Principles of breeding, maintaining and working with diabetic and non-diabetic BB/Wor-rats

by Axel Kornerup Hansen, DVM, Møllegaard Breeding Center.

Introduction

The BB/Wor-rats has been used in diabetes research for more than 10 years. Diabetes in this animal model has a lot of similarities to human juvenile diabetes, but also characteristics not seen in humans. Since 1986 we have been breeding BB/Wor-rats at our breeding center. In this article some of our experiencies on breeding, maintaining and working with these rats will be refered.

History

The spontaneously diabetic rat, The BB/Wor, started its history in 1974 at the Bio-Breeding Laboratories of Canada Ltd., Ottawa.

In the beginning of 1974 an increase in the number of deaths among the weaned animals of the Wistar colony manifested itself amounting. The dying animals were extremely cachectic without any other pathological deviation.

It was decided that all weaned animals were to be weighed every second day in order to make it possible to identify the affected animals before they died. During the first three months 15 rats were selected for closer examination. It was noted that the bedding of affected animals was much wetter than usual.

Daily intake of fluid was found to be much higher among affected rats when compared to normal rats. Glucosuria, ketonuria, elevated plasma glucose and positive glucose output were found.

Histology of pancreas was carried out, and fibrosis was found in the islets of Langerhans together with a total absence of beta cells. Thus the diagnosis, insulin-dependent diabetes mellitus (IDDM), could be made.

Subsequently, the affected animals were treated daily with insulin. By father – daughter mating the incidence was raised to about 28 %. Both diabetic animals and non-diabetic offspring of diabetic animals were used in the breeding. (7).

The rats thus bred were called BB-Wistar-Ontario-rats. In 1977 *A. Like et al.* received rats from this colony for further inbreeding at the University of Massachusetts in Worchester, USA. The aim of this inbreeding was to produce rats with a high, and predictable incidence of diabetes.

The following inbreeding of 20 generations resulted in six lines with an incidence of more than 50 %, called diabetes prone (dp), and four lines with an incidence of less than 50 %, called non-diabetes prone (ndp), correspondingly.

All lines are listed in table 1.

Table 1.

BB/Wor-lines:
Dp: BA, BB, BC, BE, NB, PA Ndp: WA, WB, WC, WD

The inbred rats now were called BB/Wor.

In 1986 we received the first breeding animals of the lines BB and WA and in 1988 we also received breeding animals from the line WA.

Nomenclature

A correct nomenclature starts by stating BB/Wor followed by the ICLAS designation of the breeder, ending with a line specification (10). Our three colonies, for instance, are designated BB/Wor/Mol-BB, BB/Wor/Mol-WB and BB/Wor/Mol-WA, respectively.

Owing to considerable differences between the various lines, it is unacceptable to refer to the applied rats as being BB/Wor in refe-

Table 2. Incidence and onset-time of diabetes in BB/Wor/Mol-BB

Incidence, pct.	74	
	mean	s.d
Onset-time, age in days	84	11
Ref: 9		

Table 3. Clinical symptoms at the onset of diabetes.

Reduced general condition
Increased drinking desire
Tachypnoe
Weight loss of 5–20 % of body weight
Increased urination
Dull erect look of the coat

rences etc. without giving an indication of origin of lines, too.

Clinical Picture

50 to 90 % of dp BB/Wor rats develop diabetes around day 75, 85 or 95 depending on the line in question. Normally, 85 % of the rats developing diabetes will have done so before day 120. Data estimated on weanlings from our colony are fiven in table 2. The onset depends very much on environmental factors (see later). In table 3 some of the clinical observations, which can be done around the onset-time are listed. In table 4 a number of clinico-chemical values are stated. In table 5 some of the pathological deviations to be found commonly in dp BB/Wor-rats are listed.

