PREVENTION OF INSULIN RESISTANT DIABETES
Introduction

David M. Player, MD
Health by Design Program Manual

Introduction

Insulin Resistance and Health and Nutritional Coaching: What in the world do they have to do with each other? Diabetes has everything to do with lifestyle management, because with optimal lifestyle management, most of the diabetes in America would not exist. This terrible disease, which causes tremendous loss of life and limb, blindness, kidney failure, heart disease and a host of other problems, is in many cases, totally preventable.

During my 30-plus years as a nephrologist in South Texas, I was privileged to care for several thousand people with diabetes. In fact, almost everyone I saw in my dialysis clinics for those many years had diabetes. Most had experienced diabetes for over 20 years by the time I became involved in their care, but for a few, their diabetes was of shorter duration. Regardless of duration of the diabetes, however, almost all of my diabetic patients had one thing in common. They had been substantially overweight for a critical few years of their lives. Whether after pregnancies or after years of overindulgence, the common denominator for many of my patients was a prolonged period of excessive body fat storage. After several years of driving to dialysis clinics around South Texas, I knew in my spirit that the vast majority of dialysis patients likely would never have had kidney failure had they maintained optimal body composition and weight throughout their lives. In other words, if – for most of my patients – there had been ideal body weight and composition, there likely would have been no diabetes, and if there were no diabetes, there would have been no kidney failure.

For me then, the next 30 years would be committed to a combination of caring for those with diabetic kidney failure and working to prevent what was at the root of most of it – abnormal body composition. Health by Design and its current Health and Nutritional Coaching Programs are all about prevention of diabetes and other related problems. It is our sincere hope that the following several chapters will prevent thousands – perhaps hundreds of thousands - of cases of diabetes. For those who have diabetes already, these materials will hopefully provide insight that will help in the daily management of this health problem.

PREVENTION OF INSULIN RESISTANT DIABETES
Chapter 1

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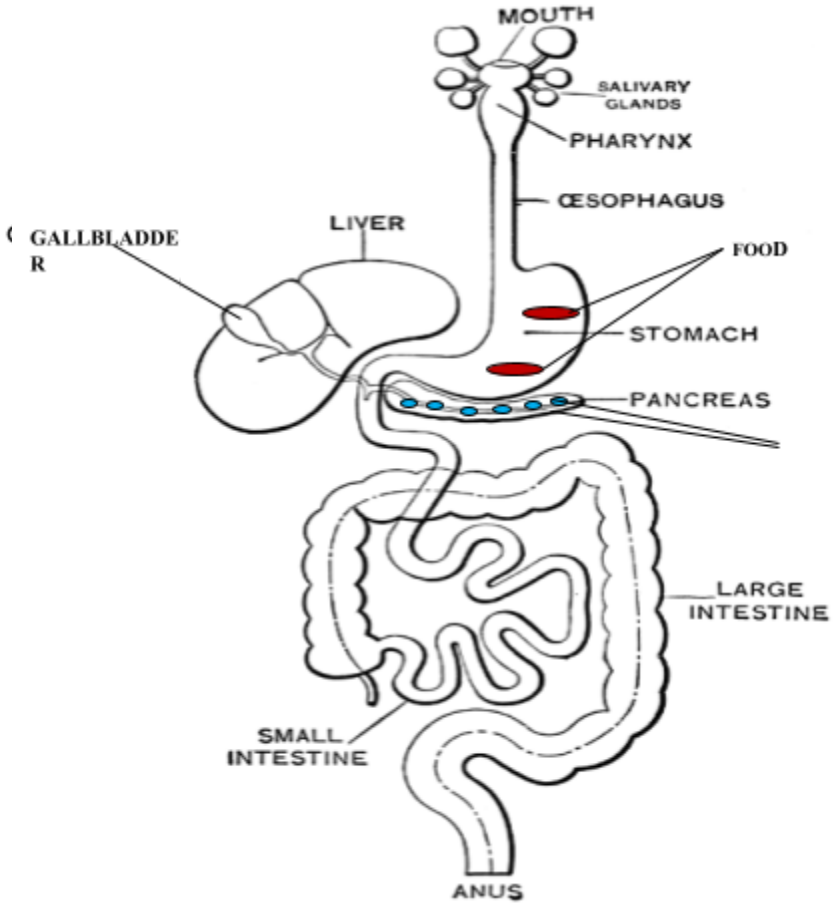
I. Anatomy of Diabetes

To understand diabetes, one needs to begin with an anatomy lesson covering the upper gastrointestinal system. Figure A. below depicts the major players in the saga of diabetes and related diseases.

Figure A.

