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*Review Articles*

# The Diabetic Syndrome of the 'BB' Wistar Rat: Possible Relevance to Type 1 (Insulin-Dependent) Diabetes in Man

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**Summary.** The diabetes which occurs spontaneously in the 'BB' Wistar rat has many affinities with human Type 1 (insulin-dependent) diabetes. It occurs in a non-obese, standard, laboratory rat derived from a non-inbred Wistar line. Both sexes are affected, with onset corresponding approximately to the time of sexual maturation. Both genetic and immune factors are involved in the aetiology, but their precise nature remains to be defined. Evolution of the overt clinical syndrome occurs over a period of hours to a few days. An intense insulitis is found, accompanied by selective destruction of B cells. Although insulitis may precede diabetes by many weeks, within 7–21 days after glycosuria the B cells are completely destroyed and have disappeared and the islets are few, small and with little residual inflammation. If untreated, marked wasting of body tissues, including fat and muscle protein, dehydration, and ketosis supervene. Careful study of littermates reveals glucose intolerance in 10%–25%, accompanied always by insulitis and these rats may subsequently develop insulin-dependent diabetes. Marked lymphopenia, mainly of thymus-derived (T) lymphocytes, both precedes and is sustained during glucose intolerance and overt diabetes. This lymphopenia appears to be associated reliably with insulitis, and may be a simple marker of susceptibility thereto. Abnormalities of nerves, testicles, and a tendency towards increased frequency of lymphomas have been found. Further research in this animal could lead to insights into aetiology, pathophysiology and complications potentially applicable to man.

**Key words:** Type 1 (insulin-dependent) diabetes, animal 'model', lymphopenia, immunity, insulin, glucagon, neuropathy.

The study of animals displaying spontaneous diabetic syndromes has contributed significantly to understanding the diabetic syndromes of man. To date, most such animals have been representative of insulin-independent forms, demonstrating obesity as well as hyperglycaemia. An ideal animal model of Type 1 diabetes should include a definable genetic susceptibility linked to the major histocompatibility system and evidence of both cell mediated and humoral immune events, possibly initiated by environmental precipitating factors. In addition, the pathological hallmark should include selective islet B cell destruction accompanied by insulitis in the early stages. The severity of this lesion should determine the clinical picture. This review is intended to alert the research community to the existence of the 'BB' rat, to describe its known characteristics, to highlight its potential for future research, and to identify certain of the problems anticipated in such research. This rat syndrome currently represents the closest homology of diabetes in laboratory animals which might be compatible with Type 1 diabetes in man.

The spontaneously diabetic 'BB' Wistar rat was discovered serendipitously in 1974 in a commercial breeding facility whose initials we selected to name it (the BioBreeding Laboratories, Ottawa, Ontario). From our characterization of the syndrome [1–5], interest has grown in its potential for elucidating many of the unknown factors in this type of diabetes. We suggest that the nomenclature for rats derived from current and future colonies be maintained as 'BB'. However, it is expected that the characteristics will vary ('drift') with time in different breeding colonies, especially if inbred. Accordingly, it is suggested that each laboratory adopt a supplementary designation such as 'BB/W' selected by Like and associates to designate their colony by its location in 'Worcester'. Already rats have been referred to in publications as

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'BBW' (for 'Wistar') or 'BBL' (for BioBreeding Laboratories), and the potential for confusion is apparent. Thus it is strongly recommended that Ottawa-derived rats be designated 'BB', and that each breeder add an identifier based upon the location of the colony (e.g. BB/T, for Toronto).

This strain of rat appears very susceptible to the development of pulmonary and other infections by common varieties of bacteria, mycoplasma and viruses. Thus it has been necessary to develop facilities in which the rats are 'germ-free', using barriers to prevent such infections from occurring or spreading. These precautions should be borne in mind by any worker planning to perform chronic studies or to establish a new breeding colony. (Rats for breeding or research may be obtained by application to Dr. P. Thibert, Animal Resources Division, Health Protection Branch, Health and Welfare Department, Government of Canada, Ottawa, Ontario.)