Immunology

A high incidence of infections as well as the existence of lymphoid hyperplasia, spontaneous granulomes without demonstrable microorganisms, lymphoma, eosinophilia and lymphocytopenia point in the direction of the fact that BB rats are immune-deficient animals, in which diabetes is only one of the ways the deficiency manifests itself (35). A considerable higher incidence of infections and spontaneous deaths have been registered in the BB/Wor/Mol-BB colony than by other of our rat colonies. This has, however, not been statistically compared.

The development of type 1 diabetes is due to an autoimmune process.

Already neonatally, dp BB/Wor rats suffer from pronounced lymphocytopenia, most of it being a T-cell lymphocytopenia (18). Dia-

Table 4. Clinisco-chemical values in connection with diabetes onset in BB/Wor-rats.

	Diabetic animals				Normal values		
Plasma	Value		Day of Measurement after onset	Ref.	Value		Ref.
Clucose	15 to 30	mmol/l	0	*, 18	3 to 8	mmol/l	*
Ketone	5 to 8	mmol/l	0	18			
TRG	3.5 to 8.5	mmol/l	0	18	0.5 to 2.1	mmol/l	**
IRI***	0	ng/ml	8	18	1 to 2	ng-ml	18
IRG****	600 to 800	pg/ml	16 to 20	18	200 to 300	pg/ml	18
Urine							
Glucose	> 25	mmol/l	0	*	0		*
Ketone	4–10	mmol/l	0	*	0		*
24-hour diuresis	> 100	mmol/l	0	*, 18	5 to 10	ml	*

* Own observations
** Estimated on outbred Wistar rats by Scantox Biological Laboratory
*** Immune-reactive insulin
**** Immune-reactive glucagon

Table 5. Pathological anatomy of the BB/Wor-rat.

Lesion	Incidence in dp lines Compared to ndp lines	Ref.	Also seen in human IDDM
T-cell-lymphocytopenia	100 %	12	No
Insulitis (mononuclear infiltration in the islets of Langerhans)	100 % in diabetic animals – also seen in non-diabetic animals	17,29	Yes
Immune deficiency symptoms	100 %	5,35	No
Testicular atrophy	High	35	Yes
Hepatic lipidiosis Pancreatitis Lymphocytarian thyreoiditis	Increased	35	Only with a low incidence
Hypoglaemical disorders of brain Central pontine myelinolysis	Slightly increased	35	Only with a low incidence
Gastric erosions	Increased	35	No
Idiopatic megacolon	Slightly increased	35	No

betes in the ndp lines is not attended by lymphocytopenia (non-lymphocytopenic diabetes).

Genetics

Histocompatibility

All BB/Wor-rats have the MHC-haplotype RT1-u. Diabetes in the BB/Wor-rat seems to be related to this MHC-haplotype, which is analogous with human type 1 diabetes. The application of monoclonal antibodies against RT1.D products shows that exactly RT1.D constitutes the most important part of the RT1-complex in the development of diabetes (8).

Lymphocytopenia

Mating experiments show that there is a recessive autosomal non-MHC-coupled gene 1, which is lymphocytopenic (2, 6). Animals with lymphocytopenic diabetes are always lymphocytopenic, whereas lymphocytopenic animals are not always diabetic. As far as this gene is concerned the selection has taken place in the fourth generation of inbreeding, so that none of the W lines holds the recessive lymphocytopenic gene today (6). Lymphocytopenia is not a characteristic of human IDDM.

The non-lymphocytopenic diabetes has not been as carefully explained as the lymphocytopenic. It is much more unusual, anyway. In our colony of the WB-line one instance has been recorded out of 300 animals. It is characterized by a very early onset. Such animals are dominant L on the lymphocytopenic allele (6).

Penetrance and onset of diabetes

Butler et al. state the heretability of the onset to be only between 0.06 and 0.16 (6). My own observations also indicates, that the onset-time monitored on our BB/Wor/Mol-BB-colony in our stables does not correspond to onset-times registered on BB/Wor/Mol-BB-rats in other facilities.

