Elevated Transaminases and Hepatomegaly in an Obese Diabetic*

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A 61-year-old obese female presented with hypothyroidism, insulin-independent diabetes mellitus, and asymptomatic hepatomegaly. The diagnostic evaluation of hepatomegaly with elevated transaminase is discussed. Liver biopsy findings are discussed. Plans for therapy are presented and evaluated.

DR. JEFF BENDER (Resident in Medicine): The patient is a 61-year-old white female who was admitted to the hospital in September 1981 for elective evaluation of three problems for which she had been followed over the last seven months. Those are diabetes mellitus, hepatomegaly, and hypothyroidism. The patient has a past medical history significant for a transmural inferior wall myocardial infarct (MI) in 1975, complicated by mild congestive heart failure, and a subsequent subendocardial MI one month later. At that time, her only major problem noted was obesity, which was long-standing. Her weight in 1975 was 220 pounds. She was followed in the Primary Care Center, and in 1976 she was first noted to be hyperglycemic. She was treated initially with diet and attempted weight control, but this was unsuccessful and her weight remained in the 215-220 pound range. Her plasma glucose concentrations over the next two years rose to the 300 to 400 mg% range, and the patient was started on 15 units of NPH insulin per day. Subsequently this was increased to 26 units of insulin per day, which brought her glucose level down to the 150 to 300 mg% range. By mid-1979 she had been lost to follow-up and consulted an outside physician. Her weight remained high, and when she returned to the Primary Care Center in February 1981 her weight was still 215 pounds. During the intervening period her insulin had been gradually increased. She was then being treated with 60 units of NPH in the morning and 30 units of NPH in the evening. Her fasting blood glucose ranged from 208 to 450 mg%, and her urine was positive for glucose, but negative for ketones. The initial attempt at management consisted of increasing her insulin to doses as high as 70 units in the morning and 40 units at night. This resulted in only a modest improvement, if any, with blood glucose levels persistently 300 to 350 mg%. She also had a five-pound weight gain to 220 pounds. Because of her apparent resistance to insulin, an oral hypoglycemic agent was added in June 1981. With the addition of Diabinese her insulin requirements decreased. The addition of Diabinese seemed to dramatically improve her glucose tolerance with blood glucose falling to the low- to mid-200 mg% range. Subsequently her Diabinese was increased to 500 mg per day, and NPH insulin was tapered from 70 to 40 units of NPH insulin during the morning and from 40 to 10 units at night.
Her second problem was hepatomegaly. She had no history of liver disease, no history of alcohol abuse or excess, and, in the past, she had always had normal abdominal exams and abdominal films which showed normal liver and spleen size. When first seen in February 1981, she had a very firm liver, palpable a full six to seven finger-breadths below the right costal margin, with a 20 cm span. A spleen tip was not felt, although it was subsequently reported to be present by other observers. Her liver function tests in February showed an SGOT of 89 with all other liver function tests normal. Because the SGOT remained elevated two to three times above normal, a further work-up was begun. Assays for hepatitis antigens and antibodies were negative, a 5' nucleotidase level was markedly elevated at 29, but the alkaline phosphatase level was normal, and antinuclear antibodies (ANA) were somewhat elevated at 1:64. Serum iron and iron binding capacity and serum protein electrophoresis were normal. Serum cholesterol, 235 mg%, and serum triglyceride, 232 mg%, were slightly elevated. An ultrasound of the abdomen was normal except for hepatomegaly, splenomegaly, and increased echogenicity diffusely present in the liver. The liver-spleen scan showed hepatomegaly with inhomogeneous uptake and a large shift of colloid to an enlarged spleen, compatible with hepatocellular disease. During the course of this further work-up, her exam did not change. Her liver remained the same in size, and her SGOT level was consistently between 60 and 100 units. SGPT values were similarly elevated. The liver service was consulted in August 1981, six months after the abnormalities were first noted. They recommended that a biopsy be performed, and this was the reason for the patient's admission in September.