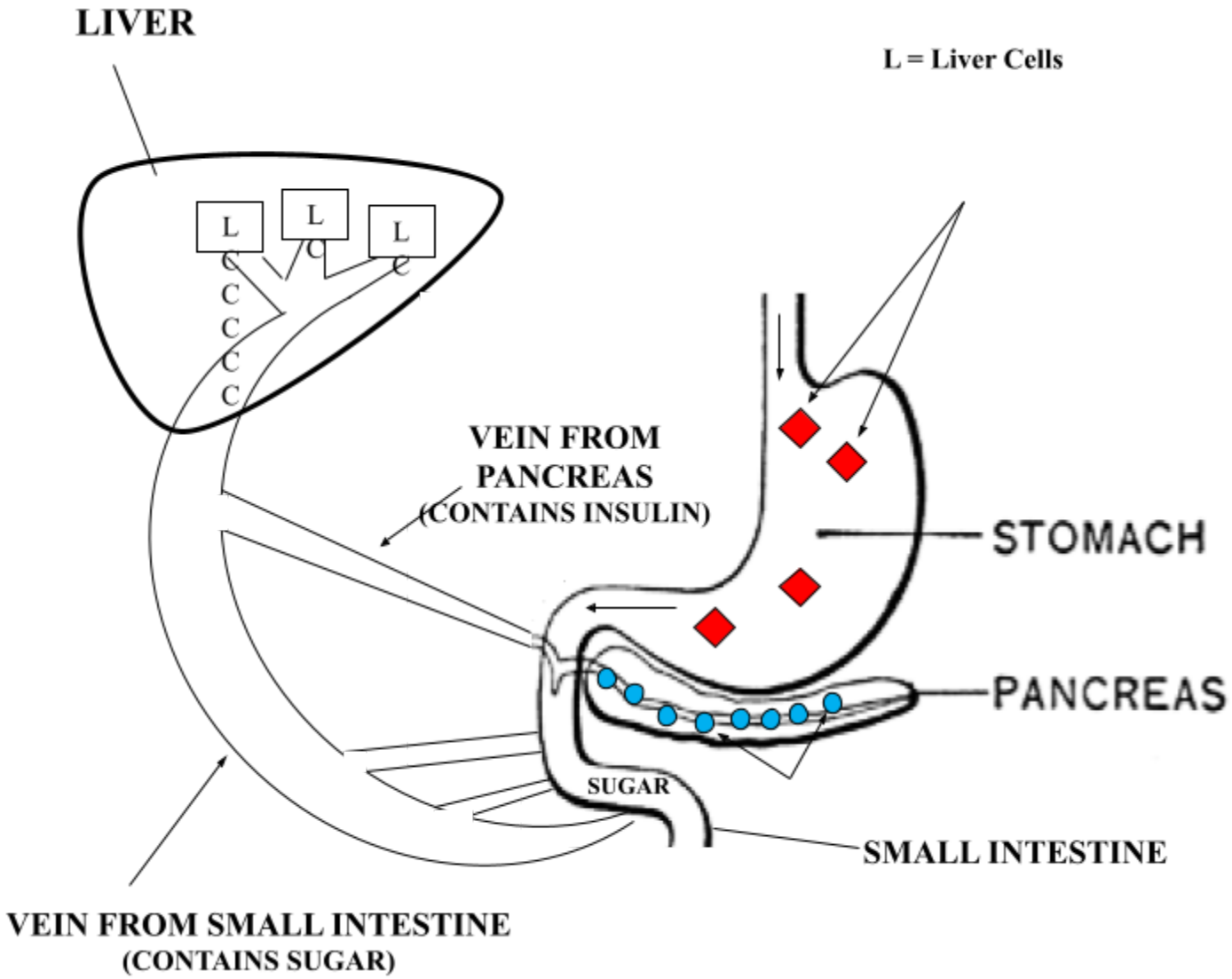


A bolus of food passes down the esophagus to the stomach where acid and several enzymes begin digestion of proteins, carbohydrates, fats, and alcohol in the food. These nutrients are absorbed along the course of the small intestine, and enter the blood in veins that drain into the liver. Some of the blood eventually gets to the heart and is pumped to the pancreas where tiny nests of glandular cells called beta cells examine the blood coming from the intestine and determine whether there is any sugar or sugar alcohol in the food being digested. All carbohydrates are eventually broken down into sugars during digestion. If there is any sugar (digested carbohydrate) in the food, the beta cell sensors will analyze how much sugar was added to the blood and release an appropriate amount of the beta cell secretory hormone (insulin) into the blood. Amazingly, in healthy people, just enough insulin is released into the blood, causing the sugar from the food to be used in cells of the liver, muscles, and other

tissues. This process brings the sugar back to the level present before the food was eaten. It is amazing how this system works, and for most of us, it works well over our lifetime. Unfortunately, in some people the system does not work well (diabetes) and that is why this chapter is being written.

In Figure B. we follow some insulin out of the beta cells, and sugars out of the intestine into the veins and up to the liver where the sugar is needed for fuel.

Figure B.