The genetic disposition for the penetrance and onset-time of diabetes has not been significantly clarified. *Brogren et al.* points at one single diabetogenetic gene which is recessive, non-MHC-linked and autosomal (2). *Kloeting et al.* reject a simple autosomal hereditary succession (15). *Butler et al.* postulate that diabetes penetrance is controlled by three genes, A, B and C, of which all dp lines are said to have the genotype AABB, whereas lines with a high incidence are cc, and lines with a lower incidence are CC.

The same author also postulates three genes for the onset, E, F and G. This is done on the basis of the standpoint that the lines can be divided into lines with early, medium and late onset, respectively, corresponding to approx. day 75, 85 and 95 (6).

Positive and negative influence on the phenotype

Environmental factors

The phenotypical expression, clinical diabetes, may be influenced by various environmental factors. Some of these possible factors are listed in table 6.

Table 6. Environmental factors influencing diabetes incidence in dp BB/Wor-rats.

Factor	Influence	Reference
Synthetic diet compared to a natural diet	negative	28
Mycoplasma-infections	negative	13
Immune-modulation	negative	14

Pharmacological immunosuppression

In our BB/Wor/Mol-BB colony we have, as a matter of routine, treated all breeders – those of the foundation stock excepted – with cyclosporine A. A reduction in the incidence from 74 % to 46 % has been achieved. The results are given in table 7. Even greater reduction has been achieved by *Stiller et al.* (33) and *Like et al.* (16). According to our experience the insulin dose to cyclosporine-A-treated, which in spite of the treatment develops diabetes, is approx. 50 % of the dose to non-treated rats. This corresponds to observations made by others (37).

Table 7. Results of routine treatment of BB/Wor-breeding animals with cyclosporine A.

Dosis mg/kg/day	20
Application	i.p.
Age at start, days	50
Age at end, days	60
Treated animals, no	120
Incidence, treated, %	46
Incidence, non-treated, %	74
Chi-square	19.4
P <	0.005

Transplants

Two categories of transplant experiments are significant in connection with BB/Wor rats (21, 22, 23, 24, 34). The first one is concerned with whether it is possible to cure or prevent diabetes in the BB-Wor rat by transplanting cells from non-diabetic animals. The other one is concerned with the possibility of transferring diabetes to other animals by transplanting cells from BB/Wor rats.

In our own colony we have made attempts with splenic cell transplants from ndp WB to dp BB. Half the content of leucocytes from the spleen of an adult WB was transplanted to a 25 days old BB. I.v. as well as i.p. application was used. The incidence of diabetes among the treated animals was, however, not significantly different from that of the rest of the colony. This is in contrast with findings of *Rossini et al.* (26, 27).

Postdiabetic complications

Diabetic BB/Wor-rats lines may develop some postdiabetic changes analogous with those observed in human diabetics. Some of the most important are listed in table 8.

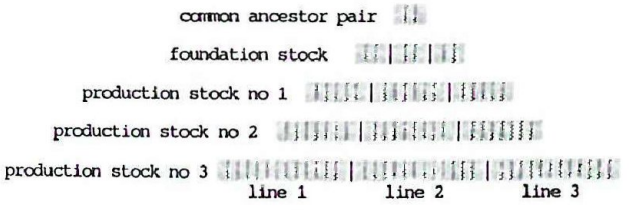
Breeding

All lines of BB/Wor rats should be maintained by means of strict inbreeding. It is acceptable that a pyramid is built up as illustrated in figur 1. The foundation stock counts approx. 10 pairs, which are all brother × sister mated, from which first, second and third production stock is created for the purpose of producing animals for research. It is not strictly necessary that brother × sister mating is practiced in the production stocks, too. However, in the breeding of dp lines each animal must necessarily be registered, and therefore brother × sister mating might as well be practiced.

The continuation of the breeding from generation to generation must only take place

Table 8. Postdiabetic complications of diabetic BB/Wor-rats and human with IDDM.