## Aetiology

Two major factors are involved in the insulitis, a genetic and an immunological component. One hypothesis regarding the genetic mechanism is that the inheritance is autosomal recessive, involving a single gene but with 50% penetrance (L. Butler, unpublished observations). This inference is based upon pedigree studies and the distribution of diabetics produced by diallele crosses. The studies of Colle et al. indicate that the occurrence of diabetes in these rats is linked to the major histocompatibility (RT1) locus [6]. Precise definition of the genetics will have to await further study and the development of inbred lines (presently at the twelfth of the requisite 20 generations) or the transfer of the mutant gene(s) to already inbred strains.

Multiple lines of evidence suggest that altered immunity is involved in the aetiology of the syndrome, including (1) insulitis, (2) lymphopenia, affecting mainly thymus-derived (T) lymphocytes, especially the subset which includes helper T cells, (3) passive transfer of insulitis, (4) anti-lymphocyte serum (ALS) effects, (5) effects of neonatal thymectomy, (6) results of bone marrow transplantation, (7) presence of islet cell surface antibodies, (8) occurrence of thyroiditis, (9) increased incidence of lymphomas, and (10) possibly, the susceptibility to infection referred to above.

The morphology of the insulitis is described below. Earlier studies suggested that it appeared in an intense, fulminant manner just prior to clinical diabetes [1–5]. It is now known that it occurs in mild form in some young rats (50–65 days) [7], in all rats with lymphopenia with and without glucoregulatory abnormalities [8], as well as in a more intense form in rats with glucose intolerance [2–5].

Marked lymphopenia is present in insulin-dependent diabetic rats [8–12]. It is present in blood, thymus, spleen, lymph nodes and thoracic duct lymph [8–11]. It is particularly noteworthy that peripheral blood lymphopenia is present at weaning, preceding any measurable metabolic disorder [8, 9]. Since it is systematically associated with insulitis, it thus appears useful as a marker for susceptibility to the syndrome [8, 9]. The greatest reduction appears to be in $T^+$ lymphocytes [8, 9, 11]. Although the proportions of B lymphocytes are normal or even increased [8, 9], there is an absolute reduction in their total number. The major subset of T cells which is decreased appears to be reactive with monoclonal antibody W3/25, which recognises helper-T cells [8, 11]. The lymphopenia is as yet unexplained, but could be related to the presence of circulating antibodies to spleen lymphocytes [12]. However, the thymic helper-T cell deficit also suggests the possibility of a disorder of thymocyte maturation [8].

Passive transfer of insulitis has been achieved by injection of blood and spleen lymphocytes from newly-detected diabetic rats, intraperitoneally and intravenously into athymic nude mice [10, 13]. Whereas mild to moderate mononuclear cell infiltration and islet B cell loss from the mouse islets were shown morphologically, hyperglycaemia was not present. Immune intervention in both established diabetic and presumed susceptible rats has yielded very provocative results. The administration of rabbit anti-rat ALS to newly-diagnosed overtly diabetic rats reversed the hyperglycaemia in 36% [14]. Furthermore, ALS seemed to prevent diabetes in the littermates of these rats. An influence of ALS on the course of the diabetic syndrome was also inferred by Naji et al. [15] in their studies on transplantation of islets from Wistar Furth into 'BB' diabetic rats (both being type $RT1^u$) immunosuppressed with ALS. Neonatal thymectomy has also been reported to decrease the incidence of diabetes in susceptible litters [16]. In the course of experiments to render 'BB' rats tolerant to later islet cell transplants, Naji et al. found that bone marrow transplantation independently appeared to decrease the incidence of diabetes in the recipients [17].

The foregoing are consistent with cell-mediated immunity being implicated in the islet lesion, but do not exclude a role for humoral immunity. We have been unable to detect islet cell cytoplasmic antibodies (Tingle, A., Nakhooda, A. F., Marliss, E. B., unpublished data). However, using the $^{125}$I-protein A method [18], islet cell surface antibodies reactive with islets from normal Wistar rats are found [12]. They are present in most diabetic rats within 0–25 days after detection of glycosuria. Interestingly, there is a highly significant correlation in appearance and in amounts

between islet cell surface antibodies and spleen lymphocyte antibodies.