The third problem that had been noted in this patient was hypothyroidism. This diagnosis was not suspected until Dr. Riely on the liver service saw the patient in August and noted that she had some eyebrow loss and a hoarse voice. Thyroid function tests at the time showed an estimated free thyroxine (EFT) of 0.1 with a TSH of 56. The patient was begun on Synthroid, but a very low dose was used because of her history of heart disease.

During the next six months the patient had multiple additional complaints, including atypical chest pain, diffuse abdominal pain, multiple joint aches, depression, and dyspnea on exertion. She was a difficult historian, and there was an emotional overlay to her complaints. Nevertheless, it was decided to admit her in September to perform a liver biopsy, to further evaluate her atypical chest pain, and to improve control of her diabetes.

At the time of admission she was a well-developed, well-nourished obese white female. Her medications were insulin, Diabinese, digoxin, Lasix, and Synthroid (50 µg/day). Her blood pressure was normal, as it always had been. Her skin showed some decreased hair but was otherwise normal. The chest was clear. The cardiac exam was normal with no murmurs or gallops. The abdominal exam showed that she was obese and had mild right upper quadrant tenderness over her liver, which was 16 to 18 cm in span and very firm to palpation without discrete nodules. A spleen tip was felt by some observers. Her neurologic exam was normal with normal reflexes. Her initial laboratory data included a normal BUN, normal electrolytes, a hematocrit of 40 percent, a normal white cell count with normal differential, platelets of 170,000/mm³, normal PT and PTT, and urinalysis which was normal except for 2+ glucose by dipstick. Her chest X-ray was normal, and her cardiogram was compatible with an old inferior wall MI.

**Physician:** Did she have anti-thyroid globulins?
DR. BENDER: Yes, her titer was 1:60.

DR. RALPH DEFRONZO (Associate Professor of Medicine): This is an interesting lady, and there are two major problems that I want to focus on today. One is the work-up of an asymptomatic person with an elevation of the serum transaminases, and the second is the approach to treatment of her diabetes and obesity. Table I is a rather simplistic approach to the individual who is asymptomatic, and who has elevated serum transaminases. This scheme is designed to look at the very selective patient who has only an increase in the SGOT without elevation of other liver function tests or other clinical signs or symptoms.

There are several things that one must rule out very quickly. Remember that SGOT is present in many tissues. Therefore, first we must establish that the SGOT is coming from liver. It is very common for a muscle disorder to cause an increase in the SGOT, and, in particular, it is common to see an increased SGOT in joggers. Obviously this lady who weighs 220 pounds is not a jogger, so it is unlikely that we are going to be confused by that syndrome. However, in joggers the SGOT may be persistently elevated. This etiology is easily excluded by obtaining a CPK level. People who have the “jogging syndrome” will have elevation in CPK along with the

**TABLE I**
Elevated Transaminases in Asymptomatic Patient

| A. Ascertain Hepatic Origin: |
|-------------------------------|
| 1. SGOT occurs in all body tissues, especially liver, heart, skeletal muscle; SGPT is present primarily in liver and to a lesser extent in kidney and skeletal muscle. |
| 2. Check 5’ nucleotidase and CPK. |
| 3. History and physical examination. |
| 4. Rule out “jogger’s syndrome.” |

| B. If Hepatic: |
|----------------|
| 1. Unresolved hepatitis |
| Parenteral drug abuse |
| Chronic persistent hepatitis |
| Chronic active hepatitis |
| Check HBsAg, anti-HBs, anti-HBc |
| Alcohol |
| Diabetes (GTT) |
| Obesity |
| Lipoprotein disorder (cholesterol, TG) |
| Inflammatory bowel disease (diarrhea) |
| 2. Fatty liver |
| Aspirin |
| Isoniazid |
| TYLENOL |
| Methotrexate |
| 3. Toxic hepatic injury |
| Aspirin |
| Isoniazid |
| TYLENOL |
| Methotrexate |
| 4. Wilson’s disease |
| Ceruloplasmin |
| Kayser-Fleischer rings |
| 5. Hemochromatosis |
| Iron/total iron binding capacity |
| Ferritin |

| C. Further Work-Up: If no clue to pursue: |
|------------------------------------------|
| Liver-spleen scan |
| Abdominal ultrasound |
| Pancreas |
| Gallbladder |
| Liver biopsy |

(Surprises: Granulomata, passive congestion, tumor)
SGOT. This patient's CPK was not elevated. Her SGPT was elevated as well. It also is present in other tissues, including skeletal muscle and kidney, although it is a little more specific for the liver. In addition, this patient had an elevated 5' nucleotidase, and this led to the feeling that the SGOT was coming from the liver. The physical finding of significant hepatomegaly was consistent with this impression.