Lesion	Ref.	BB/Wor	Human IDDM
Neuropathy			
PNS	30, 32	+	+
ANS	36	+	+
Glomerulopathy	3	(+)	+
Thombocyte alterations			
Reduced aggregation	11	+	+
Increased cyclic GMP	11	+	+
Plasma			
Growth inhibiting factor	11	–	+
Retinopathy			
Reduced pericyte/endothal ratio	31	+	+



Figur 1

Principles of inbreeding

from the foundation stock. In the foundation stock each generation has a length of app. 6 months. Every third generation a new common ancestor is selected from the fore-going foundation stock or from a selected reference colony.

For security purpose it is convenient to part the pyramid into three strictly separated lines, so that if one line is struck by contamination or mutation it can be closed without ruining the colony.

Even with an restricted inbreeding, genetic modification should be expected in some of the loci which are not registered currently. One then has the choice of accepting that one's colony is different from other colonies, or of seeing to it that its genetic modification is the same as in other colonies by exchanging breeding material. Each third generation, a new pair of breeders is purchased for our colonies from the colonies in Worcester.

Butler et al. observed no statistical difference in the incidence of diabetes among weanlings after mating of diabetic animals with one another, diabetic with non-diabetic, and non-diabetic with one another (6). I have made equal observations in our BB/Wor/Mol-BB-colony.

Diagnosis and therapy

From day 55 all dp rats are daily weighed and examined for glucosuria and ketonuria by means of Gluketur teststrips (Boehringer-Mannheim). At the setting in of diabetes the diagnose is confirmed by measuring of blood sugar (Reflolux II, Boehringer-Mannheim) by bleeding tail puncture. In a breeding colony such as ours, insulin therapy is started already when blood sugar has been registered at 10 to 12 mmol/l. Diabetic animals are treated with insulin once a day using Novo Ultralente Heattreated Insulin diluted to 10 i.u./ml. Newly diabetic animals may be treated according to table 9.

Animals loosing more than 5 % of their body weight from one day to the other routinely have their blood glucose monitored and their insulin dosis changed if necessary.

Dehydrated and/or ketotic animals are treated with 10 to 20 ml of Ringers lactat s.c., but prednisolon s.c. may be used, too. Later on in the treatment it is attempted to keep the animals on a urine sugar level of 10 to 20 mmol/l, and without any ketonuria. Each

Table 9. Starting dose in i.u. insulin. Plasma glucose mmol/l.

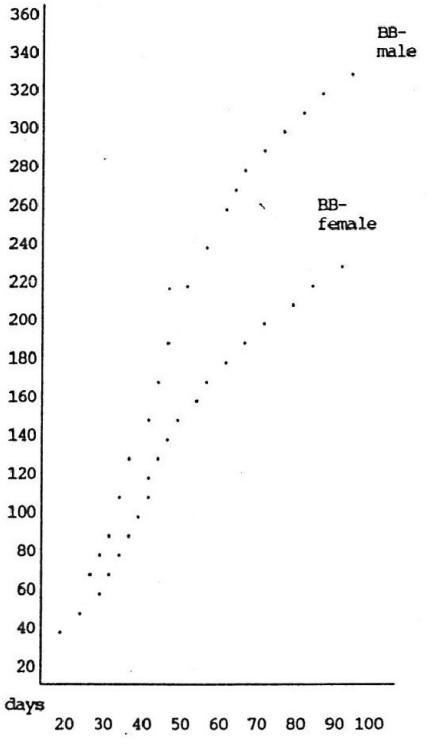
Body weight g	10 to 14	15 to 19	20 to 24	> 25
100	0.6	0.8	1.0	1.0
150	0.8	1.0	1.2	1.4
200	1.0	1.2	1.4	1.6
250	1.2	1.4	1.6	1.8
> 300	1.4	1.6	1.8	2.0

week the blood sugar is measured, and efforts are made to keep it at 11 to 18 mmol/l. In rats the blood sugar will reach its maximum 2 to 4 hours after the lights has been switched on in the shed. Therefore, examination and treatment should take place within these hours.