A further analogy of this rat and human syndrome is that lymphocytic thyroiditis is present in a large portion of such rats [19]. However, biochemical evidence for altered thyroid function has not been adduced. Data are not yet published as to the presence of autoantibodies to the thyroid, other endocrine glands, or gastric parietal cells. In view of the association of immunoproliferative lesions with immune disorders in man and certain animals it is noteworthy that the diabetic 'BB' rat shows an increased incidence of lymphomas, which include immunoblastic sarcomas and plasma cell lymphomas [20, 21].

These preliminary but provocative immunological results provide the basis for detailed research into the immunology of the syndrome. Several possible mechanisms seem worth exploring. The first is that a virus or otherwise-induced alteration in islet B cell major histochompatibility antigens may be responsible for initiation of an immune response resulting in cell destruction. No direct evidence for such a mechanism exists. However, the demonstration of HLA-DR antigens in human islets [22] suggests that major histocompatibility antigens be sought and characterized in 'BB' rat islets. The second possible mechanism is that the primary defect lies outside the islet, and results in cytotoxic cells directed toward certain normal determinants on islet B cells. Whether this is related to the demonstrated helper-T cell subset deficiency or otherwise mediated remains an open question. The decrease in total helper-T cell numbers suggests a more complex mechanism than the alternate hypothesis of a selective suppressor cell deficit. A third possible mechanism is that the syndrome involves a deficit in a whole class or subclass of lymphocytes, with the same result. A fourth is that humoral immunity plays a role in the destruction of insulin-secreting cells. The nature and functions of both the islet cell surface and lymphocyte antibodies require elucidation. The possibility of an endogenous antibody against a subset of lymphocytes as the inciting event, resulting in disequilibrium among subsets, must now be entertained.

Despite the interest in genetic and immunological factors in genesis of the diabetic state, all other known factors need to be considered and some studied in detail. Obesity can be excluded. Hyperinsulinaemia (and the expected concomitant insulin receptor alterations) may occur before overt diabetes, and requires more detailed evaluation. Some environmental factors in initiation of the insulitis can be excluded by the occurrence of diabetes in Caesarean-derived, gnotobiotic rats [23]. But the possibilities of transplacentally transferred viruses, viruses not specifically sought for, or other environmental agents, cannot be omitted.

## Pancreatic Islet Pathology

The morphological features associated with the islet B cell destruction have been described previously [7, 14, 24, 25]. Correlation among 'clinical', and anatomical data allows for the following formulation. Cell destruction occurs, with an inflammatory infiltrate consisting mainly of mononuclear cells. The time at which this commences remains to be identified. In glucose intolerant animals insulitis may be mild to moderate and appears to affect islets randomly, with a variable number being completely spared. With early overt diabetes [1, 2] all islets are involved in an intense inflammatory process. This distorts islet architecture, with extensive destruction of B cells, and degranulation of surviving cells. These features are shown in Figure 1. Once severe diabetes has been present for even a few days, islets decrease in numbers and size, and are termed 'end stage'. Such islets show little or no insulitis, virtual absence of B cells and by immunocytochemistry, relatively increased numbers of A cells, and infrequent D (somatostatin) and pancreatic polypeptide cells [7, 14, 24]. The time course of evolution of these changes is probably very rapid. Within 4 days of overt diabetes, some rats show mainly 'end stage' islets, and by 7–14 days virtually all remaining islets are of this type (Fig. 1).

The extractable pancreatic hormone contents correlate with the described morphological changes. Insulin content in untreated ketotic rats is less than 0.1% of normal, and only 2% of normal in treated rats [1]. Untreated diabetic rats show reductions in immunoreactive glucagon content to one-third normal values but are restored to normal with treatment. Patel et al. [24] reported decreased volume density of glucagon cells in treated diabetic rats without altered content. These discrepancies may be accounted for by the durations of follow-up of both untreated and treated groups in the two studies. A 50% reduction in immunoreactive somatostatin content was found in both treated and untreated rats, but with a disproportionately greater reduction in volume density of somatostatin cells [24]. The suggestion has been made that in ketotic rats either A and D cells may be involved in the same process which destroys the B cells, or that the integrity of these cells depends upon a minimal local concentration of insulin [7].