In working up such an individual there are five disease categories that one has to think about. It is possible that this lady could have an unresolved hepatitis, and the most likely cause of this would be either hepatitis B or non-A, non-B hepatitis. Hepatitis A does not progress to chronic persistent elevation of the SGOT, or at least there has not been a case report described yet. One should look for the presence of hepatitis B surface antigen as well as antibodies to the surface antigen and the core antigen. That was done in this lady, and they were all negative. It would also be unlikely that this lady has chronic active hepatitis. Although this could be an early presentation of chronic active hepatitis, one usually sees other abnormalities in the liver function studies. Clearly, what she has could be consistent with chronic persistent hepatitis, although the significant degree of hepatomegaly would argue against this. With an elevated SGOT in the context of a significantly enlarged liver, one has to pay serious attention to fatty liver disorders. The most common of these, from a purely statistical basis, is going to be that associated with alcohol. This lady and her family were questioned on numerous occasions about alcoholic intake, but no history of alcoholism could be determined. Two other disorders which can be associated with fatty liver and an increase in the transaminases are diabetes and obesity. An elevation in the SGOT and hepatomegaly have also been reported with certain lipoprotein disorders, even in the absence of diabetes and obesity. We know that this patient had elevated serum triglyceride and cholesterol levels which would place her in the Type IV category. Inflammatory bowel disease can also cause fatty liver with an increase in the transaminases, and one should always ask about a history of diarrhea. Obviously, there are certain drugs which can present with this picture, and one must take a careful drug history. Aspirin and Tylenol are two of the big offenders. Many people, particularly in this area, are on Isoniazid for prophylaxis against tuberculosis, and the physician should also inquire about this medication. The use of methotrexate has been described to cause a similar syndrome. Two other disorders which one must consider are Wilson's disease and hemochromatosis. The work-up for these includes a careful eye examination and a serum ceruloplasmin level and iron binding capacity. In this woman, they were all normal.

Dr. Riely, could you please comment on the work-up I've outlined at this point? When would you move to a liver biopsy? What would you expect to find in the biopsy, and how might it alter your therapeutic approach to this particular lady?

Dr. Caroline Riely (Associate Professor of Medicine and Pediatrics): For asymptomatic elevations in SGOT alone, I would not move directly to a liver biopsy, but, by the time I saw this patient, she had abnormal liver function tests for six months which would make it more appropriate. On the other hand, the most remarkable thing about her was not the SGOT elevations, but the gigantic liver, which should direct your work-up much more strongly than just the SGOT elevations. Looking at your list, I'd like to emphasize that the "jogger's syndrome" you described is not rare. I have seen two patients referred to me in the last year for elevated SGOT and SGPT who were joggers.

Dr. DeFronzo: That is an important point, since there is a tremendous jogging and exercise fad now.
DR. RIELY: Considering the rest of your list, inflammatory bowel disease is more likely to present as a chronic active hepatitis or maybe a chronic persistent hepatitis, rather than as fatty liver. Tylenol ingestion should not produce an SGOT elevation, unless it is used in large amounts. Aspirin may elevate the SGOT. Wilson's disease I consider in everybody, since it is totally treatable. However, the oldest patient that I know of was 52 at the time he presented with asymptomatic esophageal varices. The oldest patient we have seen here was a 42-year-old lady who came in with a picture that resembled fulminant hepatitis. So, it is unusual to present with it in old age. The other thing that often is forgotten is that anything which affects the body can affect the liver. Certainly, thyroid disease, both hyper- and hypo-thyroidism, alone can produce abnormal liver function tests. Cardiac disease is a common cause of abnormal liver function tests, particularly any condition which raises right-sided pressures.