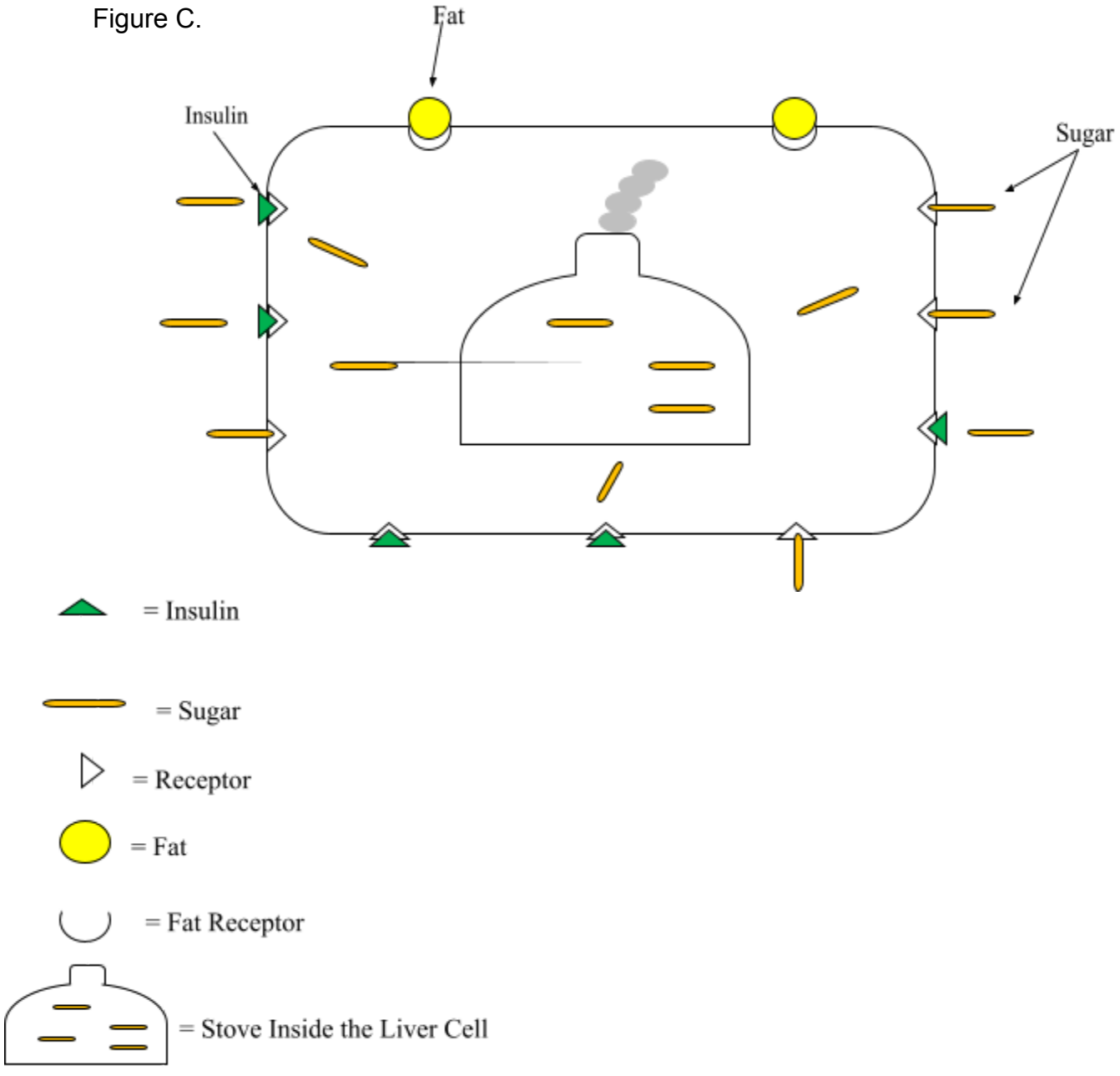


Actually, every cell in the body needs sugar for fuel, but I have used liver cells as an example because the liver burns more than 25% of all the fuel required by our body in a day. The liver is critical because it is the first major user of fuel that receives sugar from

the intestine and insulin from the pancreas. The liver (and muscle) is also capable of storing sugar in its cells. This sugar can be used as fuel for our brain and other tissues when we are not eating. When we are not eating, sugars are released from the liver and muscles to keep our blood sugar normal. When we eat, however, the liver takes up and stores sugar as glycogen.

In figure C., we see what happens when sugar and insulin arrive at the outside of a liver cell. The liver cell needs sugar as a fuel for the stove (furnace) within it (mitochondria). Sugar can enter the cell only when insulin (the dark triangles) fit into the docking port (insulin receptors) on the wall of the cell. There can be plenty of sugar present to supply fuel, but if there is no insulin to open the docking port, almost none of the sugar gets into the cell, and the cell begins to starve. The cell has a few fat receptors and can use a little fat for fuel, but this process is blocked by the presence of insulin.

Figure C.



Obviously, the best system for health of the cell and creation of energy, is one in which there is just enough sugar and just enough insulin to help the sugar get into the cell. Fortunately, for most of us, this is exactly what happens. There is just enough sugar and just enough insulin and everything works well!

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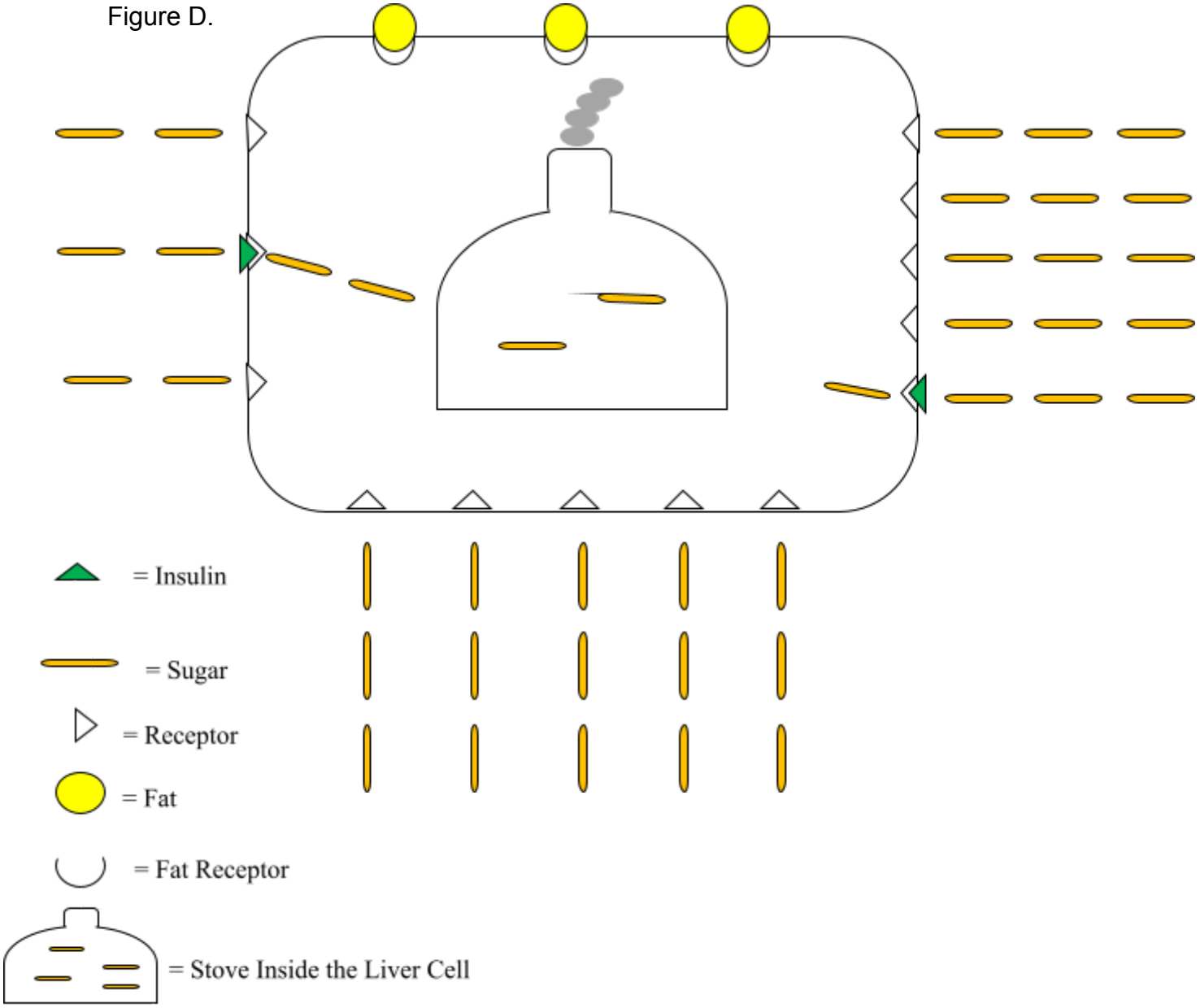
II. What Goes Wrong? (Type I Diabetes)