## Features of the Diabetic Syndrome

Considerable information is available on the clinical forms of the syndrome, their time courses, the corresponding anomalies of hormone secretion, and the metabolic consequences thereof [1–5, 26]. The 'clinical' presentations are schematically presented in Fig-

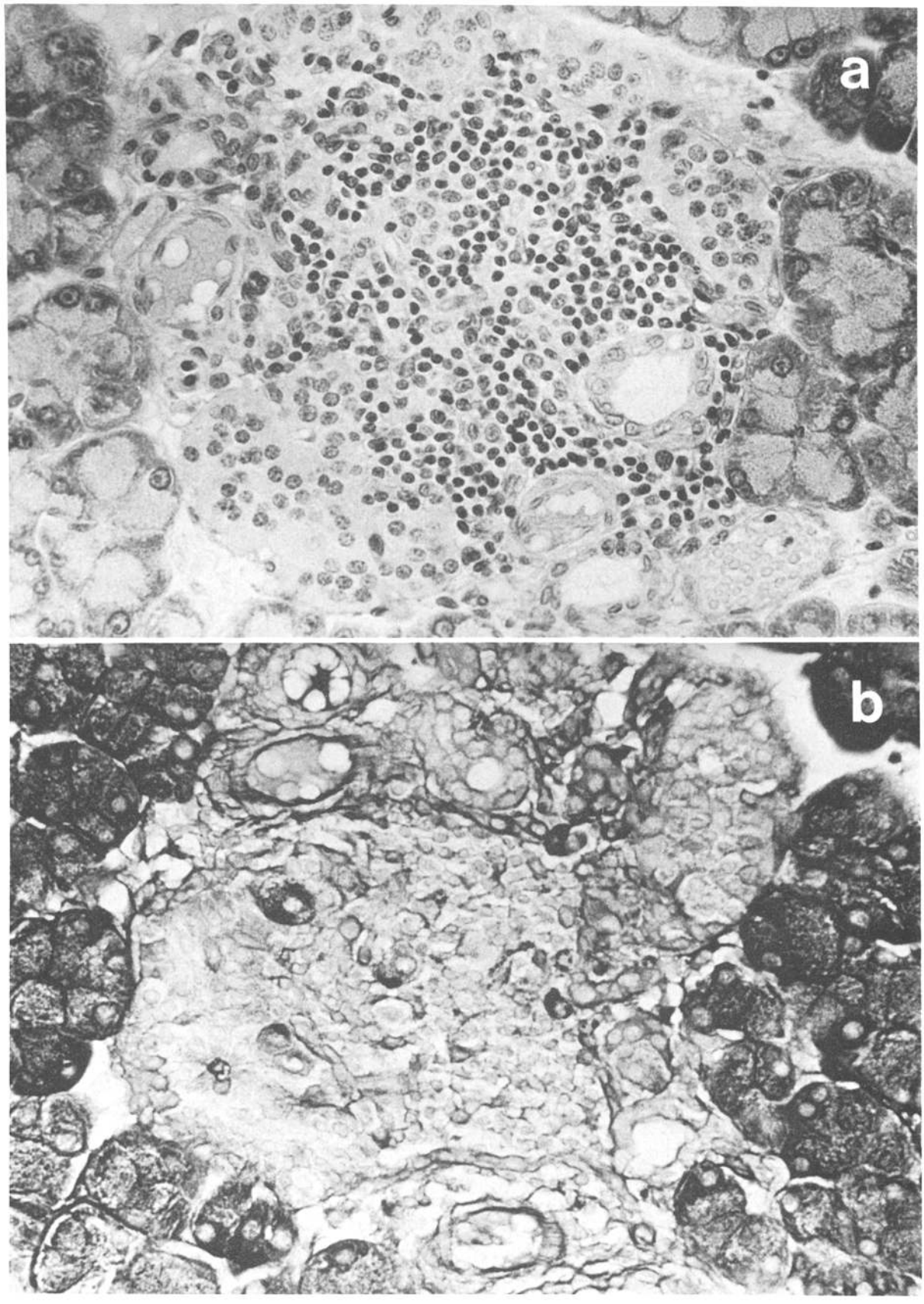


**Fig. 1 a and b.** Light micrographs of pancreatic islets from a spontaneously diabetic 'BB' rat, 4 days after glycosuria has appeared. **a** stained with hematoxylin and eosin; **b** glutaraldehyde fuchsin stain to show B cells by dark staining of their cytoplasm. An intense insulitis is present, with marked mononuclear cell infiltration, disruption of islet architecture, extensive B cell destruction and degranulation of surviving cells. Only a few positively stained B cells are seen ( × 504)