For someone who has an asymptomatic elevation of SGOT of six months' duration, in whom appropriate work-up has been pursued without identifying the cause, I would recommend a liver biopsy to clarify the situation. In someone with hepatomegaly and elevated liver function tests, I would biopsy sooner to determine whether there is an infiltrate in the liver.

DR. DEFROUNZO: So there are many things on this list that can cause an elevation of the SGOT. Some of them will cause other abnormalities in liver function studies, but if you put together the age, the associated medical conditions, and the markedly enlarged liver you would agree that we're probably talking about those conditions described under the category of fatty liver disease.

DR. RIELY: I think what that means is infiltration. The infiltration is less likely to be inflammatory infiltration because that does not produce such big livers. It is more likely to be due to something in the liver cells themselves, like fat or glycogen, or something in other cells in the liver, as in Gaucher's disease, or something not in the cells, but infiltrating the liver, such as amyloid.

DR. DEFROUNZO: Would you have treated this patient's hypothyroidism to see if her liver abnormalities corrected before doing a liver biopsy?

DR. RIELY: I had suggested that we make her euthyroid, and if the SGOT was still abnormal, that we proceed with a biopsy. However, her case was complicated by her diabetes and heart disease, and we were reluctant to make her euthyroid abruptly.

DR. DEFROUNZO: She did have a liver biopsy. Could we see the results of the biopsy?

DR. KEN BARWICK (Assistant Professor of Pathology): Let me give credit to Dr. Gerald Klatskin who originally read and interpreted this biopsy. The histologic changes of the biopsy are classic for alcoholic liver disease or for a few other processes, as I will mention. On a low-power view of the needle biopsy, one sees broad, regular bands of fibrous tissue that stain blue with the Masson-trichrome stain. At low power one ascertains whether the lobular architecture is preserved. In this specimen it is difficult to find the central and portal areas. This architecture has been completely effaced and essentially destroyed. In addition to that, there are regenerative nodules of hepatocytes with only minimal suggestions of normal lobular architecture. The other finding that is quite striking at low power is the massive degree of steatosis (Fig. 1). So we have low-power evidence of a fibrosing process which is almost certainly cirrhosis and that has totally destroyed the architecture. One cannot find central vessels in looking through this biopsy, and one can see that it has rather irregular fibrous scarring. The nodules are somewhat similar in size, although that is a hazardous thing to determine on a biopsy of such
small size. So we have at low power a type of cirrhosis that would fit into either micronodular cirrhosis or Laennec's cirrhosis. At high power, using Masson-trichrome stain, one can see the expanded portal areas in which there are entrapped portal triad arteries and veins. It is important to ascertain whether there is an ongoing injury being rendered upon the hepatocytes, and, if so, what is the degree of activity. To determine whether or not there is ongoing injury, one studies the lining plate of hepatocytes around the triads, which should be a full layer; this is called the limiting plate. It is rather difficult to define a limiting plate in cirrhosis as well-formed as this, but by looking along the lining plates along the fibrous bands, there is definitely an erosion of these cells. One could then try to determine whether the hepatocytes in that area show either inflammation or hepatocellular injury. As we move on to very high power we see that the cells adjacent to the fibrous tissue are enlarged. This is often called ballooning, and the name "balloon hepatocyte" fits very well. Within the cytoplasm, C-shaped or serpentine beaded coagulums are present, representing Mallory bodies (Fig. 2). We can see these in a number of hepatocytes present. When we look into the fibrous tissue to determine whether there is ongoing inflammation, we find it is mild. The inflammatory cells which are present are predominantly neutrophilic, as opposed to lymphocytes and plasma cells, the latter being consistent with a post-viral injury pattern. The neutrophils are consistent with an alcoholic injury. There are scattered cells which are shrinking and dying. These are called acidophilic bodies. They are not frequent in this specimen.
One can thus determine that there is continuing insult and it is being rendered to the hepatocytes, which is of a mild to moderate degree.