Special care is required in connection with animals with young. It is important that their blood sugar is kept on a level sufficiently high to ensure that the litter of young does not die from reduced lactation. On the other hand, an irregular and insufficient insulin therapy will also cause abortion. It is however, to be preferred that the female breeders are slightly ketotic rather than hypoglycaemic.

All diabetic animals are to be weighed every day in order to correct insuline dose in the case of weight loss.

figure 2.

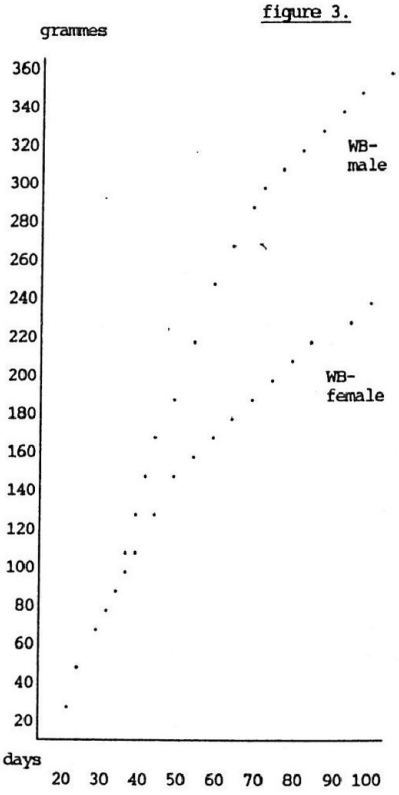


Numbers of animals in test, BB/Wor/Mol-BB: 10 males, 10 females
Diet: Altromin 1314, mod. to 20% protein.

Standard deviation, grammes:

Age,days	28		63		84	
	M	F	M	F	M	F
BB-line	9	6	24	6	24	7

figure 3.



Numbers of animals in test, BB/Wor/Mol-WB: 10 males, 10 females
Diet: Altromin 1314, mod. to 20% protein.

Standard deviation, grammes:

Age,days	28		63		84	
	M	F	M	F	M	F
WB-line	11	11	16	8	20	9

Animals in their active growth period should have their insulin dose raised by 0.2 i.u. for each 20 gram weight gain.

Brownscheidle et al. found that by means of Alzet pumps implanted with insulin, abortion could be reduced to a level equal to that of normal Wistar rats (4). In the colony of the Western General Hospital in Edinburgh two daily insulin treatments are given to animals with young; ultratard insulin in the morning and monotard in the afternoon (1). In our colony animals with young are treated only once a day, but we have been able to weane a major number of the young by removing the neonatal young from the mother and lay it to a non-diabetic nurse, primarily Lewis rats. However, we have not made statistics on these results.

Growth

For BB/Wor/Mol-BB and BB/Wor/Mol-WB animals we have estimated the growth curves in figures 2 and 3.

Summary

The background for the development of the BB/Wor-rat as a model to be used in the diabetes research is described. The most essential pathological and clinical aspects are also described. Experiences from the breeding and therapy are refered and results on lowering the incidence by treatment with cyclosporine-A and injections of immunocompetent spleen cells are given.

Resumé

Baggrunden for BB/Wor-rottens oprindelse beskrives, ligesom den væsentligste patologi og klinik beskrives. Der videregives erfaringer omkring avl og terapi. Der omtales og vurderes resultater fra egne forsøg på at opnå en lavere incidens af diabetes blandt avlsdyrene ved behandling med cyclosporin A og transplantation af immunkompetente miltceller.

Yhteenveto / K. Pelkonen

Artikkelissa kuvataan BB/Wor-rotan taustaa mallina sokeritautitutkimukselle. Olennaisimmat patologiset ja kliiniset piirteet kuvataan myös, sekä kerrotaan näiden eläinten siitostamisesta ja hoidosta sekä ennaltaehkäisevistä hoitotuloksista, joita on saatu syklosporiini A-käsittelyllä ja immunokompetenttien pernasolujen injisoinnilla.