ure 2. Genetically susceptible rats may be 'potential' diabetics (a), or progress to severe insulin-dependent diabetes either without a demonstrable period of glucose intolerance (b), or after impaired glucose tolerance persists for variable periods of time [3]. Other rats with persistent impairment of glucose tolerance may remain as such (c), but frequently progress to the overt syndrome (d), while those with single or inconsistent abnormalities do not necessarily do so. A few, well documented spontaneous remissions from overt diabetes have been observed (e) [3–5, 14]. Hitherto, susceptible rats and 'potential' diabetics could not be identified by any anthropomorphic or hormonal metabolic variable studied. They can now be identified by the presence of lymphopenia [8, 9]. Impaired glucose tolerance is present in 10%–25% of littermates of diabetic rats, the frequency varying with the genetic origins of the litter studied, as well as with the provocative tests used. A single abnormal intraperitoneal, intravenous or intragastric glucose tolerance test should not be taken as evidence of impaired tolerance. When sustained, however, or when different tests give consistently abnormal results, an associated insulitis is almost invariably found. Detailed challenge studies have shown two groups of insulin secretory anomalies in rats with normal fasting glycaemia but abnormal responses to challenges [2, unpublished observations]. The majority have low fasting and post-challenge insulin responses to intraperitoneal and intragastric glucose and intraperitoneal tolbutamide, but normal responses to arginine. Both early and later phases of insulin response to intravenous glucose are impaired. A smaller group has hyperinsulinaemic responses to intragastric glucose, intraperitoneal tolbutamide and to arginine. All of the former have insulitis and most progress to Type 1 diabetes. Thus not only is there evidence for a subset or stage in the syndrome with marginal insulin secretory reserve made manifest by challenge tests, but there is also evidence suggesting abnormal B cell responsiveness and/or secretory products. These findings, as well as receptor status and insulin sensitivity, require further study.

Overt insulin-dependent diabetes occurs from 40–140 days with a mean age at onset of glycosuria of about 90 days. The dramatic feature of this form is the rapidity of progress from normal to grossly decompensated, with a time course measurable in hours to days [1, 2, 4, 26]. Typically, hyperglycaemia (20–30 mmol/l), polyuria and polydipsia (100 ml/day), glycosuria (10 g/day), hyperketonaemia (5–8 mmol/l) and ketonuria (2–3 mmol/day), weight loss and dehydration develop. This state is accompanied by hypoinsulinaemia (unmeasurable by 4–8 days), and relative or absolute hyperglucagonaemia. Urea nitrogen and 3-methylhistidine excretion double, renal ammoniagenesis increases sixfold [27], and elevations in blood levels of branched-chain and other amino acids occur [1, 4]. In contrast with the human counterpart, blood alanine is normal and glutamine is elevated.

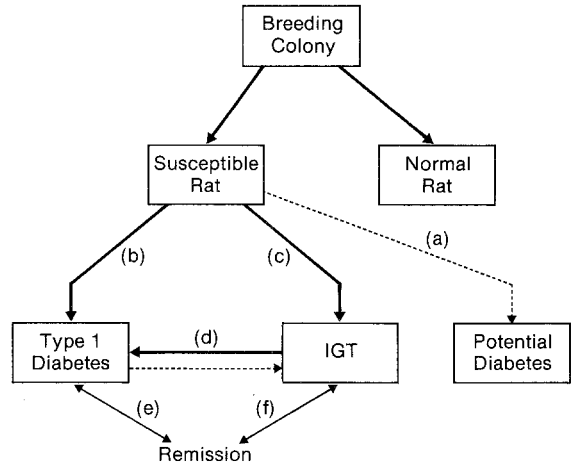


**Fig. 2.** Presentations of diabetes in the 'BB' rat. Among those rats susceptible to development of diabetes, some must be 'potential' diabetics (*a*) since they may be genetically predisposed but do not demonstrate it during the period of observation. Lymphopenia may be a useful marker for susceptibility in these rats. The overtly Type 1 (insulin-dependent) diabetic rats (*b*) and those with impaired glucose tolerance (IGT) (*c*) are described in the text. Frequently, rats with IGT progress to overt Type 1 diabetes (*d*), the obverse occurring less frequently. Total remission from both Type 1 diabetes (*e*) and IGT (*f*) occurs only infrequently