So, in summary, the diagnosis is that of cirrhosis which is a Laennec's or micronodular type. There is very prominent fatty necrosis and an infiltrate which is predominately neutrophilic. As I mentioned earlier, these are changes which are very typical, indeed, classic, for alcoholic hepatitis. It has been appreciated recently that the differential of this histologic pattern is broader than that, however, and includes diabetes mellitus, obesity, non-alcoholic steatohepatitis, and post-ileojejunal bypass. The appropriate choice from these possibilities must rest upon clinical history.

DR. DEFRONZO: Are there any questions about the biopsy?

PHYSICIAN: Did you stain for glycogen?

DR. BARWICK: Yes, the specimen was stained for glycogen. There was some glycogen present, but it was minimal.

DR. DEFRONZO: The findings in this patient point to the entity of non-alcoholic steatonecrosis. One of the first articles to address this problem was published by Leevy [1]. He reviewed 270 patients who had a histologic picture of cirrhosis and fatty change and found that 77 percent of these people consumed very large amounts of alcohol. On the other hand, he found that 23 percent of the population had this exact histologic picture but with no history of alcohol consumption. In the non-alcoholic fatty liver group there was a high prevalence of diabetes mellitus, including both non-insulin-dependent and insulin-dependent patients. There was also a high incidence of obesity. Not listed in his differential is the possible association with lipoprotein disorders. He also reported a high incidence of heart disease, and several other series show that heart disease frequently occurs in association with non-alcoholic fatty liver. Leevy postulated that there are four possible mechanisms via which one could develop a fatty liver: (a) there could be an increase in free fatty acid delivery to the liver cell; (b) there could be a decrease in fatty acid oxidation by the hepatocytes; (c) there could be an increase in lipid synthesis by the hepatic cells; or (d) there could be decreased packaging of the lipid into lipoproteins by the liver cells, leading to a reduction in transport to peripheral tissues. We now know that alcohol, diabetes, and obesity affect each of these steps. Toxic drugs and alcohol have been postulated to cause fatty changes in the liver by all four of these mechanisms. However, it appears that the primary cause of this fat accumulation is a marked decrease in fatty acid oxidation, due to decreased efficiency of the Kreb's cycle. In diabetics there also appears to be an increased delivery of fat from peripheral stores to the liver. There is also some evidence to suggest that there is a primary increase in triglyceride synthesis within the liver, as well as a defect in the apoprotein necessary to package the lipids into lipoproteins and transport them to the periphery. The etiology of the fatty liver in obesity is less well-established. Some investigators have postulated that there is an excessive amount of glucose as well as fat in the diet which is being directly deposited in the liver.

Two recent articles have addressed the problem of non-alcoholic fatty liver. One is a series published by Ludwig et al. [2], from the Mayo Clinic. In 20 patients with non-alcoholic steatohepatitis, they found a high incidence of obesity (90 percent) and diabetes mellitus (25 percent), as well as a significant number of patients with hyperlipoproteinemias, particularly Type IV (25 percent). Again, they also found that a significant percentage of these people have cardiac disease (35 percent). Dr.
Riely, is there anything else known about the association between heart disease and this entity?

**DR. RIELY:** I do not think that they are causally related. All these patients are older, in their 50s, usually, and cardiac disease is very common.

**DR. DEFRONZO:** It would appear that cardiac disease occurs quite frequently, but no one really knows whether it has any etiologic significance. Dr. Ludwig pointed out in his article that patients with non-alcoholic fatty liver frequently develop polymorphonuclear infiltration, necrosis of liver cells, Mallory bodies, alcoholic hyaline, and fibrosis that would eventually lead to cirrhosis. In a subsequent paper by Adler and Schaffner [3] similar findings were observed. They also emphasized the frequent occurrence of lipoprotein disorders unassociated with diabetes and obesity. Most recently Denis Miller and Gerry Klatskin have looked at a similar group of 27 people here at Yale [4]. Again, the histological changes they found were indistinguishable from those observed in alcoholic cirrhosis. They also reported that some of these patients can develop advanced signs of liver disease in addition to hepatomegaly. A large number had splenomegaly (nine), or developed ascites (nine), jaundice (seven), encephalopathy (four), and varices (seven). So this is not a benign disorder, even though it is not associated with alcohol.