Figure D. shows a picture of the <u>first and most serious</u> situation that can go wrong with the liver cell and its fuel system.

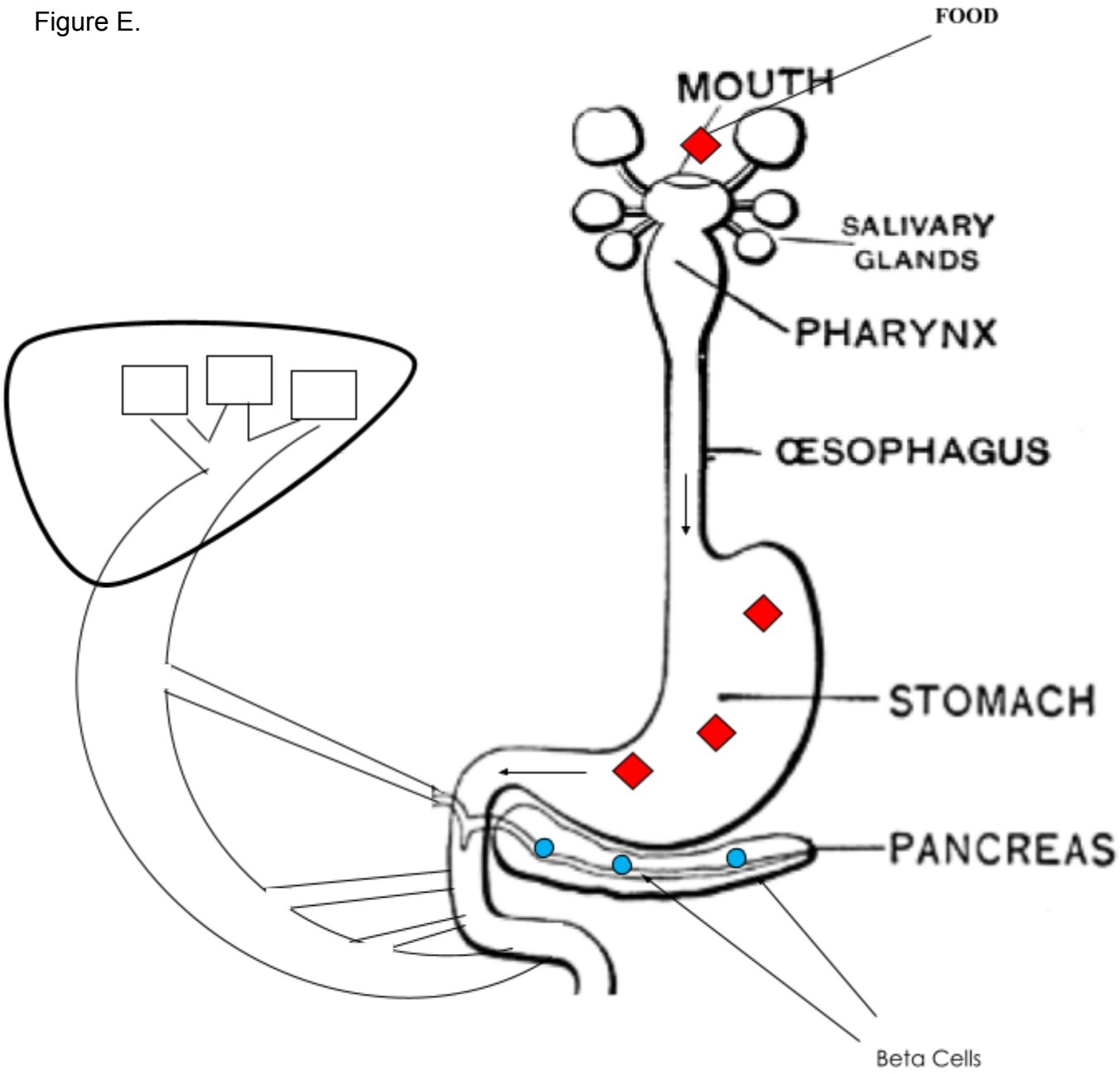
Figure D.