Hormone secretion shows several notable features in these insulin-dependent rats. No insulin response to several secretagogues has been found. Though intraperitoneal arginine resulted in excessive immunoreactive glucagon responses [1, 2], subsequent intravenous infusion studies have shown lower than normal portal vein responses, despite elevated prechallenge concentrations in many rats (P. Poussier, A. F. Nakhooda, and E. B. Marliss, unpublished data). Patel et al. showed elevated portal and peripheral glucagon concentrations [24]. Boden et al. found a subnormal response to amino acids in an isolated, perfused pancreas preparation, but impaired suppression by glucose [28]. Altered neural control of glucagon secretion has also been found, raising the possibility of diabetes affecting adrenergic receptor mechanisms [29].

Elevated immunoreactive somatostatin concentrations are found in portal venous plasma [24, 30], and reduced to normal after insulin treatment. Decreased content and D cell numbers were found in the pancreas in uncontrolled diabetes [7, 24], leading to the suggestion of a gut origin of the hypersomatostatinaemia. However, the perfused pancreas showed in-

creased response to glucose plus amino acids [28]. Thus the several anomalies of somatostatin secretion in this rat remain unexplained. Growth hormone levels and bursts of secretion were found to be normal before and during early Type 1 diabetes, but secretory episodes decreased with severe metabolic decompensation and weight loss [26].

A number of additional findings are worthy of note. Hepatic carbohydrate metabolism was assessed in unperfused and perfused livers from overt diabetic rats by Appel et al. [31]. Their findings were consistent with insulin deficiency and relative glucagon excess, and with the metabolic adjustments reported above. Total collagen mass and net synthesis were found to be altered in a tissue-specific manner following insulin-treatment [32]. Total collagen mass was decreased in skin, unchanged in the aorta, and increased in the intestine, whereas $^{3}$H-proline incorporation into collagen was decreased in both skin and aorta and increased in intestine. An increase in the formation of thromboxanes in platelets and a decreased formation of prostacyclin in the aorta were found in diabetic rats [33].

## Neuropathy

A systematic study of the structure and function of the peripheral nerves has demonstrated this rat to be an excellent model for the study of neuropathy [34–37]. Many of the changes found are similar to those seen in morphological studies in man. The earliest change is a decrease in motor nerve conduction velocity to 80% of control after 3 weeks of diabetes, and it is measurable before structural changes appear. Potential clamp analysis of single myelinated fibres at this stage shows decreased sodium equilibrium potential and decreased sodium currents, due to high axoplasmic sodium concentration [36]. A further decrease in conduction velocity at 4 months corresponds with the time of appearance of abnormal accumulations of glycogen in distal axons. Decreased conduction was found also by Mendell et al. [37], who reported slowing of fast axonal transport. Striking axonal changes are apparent, especially in large myelinated fibres, after 6 and 10 months. Typical findings include granular disintegration of normal structural elements with accumulation of dense fibrillary material, demyelination, and degeneration of Schwann cells. In late stages of the disease axonal sprouting and remyelination are prominent. Unmyelinated nerve fibres show axonal fragmentation, atrophy and are often denuded from the supporting Schwann cells. Such abnormalities are similar to those described in human painful diabetic neuropathy [38] and in the spontaneously diabetic mouse [39]. Endoneurial vessels display marked basement membrane thickening, but without increased permeability to horseradish peroxidase [35].