Drenick et al. [5] studied obese people with non-alcoholic fatty liver. They treated these people either by a total fast, by a hypocaloric weight-reducing diet, or by intestinal bypass. Pre-treatment biopsies demonstrated non-alcoholic hepatic fatty infiltration and cirrhosis. On follow-up, the group treated by fasting and the group treated by diet had almost complete resolution of their liver disease. In contrast, those who were treated with intestinal bypass got much worse. It is now well known that intestinal bypass is associated with its own type of cirrhosis and fatty infiltration. In summary, this article suggests that weight reduction can be an effective means of treating the liver disease. There also is some anecdotal evidence that tight diabetic control will alleviate the liver disease in diabetic subjects. How should one approach the treatment of the metabolic derangements that occur in diabetic and obese people? In order to begin treating such individuals, one must have an understanding of the mechanisms underlying the glucose intolerance in such patients.

I'd like to review some studies that we've carried out to define the mechanism of glucose intolerance in obesity and in diabetes mellitus. We have employed the insulin clamp technique to quantitate tissue sensitivity to insulin. Briefly, the patient's plasma insulin concentration is raised by 100 u/ml and a variable glucose infusion is simultaneously given to maintain the plasma glucose concentration at the basal level. Under these steady-state conditions of glycemia, the rate at which the glucose is infused must exactly equal the rate at which all the tissues are taking up the glucose. Therefore, the total amount of glucose which is infused during the study provides a measure of the body's sensitivity to the insulin that was given. In obese individuals we have shown that the tissues of the body are severely resistant to the action of insulin. The total amount of glucose metabolized is reduced by 50 percent compared to normal individuals studied with the same dose of insulin. Thus, one of the major metabolic disturbances in obesity is an inability to respond normally to the insulin that one's own body makes or to the insulin that is infused exogenously. What about non-insulin-dependent diabetic subjects? It turns out that Type II diabetes is also characterized by insulin resistance, which may be even more severe than in the non-diabetic obese individual. The patient under discussion here was treated with insulin, and one could argue that she is, therefore, an insulin-dependent
diabetic. However, it is likely that she still has residual, albeit diminished, insulin secretion and would be classified as a Type II, or non-insulin-dependent, diabetic (NIDD). Recently, we have also demonstrated that insulin-dependent diabetics, in the absence of circulating antibodies, are markedly insulin-resistant. Therefore, whether we say our patient is insulin-dependent or insulin-independent is not going to make a difference with respect to the presence or absence of insulin resistance. It should be emphasized that the combination of diabetes and obesity will make the patient particularly resistant to the action of insulin. When thinking about treatment of such an individual, one would like to institute measures that will specifically improve the body's response to insulin. There are three things that can do this. The first is physical training. In this particular woman, we can encourage that, but it is unlikely to be very successful. The second is use of oral sulfonylurea agents. One could argue that in a diabetic who is difficult to control, either insulin-dependent or insulin-independent, if the major problem is one of insulin resistance, and if the oral agents have as their major mechanism of action an increase in tissue sensitivity to insulin, then one should see an improvement in the patient's glucose tolerance. We have looked at this using an oral sulfonylurea agent in a group of non-insulin-dependent diabetics, who had fasting glucose levels of about 200 mg%. After being on the oral agent for three days, the fasting glucose concentration decreased to 170 mg%. After three months of treatments, the plasma glucose declined to 140 mg%. This decrease in fasting glucose was found to be entirely due to a decrease in hepatic glucose production without any change in the basal insulin level. Thus, the oral agents seem to inhibit the overproduction of glucose by the liver that occurs under post-absorptive conditions. Insulin clamp experiments in those subjects show a marked improvement in insulin sensitivity, as well, after three days and three months of treatment. Therefore, oral agents appear to have a major effect of enhancing tissue sensitivity to insulin in addition to their ability to augment secretion. In fact, on a long-term basis, it is difficult to show that oral agents enhance insulin secretion. Dr. Bender, when you placed this woman on Diabinese, you noted that there was a marked reduction in her insulin requirements, and her diabetes came under better control. Was there any change in her weight or diet or other factors that could have been responsible for the improvement in glucose control?