What is wrong with this picture? As you can see, the liver cell is like the man stranded on a lifeboat in the middle of the ocean – "Water, water everywhere, and not a drop to drink!" In this case, it is "Sugar, sugar everywhere, and not a bit to use."
What is missing? – Insulin of course.

A new snapshot of figure A+B shown below in Figure E. gives you an idea of what has happened.

Figure E.



As you can see, almost all of the beta cells that make insulin have disappeared, usually having been destroyed by the body's own immune system over a period of several months – perhaps after a viral illness or other health problem. Regardless of the cause, the beta cells die, and the human being is left with no insulin to get sugar through the docking ports and into the cell. This situation is currently known as insulin deficient, or insulin dependent, or Type I diabetes, and if untreated, leads to starvation of all of the cells in the body and ultimately death.

Fortunately, since the 1930s, we have been able to produce insulin in the laboratory, and thousands of lives have been saved by the injection of insulin. Recently, inhaled forms of insulin have been developed, but no oral insulin tablets or solutions are available because swallowed insulin gets digested in the stomach before it can be absorbed in the small intestines to be used by liver cells (and other tissues).

Great advances have been made in the administration of insulin via pumps with the use of digital technology. Sugar levels can be accurately measured through the skin to program how much insulin should be given via the pump. In spite of these advances, however, insulin deficiency diabetes is still a difficult management problem and a source of much frustration and heartache. Giving too little insulin leads to high blood sugar levels, which can damage the inner lining of the tiny arteries in the eyes, kidneys, nerves, heart, intestines, and other organs. (We will talk more about this process later in this chapter and in our cardiovascular disease chapters). Giving too much insulin causes too much sugar to go into the cells quickly and may drop blood sugar levels so low that there is not enough sugar to keep brain cells working. When this happens, diabetics may lose consciousness, have seizures, and go into a deep and sometimes brain-damaging coma.

It would be best to recognize early, the disease process that causes pancreatic beta cells to die, and to stop the process with medicine. As noted previously, the process by which the situation depicted in Figure E occurs is thought to be caused by distorted activity of the human immune system. In this model, antibodies made by the immune system (white blood cells called lymphocytes) begin to be directed against the beta cells of the pancreas instead of or in addition to the virus, bacteria, or allergen that stimulated their production. No one knows why this confusion begins to occur, but some families (genetics) are more likely to have it happen than are others. Regardless of the "whys", the end result is attachment of the antibodies to the beta cells, initiation of an inflammatory reaction, destruction of the beta cells by inflammatory white blood cells called macrophages, and finally scarring and death of the beta cells. This process may take many months, and during the "war against the beta cells", anti-islet-cell antibodies can be measured in the blood. Various anti-inflammatory medicines used in patients with transplanted organs can slow down or stop this damage to the beta cells – if we know it is happening. Unfortunately, we do not routinely do blood screening tests for anti-islet cell antibodies. We usually do not find out that the war has been going on until it is too late, and most of the beta cells have been destroyed. (Figure E).

For the present, the best that we can do is to recognize what has happened, give insulin injections to replace what the dead beta cells can no longer make, and try to keep blood sugar levels near normal to prevent the damage to the body caused by low and high blood sugar levels. Low sugar levels are much more dangerous acutely than high ones – as discussed above – because our brains need a constant normal blood sugar level. As I often have told my patients, "No one has ever died immediately of a sugar level of 300-400 mg/dL (quite high), but lots of people have died of sugar levels below 30 mg/dL". Giving the right amount of insulin numerous times per day is a difficult

challenge for patients with insulin–deficient or insulin-dependent diabetes, because of the great danger of low blood sugar levels. Unfortunately, very high sugar levels are not good either and can cause chronic disease of tiny blood vessels in every part of the body. Without insulin, the cells starve to death (Figure D). With too much insulin, brain cells die, and with high blood sugar levels caused by too little insulin (or too much food sugar), tiny blood vessel damage occurs. What a challenge! Most of us just eat what we want and count on our pancreatic beta cells to do all of the above jobs. The insulin-deficient diabetic has to be lots smarter than the rest of us when it comes to food, activity, emotions, stress, infection, and hundreds of other factors that may influence blood sugar levels and health. People with insulin-deficient diabetes have to know how much sugar (carbohydrate) is in the food they are consuming. They must know how the ingested carbohydrates will affect blood sugar levels, how much insulin must be injected to keep the brain, liver and muscle cells happy while at the same time not allowing blood sugar levels to drift too high or drop too low.

Hopefully an inexpensive screening test to identify anti-islet cell antibodies will soon be available allowing us to know early on when the beta cells are being damaged. Better screening tests and wise use of these and newer medicines should ultimately allow us to save the beta cells from destruction and prevent the insulin deficient state shown in Figures D and E above.

A discussion of treatment of insulin-deficient (Type I) diabetes would not be complete without mentioning islet cell and pancreas transplants. Availability of the anti-rejection medicines discussed above (currently cyclosporine, Prograf, Cellcept, Imuran, Rapamune, steroids, etc.) has made it possible to transplant a pancreas (or islet cells, which contain beta cells, from a pancreas) from a donor to a patient with insulin deficiency diabetes. Excellent surgical techniques have allowed some such transplants to be successful and reestablish normal glucose and insulin relationships for short periods of time. Islet cell transplants are still considered experimental in the United States. Rejection can occur, and the medicines mentioned above have toxicities to kidneys and other organs while increasing future risks of infections and malignancies.

So, even with pancreas or islet cell transplants, there is a price to pay, and it would be wiser and safer and much less expensive to save the original islet cells while they are still alive and making insulin than to replace them with transplants or injected insulin after the islets have been destroyed.

