s: Metabolism Out of Control

es mellitus, the disease charac-
ed by the body's inability to
bolize glucose, manifests as one
s: type 1, or insulin-dependent
llitus, ketosis prone (IDDM); and
nsulin-dependent diabetes mel-
l). The long-term consequences
demonstrate that lipid meta-
so involved. The two types are
ally very different and will be dis-
rately. Current theories on the
characteristics of these two clas-
diabetes are shown in Figure 1.

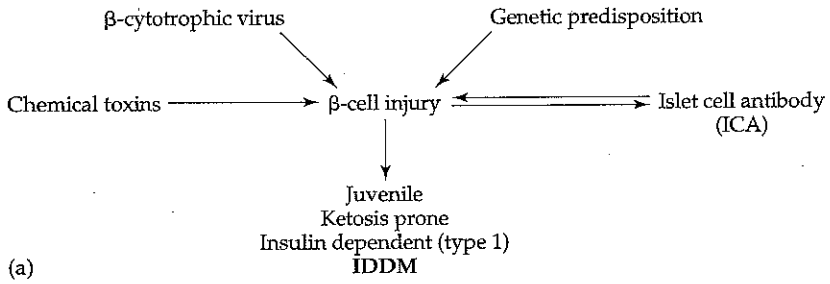
in-Dependent Diabetes Type 2)

etes accounts for 80% to 90% of
cases of the disease. The cause of
ietes has not been completely
t it appears to be associated with
ance in peripheral target tissue.
on is caused not by a failure of target cells to bind insulin but by a postbinding abnormality, arising somewhere in the sequence of events that follows the binding of insulin to its receptor and leads to the cell's normal response to that signal. Experimental evidence suggests that a primary cause for the interrupted insulin signal may be compromised synthesis or mobilization of the cell's glucose transporters (refer to the section "Glucose Transporters," Chap. 4).

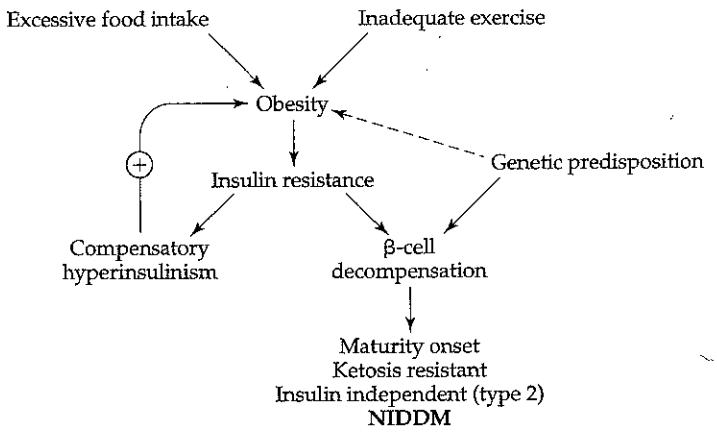
In skeletal muscle cells, insulin resistance associated with NIDDM has been shown to be caused by a reduction in glucose transporter activity, specifically the failure of the vesicles to translocate in response to insulin (see Fig. 4.8). The error can be thought of as a block or short-circuit in the insulin signal that normally initiates the translocation process. The result is a reduced concentration of transporters at the cell surface and a consequent reduction in the rate of glucose uptake. Although a similar defect was found in adipocytes of NIDDM patients, it is not the major cause of the insulin resistance in these cells. Rather, the consequence of NIDDM in adipocytes is a marked depletion of mRNA encoding the GLUT4 transporter, resulting in depleted intracellular stores of the protein [1]. This describes a pretranslational defect, meaning that it interferes with protein synthesis at a level before the translation process, the step that requires mRNA as template. Therefore, even if the vesicle translocation process were not compromised, an inadequate number of surface receptors would still be expressed upon insulin stimulation.

Insulin resistance has also been described in obesity as well as in NIDDM. Insulin resistance in obesity is mechanistically similar to the NIDDM effect on adipocytes. Reduction in GLUT4 mRNA in obese subjects results in a decrease in de novo synthesis of the transporter. Furthermore, the extent to which mRNA expression is suppressed appears to relate directly to increasing adiposity.

Figure 1 Overview of present theories of diabetes mellitus etiology. (a) depicts the factors impinging on the development of diabetes mellitus that requires exogenous insulin. This type of diabetes presently is most commonly designated as insulin-dependent diabetes mellitus (IDDM). (b) illustrates the interaction of factors that may result in non-insulin-dependent diabetes mellitus (NIDDM).



(a)



(b)