptide excretion, but this did not account for the generous insulin/C-peptide reserve in the older persons. There was no obvious difference between men and women. There were over 20 «new» cases of diabetes recognized by the glucose tolerance testing, but they all showed abundant C-peptide as well.

The 85 physician-diagnosed diabetic subjects were almost all of the adult-onset type (Type 2) by clinical criteria. It was of great interest to us to find that all but 5 of the adult-onset cases showed just as much C-peptide excretion as the age-matched subjects in the random sample of healthy adults.

This study will be continuing prospectively. At this time our preliminary conclusions from our first cross-sectional studies are, first, that the beta-cell reserve for insulin secretion does not normally diminish with increasing age, and second, that the familiar and typical adult-onset or Type 2 diabetes is not associated with significant or progressive beta-cell failure (even though some abnormalities in the velocity of insulin response have been clearly shown by others).

Now in 1988 we are just beginning to think of the practical consequences of this realization that there are at least two kinds of diabetes.

We must remember that a century ago medicine was just recognizing the existence of different specific infections causing «fever». Another 50 years and more were required before highly effective treatments were available which were based on specific microbiological knowledge. With respect to diabetes, we can look forward to increasing attention to the possibility of actually curing or preventing Type 1 diabetes with treatment based on immunology. A specific vaccine or anti-serum to protect the beta cells, for example is not beyond imagination. This is the field of research in which Professor de Leiva and his colleague Professor Barbosa are actively working.

For Type 2 diabetes, the approach must be through increasing biochemical knowledge of how insulin acts on tissues outside the pancreas, since surely defect(s) must lie there. It is possible that we will define in the future further sub-types of diabetes due to insulin resistance in various organs («liver diabetes», «muscle diabetes», and so on). The development of truly specific treatments will come, I am sure, once such knowledge has been gained.

The explosion of knowledge of diabetes during muy own lifetime is deeply impressive to me. It is a great honor to share in the recognition of the contributions that our two universities have made to that knowledge, and will continue to make in the years to come.

CURRICULUM VITAE

DE

FREDERIC C. GOETZ

NAME:	Frederick C. Goetz
DATE OF BIRTH:	June 22, 1922
PLACE OF BIRTH:	Fond du Lac, Wisconsin
MARITAL STATUS:	Married - Mary Rose Riordan, 1960
NO. OF CHILDREN:	Four
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Education:

Harvard College, Cambrigde, Massachusetts, B.S., 1943

Harvard Medical Schoo, Boston, Massachusetts, M.D., *cum laude,* 1946

Postgraduate Training:

Internship (Medicine) 1946-1947

Massachusetts General Hospital

Boston, Massachusetts

Residency

Assistant Resident	1947-1948
Resident	1950-1951
Chief Resident	1954
Medical Service,	
Massachusetts General Hospital	

Fellowships

Research Fellowship in Endocrinology with	
Dr. George Thorn	1951-1953
Damon Runyon Fellow	
Peter Bent Brigham Hospital	
Boston, Massachusetts	

MILITARY SERVICE:

Medical Officer, Medical Corps of the U.S.A.	
Army, Southern California and Korea	1948-1950

APPOINTMENTS:

Director, Diabetes Clinic	1955
University of Minnesota Hospitals	
Minneapolis, Minnesota	
Instructor, Department of Medicine	1955-1956
Assistant Professor	1956-1961
Associate Professor	1961-1968
Program Director, General Clinical Research Center	1969-1986
Professor, Section of Endocrinology	1968
and Metabolism	

MAJOR RESEARCH INTERESTS:

Diabetes and carbohydrate metabolism; regulation of insulin secretion; vascular complications of diabetes; genetic and epidemiologic aspects of diabetes.

SOCIETIES, COMMITTEES AND BOARDS:

Central Society for Clinical Research
Central Clinical Research Club
The Endocrine Society
Society for Experimental Biology and Medicine
The American Diabetes Association
Member, Board of Directors, American Diabetes Association (ADA), 1962-1968
Member, Editorial Board of Diabetes 1965-1971
ADA - Chairman, Committee on Therapeutic Agents, 1966-1971
Vice-Chairman, 1972-1973
Chairman, Committee on Research and Scientific Affairs, 1971-1977
University Group Diabetes Program - Chairman, Committee on the Kidney;
Principal Investigador, University of Minnesota Study Clinic
Twin Cities Diabetes Association - Vice President and Chairman of Committee on Research, 1969-1973
Member, Committee on Diabetes, Minnesota State Medical Association 1974-1975
American Diabetes Association of Minnesota, Chairman - Research Committee

HONORS:

Elvehjem Lecturer, Wisconsin State Medical Society, 1972
Visiting Lecturer, University of London (King's College Hospital) 1975
Upjohn Award of the American Diabetes Association, Physician-educator in diabetes, 1978
Visiting Professor, Autonomous University of Barcelona, 1981
Edmund B. Flink Visiting Professor of Medicine, West Virginia University, 1983-1984

PUBLICATIONS OF FREDERICK C. GOETZ. M.D.

Original Papers

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12. Goetz, F.C.: Respiratory quotient and nitrogen balance during tolbutamide administration. Ann NY Acad Sci 71: 46, 1957.
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14. Goetz, F.C., and Guggenheim, P.R.: The use of simple enzymatic tests for glucose in detection of diabetes. Diabetes 7: 393, 1958.
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20