For those of you reading this chapter who have insulin deficiency diabetes (so called Type I diabetes), I am in awe of you!! You are asked to deal with daily challenges that only you can understand. You must know things about foods, activities, medicines, needles, syringes, pumps, lancets, tubing, and a host of other details about which nobody but you cares. I can only encourage you to be “smarter” than the rest of us who have functioning beta cells, and push on with what must be done to stay healthy. Hopefully most of you will be able to receive an islet cell or pancreas transplant in the future – or at least be able to use technology to make it easier to receive your needed insulin. There are, as you already know, many nutritional components to the management of insulin deficient diabetes. A host of wonderful dietitians and

endocrinologists and other specialists have been writing about this topic for years. I have little to add to this extensive literature, but would encourage you to read the chapters in our Weight Management Module. The food laboratories in that course are largely oriented toward management of body composition and more specifically body fat. Nevertheless, there is some information therein that might help with management of blood sugar. The laboratories in this module will be of more specific value to you with insulin deficiency diabetes because they deal with the concept of glycemic index. The latter is unique to every food and (in short) means "when you eat a food, how much and how quickly does your blood sugar rise, and how long does it stay elevated before returning to baseline?" For those with insulin deficiency, the question is expanded to "when I eat a food, how much does my blood sugar rise, how long does it stay above baseline, and how much insulin do I need to inject to bring it back to baseline (but not too low)?" I hope that you will enjoy completing the Insulin Resistance Text and food labs.

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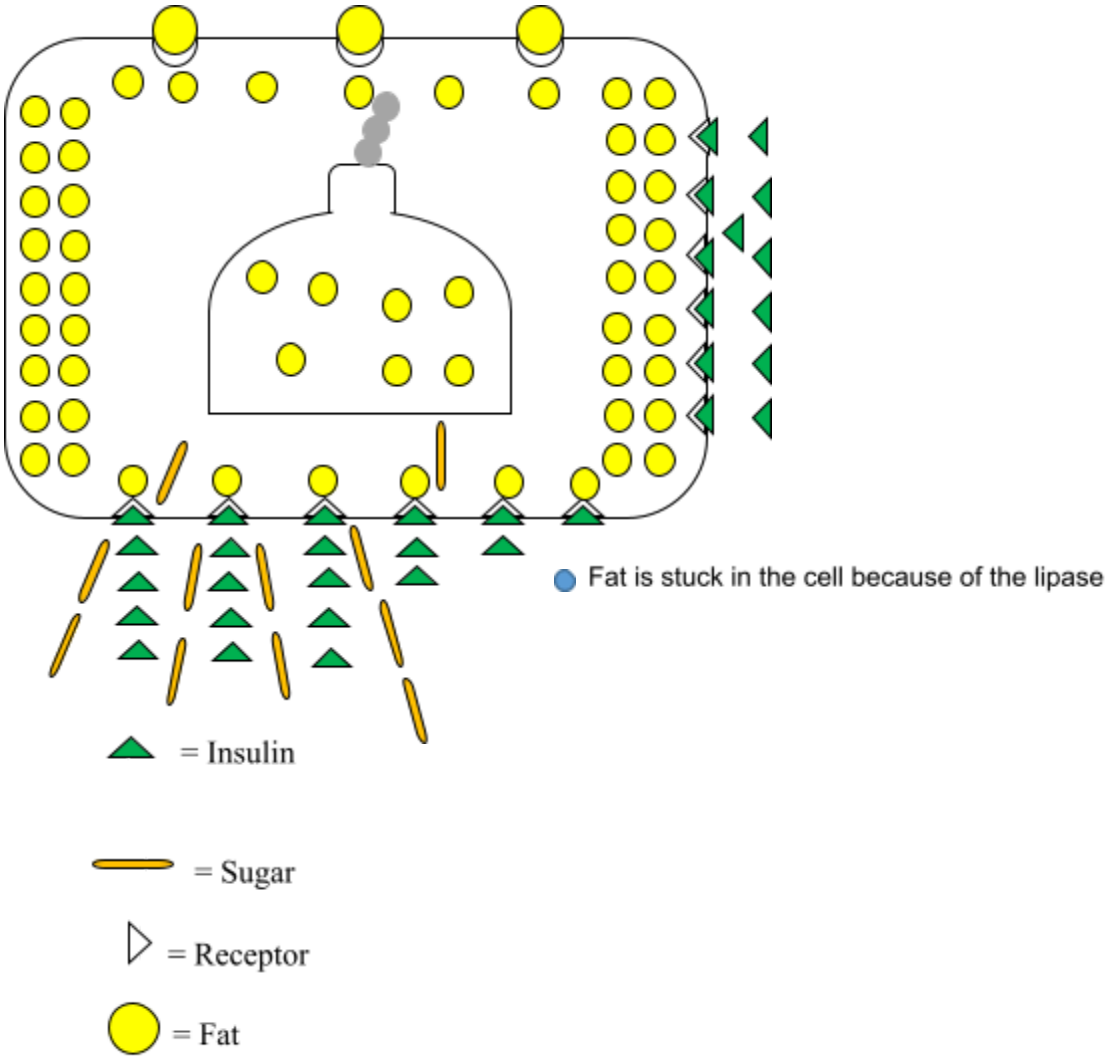
III. What Else Goes Wrong? (Type II Diabetes)

Figure F. below shows another picture (a more common one in our current society) of what can go wrong with the insulin and sugar system.

Figure F.