References

1. *Baird, J. D., A. J. Bone & U. J. Eriksson:* The BB rat: a model for insulin-dependent diabetic pregnancy. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 412–417.
2. *Brogren, C. H., K. Buschard, C. Röpke & J. Rygaard:* Genetics of the autoimmune BB-Rat in the Study of Diabetes mellitus Hereditary. In J. Rygaard, N. Brünner, N. Græm & M. Spang-Thomsen: Immune-Deficient Animals in Biomedical Research, Karger, Basel 1987, 117–121.
3. *Brown, D. M., M. W. Steffes, P. Thibert, S. Azar & M. Mauer:* Glomerular Manifestations of Diabetes in the BB rat. Metabolism 1983, *32,* 7, Suppl. 1, 131–135.
4. *Brownscheidle, C. M., V. Wooten, M. H. Mathieu, D. L. Davis & I. A. Hofmann:* The Effects of Maternal Diabetes on Fetal Maturation and Neonatal Health. Metabolism 1983, *32,* 7, Suppl. 1, 148–155.
5. *Buschard, K.:* Personal communication, 1988.
6. *Butler, L., D. L. Guberski & A. A. Like:* Genetics of diabetes production in the Worcester colony of the BB rat. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 74–78.
7. *Chappel, C. I. & W. R. Chappel:* The Discovery and Development of the BB Rat Colony: An Animal Model of Spontaneous Diabetes Mellitus. Metabolism 1983, *32,* 7, Suppl. 1, 8–10.
8. *Fuks, A., E. Colle, S. Ono, G. Prud'Homme, T. Seemayer & R. D. Guttmann:* Immunogenetic studies of insulin-dependent diabetes in the BB rat. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 29–33.
9. *Gotfredsen, C.:* Personal communication, 1987.
10. *Guberski, D.:* Personal communication, 1987.
11. *Hamet, P., H. Sugimoto, F. Umeda & D. J. Franks:* Platelets and Vascular Smooth Muscle: Abnormalities of Phosphodiesterase, Aggregation and Cell Growth in Experimental and Human Diabetes. Metabolism 1983, *32,* 7, Suppl. 1, 124–130.
12. *Jackson, R., N. Rassi, T. Crump et al.* The BB diabetic rat. Profound T-Cell lymphocytopenia. Diabetes 1981, *30:* 887–889.
13. *Kloeting, I., O. Stark & R. Brdicka:* Incidence of the insuline-dependent diabetes mellitus in BB rats: Their genetic heterogenecity and susceptibility to infection. Folia Biol. 1984, *30,* 33–42.