DR. BENDER: Her weight was stable at 215 pounds, and I don't believe she had any changes in her diet. She had been counseled for years and had not changed her diet.

DR. DEFRONZO: We are presently investigating the effects of oral agents in insulin-dependent diabetics who are relatively insulin-resistant and require large amounts of insulin. We hope that improved tissue responsiveness to insulin will improve glucose control and decrease the daily insulin requirement, since there is recent evidence to suggest that such high insulin doses may be atherogenic. This is the third case we have seen in which insulin requirements have dropped in half, and patients have come under better control. It is possible, therefore, that the oral agents can be a useful means of therapy. What about weight reduction, per se? If one takes a normal person who is overweight, but not diabetic, and reduces that person's weight, one sees a significant improvement in glucose tolerance. It has also been shown that in the obese individual there is marked hyperinsulinemia, with plasma levels often in excess of 150 μ/ml, following an oral glucose load. After weight reduction, glucose tolerance improves despite a decrease in the plasma insulin response. This can only be explained by increased tissue sensitivity to insulin. The obese diabetic with fasting glucose levels above 200 mg/dl is very different, however. Such a person has a flat
insulin response to an oral glucose load. Four large studies have shown that if this person is weight-reduced, there is improved tolerance of glucose, enhanced tissue sensitivity to insulin, and improved insulin secretion. It is now clear that even moderate obesity is associated with insulin resistance. The beta cell tries to overcome this resistance by secreting more insulin, but eventually the beta cell exhausts itself, and an insulinopenic state results. If one can reduce the insulin resistance, however, the beta cell may recover its capacity to secrete insulin. There are dramatic cases of insulin-dependent diabetics who, after weight reduction, lost their requirement for insulin. Diabetes researchers now know that weight reduction in an obese diabetic will not only decrease the insulin resistance, giving better glucose tolerance, but will allow the beta cells to recover function also. Normalizing body weight, then, is an important goal to strive for. I am going to ask Bob Sherwin to comment on the type of diet that he thinks would be beneficial for this patient.

This is not an easy problem in this lady, since she has liver disease. She will need a diet that will not make her liver disease worse, yet she needs to lose weight. If you were treating this woman, what type of diet would you recommend, and what would be the theoretical basis for this recommendation?

DR. ROBERT SHERWIN (Associate Professor of Medicine): I have a couple of comments before we discuss specific dietary recommendations. Of the available oral agents, I would not have chosen Diabinese to treat this patient, since it is the one most likely to cause hepatotoxicity. Usually it requires doses above 750 mg to do so, but in someone who has underlying liver disease I would be more cautious. I would have chosen another agent, even though Diabinese is potentially the most effective antidiabetic agent available on the market today. The other issue concerns the use of insulin in a patient with severe obesity. I personally would not have used insulin in this lady. Often, such patients show an initial response, but later they do not do very well. They often gain additional weight and become more insulin-resistant and glucose-intolerant. I would venture to guess that discontinuing her insulin, by itself, would have produced very little change in her condition.

DR. BENDER: She is now off insulin, and her glucose level is about 200 mg%.

DR. SHERWIN: Chances are that even before you started her oral agent, you could have taken her off insulin, and nothing would have changed. That has been my clinical experience.

The best way to treat this lady is by weight reduction and not by oral agents. However, it is usually easier and more effective in general terms to give oral agents because patients will take them. This patient has several strikes against her when she tries to lose weight. One is that she is a woman, and women do not lose weight as well as men for some reason. Two, she was markedly obese, and the fatter the person, the less likely they are to lose weight. Third, she had long-standing obesity, and the longer the history of obesity, the worse the outcome. If a patient becomes obese before puberty, the likelihood of success is extremely small. The best factor, in terms of outcome, is that she has some underlying disease, diabetes mellitus, and that can provide a motivating focus for the patient. But unless one has adequate motivation and an adequate follow-up system, the dietary measures that we prescribe are often not effective.