These changes are interpreted as consistent with the metabolic disorders in the early stages of the diabetic syndrome causing altered axonal energy metabolism and membrane function, which results in later compromise in structure. Axonal atrophy occurs, suggesting that primary axonal dwindling is the major underlying mechanism for the neuropathy. The axonal atrophy appears to progress to an extent beyond which its proximal part is unable to sustain the distal part and Wallerian degeneration results in the late stages (a form of 'dying-back' neuropathy). This hypothesis can be readily evaluated in the rat in a manner not possible in man.

## Other Pathological Findings

The data available on neuropathy are not yet paralleled for other typical diabetic complications, there being no published morphological studies of renal, retinal or muscle capillaries or macrovascular changes as yet. Other pathology is present in 'BB' rats, with some findings related to the diabetic state, but others apparently related to the strain of rats [40, 41]. Pneumonias with a variety of pathological forms have been identified [40]. Similarly, infestations by intestinal parasites (especially pinworms) have occurred, which may have been related to the eosinophilic infiltrates prominent in certain tissues (including pancreas) in some rats. Occasional granulomatous lesions were found in the testes, pancreas and lymph nodes [40]. One report describes testicular atrophy as a prominent feature, with 32% prevalence in diabetic rats, 25% in non-diabetics, compared with 0% in control Wistar rats [41].

## Conclusions

From the foregoing, a number of tentative conclusions may be drawn as to aetiology, pathogenesis and pathophysiology of the diabetic syndrome of the 'BB' rat. Genetic factors probably combine with a disorder involving the immune system to result in islet B cell destruction. The insulitis observed is intense and generalized, involving all islets when early overt diabetes is present. The morphological features of this syndrome are strikingly similar to those found in the pancreases of Type 1 diabetic patients early after diagnosis [42]. The process is similar, but more intense than that seen in mice treated with multiple subdiabetic doses of streptozotocin [43], or with certain viruses [44].

Current data do not allow for a definitive formulation of the immunological disorder in the 'BB' rat. In particular, the fundamental question as to whether the initial defect is one residing in abnormal pancreatic B cell antigens, or in a primary cell- or humoral-mediated immune disorder remains unanswered. However, the advantage of the 'model' over the human Type 1 diabetic is the possibility of dissection of cellular and molecular mechanisms, not yet possible in man. In particular, now that susceptibility to development of insulitis can be identified by a simple marker, that of peripheral blood lymphopenia, the stages prior to massive B cell destruction can be studied in detail. Although lymphopenia is apparently not a characteristic of human Type 1 diabetes [reviewed in 8], if disease mechanisms can be worked out in this rat, this may well lead to non-invasive techniques for testing whether such mechanisms are applicable to man. Furthermore, detailed structure-function relationships within the diseased islet can be studied. If the aetiology of at least some cases of human Type 1 diabetes can be identified by pursuit of such analogies, there is hope that intervention, prior to loss of the critical mass of insulin-secreting cells, might prevent onset. The rat could be used to establish the optimal modalities.

The degree of insulin deficiency appears sufficient to explain the spectrum of severity of clinical and metabolic decompensation, and in this respect, the syndrome is like that produced with islet B cell cytotoxins. In some rats, treatment with exogenous insulin at the onset of glycosuria has been associated with sufficient restoration (and/or maintenance) of B cells to allow for longer survival after subsequent termination of insulin therapy. In this aspect the rat might be a useful model for study of B cell regeneration/neogenesis. The demonstration of at least one type of chronic diabetic 'complication' – neuropathy – suggests that this model should be examined in detail with respect to the microvascular complications known to occur in man. In light of the apparent resistance of rats to developing macrovascular metabolic and morphologic changes analogous to those of the human, it will be of value to screen for these, but not surprising if they are not found.

The 'BB' rat has already been exploited to elucidate certain abnormalities in glucagon secretion associated with spontaneous insulin deficiency. Further study in this area may help illuminate those aspects of control of glucagon secretion as yet unclear in insulin-dependent diabetic man. Similar considerations apply to secretion of somatostatin, and possibly of pancreatic polypeptide. It is hoped that healthy, well characterized animals will soon be available to laboratories with the multidisciplinary expertise to establish detailed information on the aetiology and pathophysiology of the islet B cell loss. These and other studies in all areas of concern to both basic researchers and clinical diabetologists could well give important leads to the understanding of the human syndrome.

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