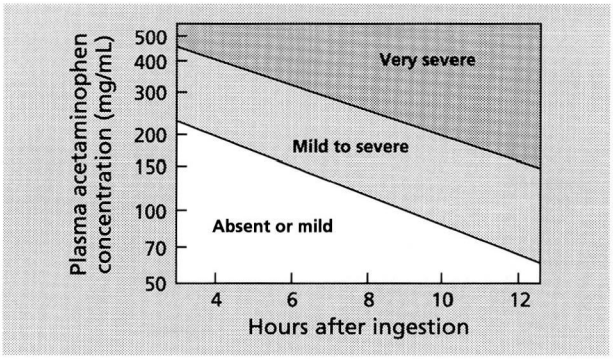

FIGURE. Likely degree of liver damage according to plasma acetaminophen concentration. Patients with values in the lowest zone will likely have only mild liver damage or none at all, and do not need specific therapy. Values in the highest zone are predictive of very serious liver damage and mandate treatment with acetylcysteine or other agents; values in the middle zone are less predictive but mandate similar treatment. From Zimmerman JH. Hepatotoxicity. New York: Appleton-Century-Crofts, 1978.

TREATMENT OPTIONS

For patients with severe hepatic damage, the only treatment is liver transplantation. In patients with a less severe condition, acetylcysteine is the treatment approved by the US Food and Drug Administration (FDA). Acetylcysteine, which is thought to help replenish glutathione, thereby neutralizing the toxic metabolite, is given orally in a loading dose of 140 mg/kg, then 70 mg/kg at 2-hour intervals for at least 72 hours. The drug is effective when given early, but the later it is given the less likely it will be successful. A major drawback is nausea and vomiting. Parenteral administration may circumvent this, but a parenteral form is not yet approved by the FDA.

Although not an FDA-approved treatment for acetaminophen overdose, cimetidine seems to offer some protection: it blocks the cytochrome P-450 enzyme system, inhibiting production of the toxic metabolite. Rabbits receiving cimetidine before or after acetaminophen overdose, or acetylcysteine before overdose, had significantly higher survival rates when compared with no treatment. Intravenous cimetidine (50 mg/hour) can be used in addition to acetylcysteine for 72 hours.

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IDENTIFYING EARLY MARKERS OF TYPE II DIABETES

THE PATH TO non-insulin-dependent diabetes (NIDDM) begins long before the blood glucose concentration rises above normal limits, perhaps as early as adolescence. Treating established NIDDM can curb complications of hyperglycemia that affect the eyes, kidneys, and nerves, but it will not halt the complications caused by hyperinsulinemia (ie, hyperlipidemia, hypertension, and accelerated atherosclerosis). Earlier identification of those at risk for NIDDM may permit earlier dietary and exercise intervention.

FROM 'FEAST OR FAMINE' TO 'FEAST OR FEAST'

The tendency toward NIDDM may have had some benefit for our ancestors, who lived in times of "feast or famine," by making it easier to store ingested glucose as fat. This would have helped them survive lean times, but it has no use in our modern, overfed society.

People destined to acquire NIDDM cannot use glucose effectively because of insulin resistance. Muscle glucose disposal can be shown to be impaired in individuals with a propensity to develop NIDDM well before the circulating blood glucose value is elevated. Among a number of postreceptor events triggered by the binding of insulin to its receptor, a defect in glycogen synthase activity has been documented to be present in some such individuals. They also have a high number of type 2 muscle fibers, which are relatively avascular, highly glycolytic, and insulin-insensitive.

After a glucose load, the blood sugar level rises, and the beta cells compensate by secreting more insulin, in turn causing down-regulation of cell-surface insulin receptors in susceptible people. Thus, the beta cells, to maintain euglycemia, must secrete even more insulin—until they manifest their genetically weak insulin secretory capacity and cannot pro-

duce more, and hyperglycemia occurs.

Hyperinsulinemia causes shunting of excess glucose into adipose tissue; it also predisposes to hypertension and hyperlipidemia, specifically hypertriglyceridemia with a concomitant low high-density lipoprotein concentration. Thus, these conditions may be early markers for the diabetes syndrome and may contribute greatly to accelerated atherosclerosis and all its problems.

SEARCHING FOR MARKERS

Hyperandrogenism

The Achard-Thiers syndrome ("the diabetes of bearded women") was first described in 1921. Low concentrations of sex-hormone binding globulin (SHBG) and high plasma insulin levels are powerful indicators for subsequent NIDDM. Abdominal obesity in women is also associated with hyperandrogenism and muscle insulin resistance. Women with established NIDDM have high levels of free testosterone and concomitantly low SHBG concentrations.

Men have fivefold higher levels of androgen than do women; however, they have a testosterone feedback mechanism that women lack. This feedback mechanism can be overwhelmed: anabolic steroids predispose men who take them to the development of glycolytic, capillary-poor, type 2 muscle fibers and insulin resistance.

In prospective studies in rats, administration of testosterone caused insulin resistance, decreased glycogen synthase activity, decreased the ratio of type 1 to type 2 muscle fibers, and diminished the capillary density. Transsexual women given testosterone have shown similar insulin resistance. In a study in women with NIDDM treated with high doses of estradiol for 3 months, SHBG levels rose, free testosterone levels fell, blood glucose control improved, and plasma insulin levels fell.

Conversely, hyperinsulinemia may cause hyperandrogenism. In studies of women with polycystic ovaries, short-term administration of insulin caused an increase in androstenedione. Glucose administration caused a concomitant increase in insulin and androgens, while weight loss caused a decease in circulating androgens, as did diazoxide administration.

Obesity

Hyperandrogenism is most often associated with truncal and abdominal obesity, while women with lower-segment obesity are minimally (if at all) hyperandrogenic or hyperinsulinemic. The more obese the woman and the more irregular the menstrual cycle, the more severe the underlying insulin resistance and the greater the risk of subsequent NIDDM.

Reactive hypoglycemia

Insulin is normally released in two phases: stored insulin within 5 to 30 minutes after a glucose load, and newly synthesized insulin within 45 to 90 minutes. As the beta cells "hyperfunction," the first phase is lost while the second phase is enhanced, at least initially, causing a rapid fall in blood glucose concentration. The central nervous system responds by releasing contrainsulin hormones, including adrenalin, causing symptoms of sympathetic overdrive like those commonly seen in hypoglycemia. Actual hypoglycemia is rare, though the classic symptoms of hypoglycemia occur almost universally. There are a number of causes for this condition, but its presence in an obese patient with a family history of NIDDM should cause the clinician to suspect the diabetes-insulin syndrome.

Acanthosis nigricans

Velvety, mossy, verrucous hyperpigmented skin with a *peau d'orange* look in the nape of the neck, axilla, beneath the breasts, and in other body folds, when seen in obese young women with no evidence of cancer, indicates insulin resistance in 90% of patients. However, it occurs in fewer than one fourth of women with insulin resistance.

Low birth weight

A very low birth weight is an independent risk factor for insulin resistance in adult life; thus, predicting NIDDM may be possible even at birth.

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