What is wrong with this p[illegible]ure? Compare this one with Figure D in Chapter 2. We have a stove cooking sug[illegible] de the cell. We have quite a lot of sugar and a lot of fat inside the ce[illegible]tove. The most striking thing to me about this figure (since I drew it[illegible]t way) is that there is lots of insulin and quite a lot of sugar outside the cell and n[illegible]nly where there is a great amount of insulin (bot[illegible]o the cell. The sugar is in the blood outside the cell, and th[illegible]de the cell, but the insulin is not doing its job at the docking ports (receptors) to get the sugar into the cell. Is there something wrong with the insulin? No – in the laboratory it is normal insulin, and there is lots of it! Where is the problem with this cell then? Well, it is a sick docking port! In

other words, there is plenty of normal insulin around to get fuel (sugar) into the cell, but the insulin receptor (docking port) is sick and does not allow insulin to do its job. Only when there is a really big amount of insulin (bottom of the cell) can the insulin push the docking port open (receptor) and allow some sugar to get to the stove (mitochondria).

Why are the docking ports (receptors) not working? The best theory is that this is a cell that has been "overfed" for a long time. More sugar than was needed by the stove got into the cell, and it was stored in the cell as fat (triglyceride). The stored fat has in some way poisoned the receptors (docking ports) so that they no longer work effectively. This has led to decreased entry of new sugar to the cell, a rise in sugar in the blood, and an increase signal for the beta cells to make more insulin (even though there is plenty of insulin sitting there at the cell ready to do its job). It appears that only when there is a really high amount of insulin can the insulin force a docking port (receptor) open, and allow some sugar to squeeze into the cell. The end result of this, of course, is a sick cell full of fat and not working well, and blood outside the cell containing lots of sugar and lots of insulin. It turns out that both elevated sugar levels and elevated insulin levels are toxic to the inner lining of big and little arteries, ultimately causing inflammation and a decreased diameter of the arteries and decreased blood flow to every important organ of the body.

So, the problem depicted in Figure F above is a cause of many of our arterial diseases and much of our cost of healthcare. Like the sailor saying, "Water, water everywhere and not a drop to drink," here in Figure F, we have, "Insulin (and sugar), everywhere and not a bit to use." The insulin is there, but it does not work because the insulin receptors (docking ports) are sick and damaged. They appear to be sick and do not work because the cell is full of toxic fat putting back pressure on the docking ports. The fat is there because the cell has been overfed with too much sugar and insulin in the blood for months or years.

The disease discussed above is obviously not insulin deficiency diabetes. It is still called "diabetes" because blood sugar levels are elevated, but it is obviously a very different problem from insulin deficiency diabetes. Its therapy should, of course, be very different. How have we doctors managed this kind of "diabetes", which has been present for many years and has been dramatically increasing in incidence in our society?

Until fairly recently most of our efforts were directed toward getting blood sugar lower by giving drugs that cause the beta cells to produce and release more insulin by injection. In other words, we tried for most of the past 50 years to put more insulin into a system that already was loaded with insulin. We did this because we did not, until recently, begin measuring insulin in the blood. Once insulin levels were measurable, we knew of course that this type of diabetes was not caused by insulin deficiency but rather by insulin resistance – (in other words the insulin is present, but does not work well).

This type of "diabetes" has been called many names like non-insulin dependent diabetes, adult-onset diabetes, Type II diabetes, etc. None of these names, of course,

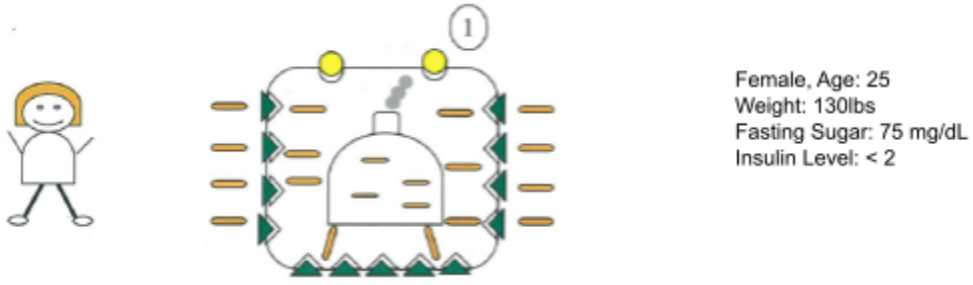
get to the root of the problem, which is “Docking Port Disease” or “Insulin Receptor Dysfunction”. None of the names describe what has caused the “docking port” problem in the first place – which appears to have something to do with accumulation of fat particles behind or inside the docking ports (receptors).

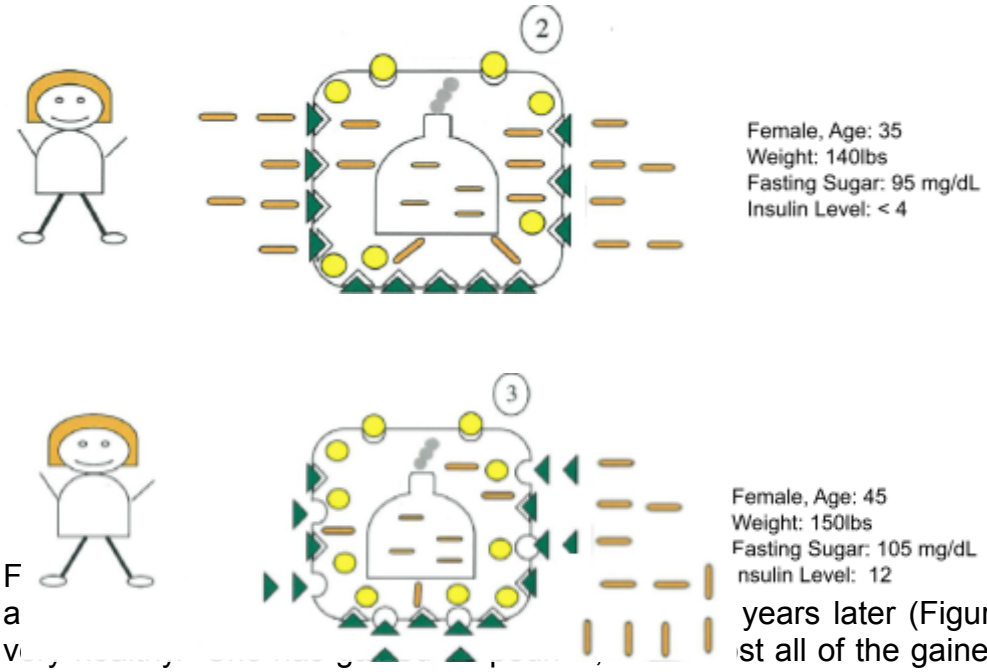
Current research is being directed toward understanding the various protein structures that provide the infrastructure of the docking ports – so that we can develop medications that make the docking port work better. We are now routinely using several drugs that seem to do this (metformin and rosiglitazone, etc). These are helping many people, but they are expensive, have potentially bad side effects, and still do not get to the root of the problem – which is fat accumulation in a chronically overfed cell.