14. *Kloeting, I., S. Sadewasser, S. Lucke, L. Vogt & H. J. Hahn:* Development of BB rat diabetes is delayed or prevented by infections or applications of immunogens. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 190–194.
15. *Kloeting, I., O. stark & u. Fisher:* Incidence of diabetes in F2 and first backcross hybrids of BB rats of different origin. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 85–67.
16. *Like, A. A., V. Dirodi, S. Thomas et al.:* Prevention of diabetes mellitus in the BB/W rat with cyclosporin-A. Am. J. Pathol. 1984, *117,* 92–97.
17. *Logothetopoulos, J., N. Valiquette, E. Maduar & D. Cvet:* The onset and progression of pancreatic insulitis in the overt, spontaneously diabetic, young adult BB rat studied by pancreatic biopsy. Diabetes 1984, *33,* 33–36.
18. *Marliss, E. B., A. F. Nakhooda & P. Poussier:* Clinical Forms and Natural History of the Diabetic Syndrome and Insulin and Glucagon Secretion in the BB Rat. Metabolism 1983, *32,* 7, Suppl. 1, 11–17.
19. *Mordes, J. P., U. McKeever, E. Handler, D. Greiner, D. Burstein & A. A. Rossini:* 'Immune modulation' of autoimmune diabetes in the BB rat. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 167–173.
20. *Nakhooda, A. F., A. A. Like & C. I. Chappel et al.:* The spontaneously diabetic Wistar rat: Metabolic and morphologic studies. Diabetes 1977, *26,* 100–112.
21. *Nakhooda, A. F., A. A. F. Sima, P. Poussier et al.:* Passive transfer of insulitis from the BB rat to the nude mouse. Endocrinology 1981, *109,* 2264–2266.
22. *Naji, A., D. Bellgrau, A. Anderson et al.:* Transplantation of islets and bone marrow cells to animals with immune insulitis. Diabetes 1982, Suppl. 4, 84–89.
23. *Naji, A., K. Silvers, H. Kimura, A. Anderson & C. F. Barker:* Influence of Islet and Bone marrow Transplantation on the Diabetes and Immunodeficiency of BB Rats. Metabolism 1983, *32,* 7, Suppl. 1, 162–168.
24. *Rossini, A. A., J. P. Mordes, E. S. Handler et al.:* Transfusion of whole blood prevents spontaneous diabetes in the BB/W rat. Science 1983, *219,* 975–977.
25. *Rossini, A. A., J. P. Mordes, R. M. Williams, A. M. Pelletier & A. A. Like:* Failure to transfer Insulitis to Athymic Recipients Using BB/W Rat Lymphoid Tissue Transplants. Metabolism 1983, *32,* 7, Suppl. 1, 80–82.
26. *Rossini, A. A., D. Faustman, B. A. Woda et al.:* Lymphocyte transfusions prevent diabetes in the Bio-Breeding/Worcester rat. J. Clin. Invest. 1984, *74,* 39–46.
27. *Rossini, A. A. & J. P. Mordes:* Helper T-lymphocytes transfusions prevent diabetes in the BB/W rat. Clin. Res. 1985, *33,* 574A.
28. *Scott, F. W.:* Dietary initiators and modifiers of BB rat diabetes. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 34–39.
29. *Seemayer, T. A., E. Colle, G. S. Tannenbaum, L. L. Oligny, R. D. Guttmann & H. goldman:* Spontaneous Diabetes Mellitus Syndrome in the Rat. III. Pancreatic Alterations in Aglycosuric and Untreated Diabetic BB Wistar-Derived Rats. Metabolism 1983, *32,* 7, Suppl. 1, 26–32.
30. *Sima, A. F.:* The Development and Structural Characterization of the Neuropathies in the Spontaneously Diabetic BB Wistar Rat. Metabolism 1983, *32,* 7, Suppl. 1, 106–111.
31. *Sima, A. F., R. Garcia-Salinas & P. K. Basu:* The BB Wistar rat: An experimental Model for the Study of Diabetic Retinopathy. Metabolism 1983, *32,* 7, Suppl. 1, 136–140.
32. *Sima, A. F.:* Natural history of structural functional alterations in diabetic BB rat peripheral nerve. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 471–476.
33. *Stiller C. R., A. Laupacis, P. A. Keown, C. Gardell, J. Dupre, P. Thibert & W. Wall:* Cyclosporine: Action, Pharmacokinetics and Effect in the BB Rat Model. Metabolism 1983, *32,* 7, Suppl. 1, 26–32.
34. *Weringer, E. J & A. A Like:* Transplantation of pancreatic islets in BB/Wor diabetes: T-cell subsets and MHC antigens. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 239–244.
35. *Wright, J. R., A. J. Yates, H. M. Sharma & P. Thibert:* Pathological Lesions in the Spontaneously Diabetic BB Wistar Rat: A Comprehensive Autopsy Study. Metabolism 1983, *32,* 7, Suppl. 1, 101–105.
36. *Yagihashi, S. & A. F. Sima:* Diabetic autonomic neuropathy in the BB rat. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 477–481.
37. *Yale, J. F.:* Cyclosporine A for prevention and therapy of type 1 diabetes in the BB rat. In E. Shafrir & A. E. Renold: Frontiers in diabetes research, Lessons from animal diabetes II, John Libbey, London 1988, 145–148.