I would be careful about the use of total fasting to help this woman lose weight. Although that would be effective in mobilizing some of her fat stores, the risks are considerable, and the potential benefits are not much greater with a hypocaloric diet. If the key thing you want to do is to have the patient lose weight, a moderate
caloric restriction diet will achieve that. It might be a little slower than total fasting, but the end result will be the same, and the patient is likely to maintain the weight loss. Our experience with total fasting patients has not been rewarding. After leaving the hospital they usually regain what weight they have lost. Therefore, I would probably put this lady on a diet containing 800–1,000 calories that supplies an adequate amount of protein, a little over 1 gram/kg of body weight. Since this woman's ideal body weight is about 50 kg I would include about 70 g of protein, and I would also include a small amount of essential fatty acids. The rest of the calories should be supplied as fat or as carbohydrates. The proportions of these do not matter much in the long run. Unfortunately, the medical profession does not ordinarily offer much more to a patient other than diet. There often is not adequate follow-up or adequate encouragement for the patient in the long term to really make it work. The best thing to do would be to refer her to a place where there are people who are following patients on a weekly basis, such as a self-help referral group. Long-term behavior modification, once weight reduction is achieved, is a reasonable approach.

DR. DEFRONZO: Dr. Bender, what has happened since the biopsy?

DR. BENDER: Dr. Sherwin mentioned that the liver biopsy might motivate her. Indeed, when her biopsy came back as severe cirrhosis, that became a strong motivating factor, and she now has lost 30 pounds. Her SGOT is now normal, and she is off insulin. I do not know how well that correlates with her liver disease, as she still has a very large liver.

DR. DEFRONZO: I'd like to point out that in the paper by Drenick et al. [5] which showed return of normal liver function in obese people who lost weight, the weight reduction achieved was greater than 100 pounds.

In summary, there are two points to be emphasized. First, non-alcoholic hepatitis can be as dangerous as alcoholic hepatitis, but correction of the underlying metabolic disorder in obesity or diabetes may improve liver function. Second, if one can reduce insulin resistance by some of the methods that we've talked about, glucose tolerance will improve, and the beta cells may recover significant insulin secretory function.

DR. ALAN KLIGER (Associate Professor of Medicine): You have a patient with hypothyroidism and anti-thyroid antibodies, along with diabetes mellitus and antinuclear antibodies. Is there a way to tie all of these together?

DR. DEFRONZO: This lady could fall into the Schmidt's syndrome of multiglandular failure. I'll ask Bob Lang to comment on this. How exhaustively would you work up such an individual? Would you test for adrenal function or look for pernicious anemia?

DR. ROBERT LANG (Associate Professor of Medicine): Hypothyroidism and diabetes are, by far, the two most common endocrine gland failure disorders that we see in the syndrome of multiglandular failure, as well as in the general population. We now know that the syndrome originally described by Schmidt [6], which was lymphocytic thyroiditis and non-tuberculous Addison's disease, is due to an autoimmune disorder. Most clinicians now include diabetes mellitus as part of Schmidt's syndrome, and, unlike this patient, most will have insulin-dependent diabetes mellitus. I personally do not work up every gland in every patient with Schmidt's syndrome, but I keep the thought in the front of my mind that it is possible that there may be failure of other glands. One needs a very high index of suspicion to
undertake a large work-up, and the physician should educate these patients to return if symptoms from other glandular failure occur.

**DR. DEFRONZO:** Although these people may develop hypoparathyroidism, pernicious anemia, and a variety of other "autoimmune disorders," as Dr. Lang has pointed out, you don't need to institute an exhaustive work-up unless the history or physical examination points to some specific organ system dysfunction.

**DR. SHERWIN:** This syndrome of multiglandular failure is extremely rare. Further, 95–99 percent of them have Type I diabetes, which is a different entity than the problem this patient has. The other thing to remember is that insulin seems to enhance the conversion of T₄ to T₃. Patients with Type I diabetes, even without antibodies, tend to have relatively low T₃ levels.

**DR. BENDER:** The patient had an elevated TSH.

**DR. SHERWIN:** Yes, she was clearly hypothyroid, but one should probably not invoke polyglandular failure in a Type II diabetic.

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