New drugs and new research are fine, but as always, if we can manage a disease process with a change in human behavior, we should do this first and avoid the cost and toxicity of pharmaceutical agents (medications).

We have known for years that many patients with so-called “Type II” or “adult onset” diabetes could keep their blood sugar lower and avoid the need for drugs or insulin injections by changing “diet” or increasing activity! I have personally seen hundreds of people who have normalized their blood sugars using these changes in behavior. I have seen many others, however, who even with increased activity and better attention to dietary detail still have “high sugars” and are called “diabetics”. A look at Figure G below will perhaps explain one of the reasons that all “insulin resistant diabetics” do not get well with just “diet and exercise alone.”

Figure G.





F y weight, perfect a years later (Figure G-B) she is still v st all of the gained fat is in her <u>hips</u> where it does not have as much influence on docking ports (insulin receptors). Her blood sugar is still normal at 95 mg/dL (but in the higher end). Her doctor compliments her on how healthy she is. Closer examination of her liver cells, however, will show that she has a little more sugar and a tiny bit more fat than she had in the same cells at age 25. She does not know it, and her doctor does not know it – but her overeating and weight gain are setting her up for too much sugar in the cell and future accumulation of <u>fat in the cell</u>.

Ten years later (after 20 years of overfeeding her cells), Figure G-C), we see a very different picture. Her weight is up only 10 pounds from her 35 year old weight, but almost all of the fat gain has been in her abdomen and not just her hips. The abdominal fat gain has resulted in more fat inside her liver cells, and is negatively influencing her docking ports (insulin receptors), and resulting in the need for a lot more insulin to keep the stove in the cell working and fueled by sugar. Her blood sugar really is not very high, but she now has the diagnosis of pre-diabetes. She already has "insulin resistance" because her docking ports are not working normally.

In Figure G-A, the HOMA-IR is 75 (sugar) times 2 (insulin) divided by 405 (constant), which equals 0.4 (a very good and low HOMA-IR)

In Figure G-B, the HOMA-IR is 95 (sugar) times 4 (insulin) divided by 405 (constant), which equals 0.7 (still an excellent HOMA-IR).

In Figure G-C, the HOMA-IR is 105 (sugar) times 12 (insulin) divided by 405 (constant), which equals 3.1 (although in the normal range, she has the diagnosis of pre-diabetes).

In Figure G-D, the HOMA-IR is 120 (sugar) times 50 (insulin) divided by 405 (constant), which equal 14.8 (a “diabetic” HOMA-IR).

Currently, anyone with sufficient insulin resistance resulting in a HOMA-IR above 4.3 is felt by experts to have insulin-resistant diabetes.

I suspect, in truth, that the diabetes really began when the HOMA-IR rose from 0.4 to 0.7.

The important point for all of us to remember, is that insulin resistance and the dysfunction of the docking ports (receptors) for insulin is a slow process, which may go on for years before it is finally associated with an elevated blood sugar level and called “diabetes”. Obviously, if high insulin levels and high sugar levels cause damage to the linings of tiny arteries, we need to be intervening in the above pathologic process long before the insulin levels begin to rise.
Had our woman in drawing A of Figure G stopped her weight gain when all of the stored fat was on her hips and not much in her abdomen, she would likely have never become an insulin resistant diabetic. This brings us to an important additional point: Not all fat storage results in Insulin Resistance. Doctors have recognized for many years that people with a lot of fat stored on their hips, but not so much stored in the abdomen, tended to have much less diabetes, high blood pressure, and high cholesterol levels than individuals who stored more fat in the central abdomen. This gave use to the saying that people who look like pears have little disease, while those that look like apples get sick with the problems mentioned above. See Figure H.

Figure H.

How we store fat is a complex subject discussed thoroughly in the "Weight Management" module of the Health and Nutritional Coaching Course. Where we store the fat, however, is very genetic and influenced by hormones, life stresses, and medications. The description of pears and apples as distinct entities or subtypes is also very artificial, because some individuals start out looking like pears and some years later look like apples. This was the case for our woman back in Figure G. Her first 10-15 pound weight gain went mostly to her hips and did not cause much problem for her docking ports or her insulin levels. Her later weight and fat gains, however, went increasingly to her central abdomen and caused accumulation of fat in her cells that led to dysfunction of the insulin receptors. I suspect that if the woman in Figure G had gotten her body weight back to 140-145 pounds (fat mostly just on her hips) that her insulin resistance would have been mostly gone, and her sugar, insulin, and HOMA-IR would have returned to nearly normal. (Even though she still had hip fat and was heavier than she was at age 25.

PREVENTION OF INSULIN RESISTANT DIABETES
Chapter 4

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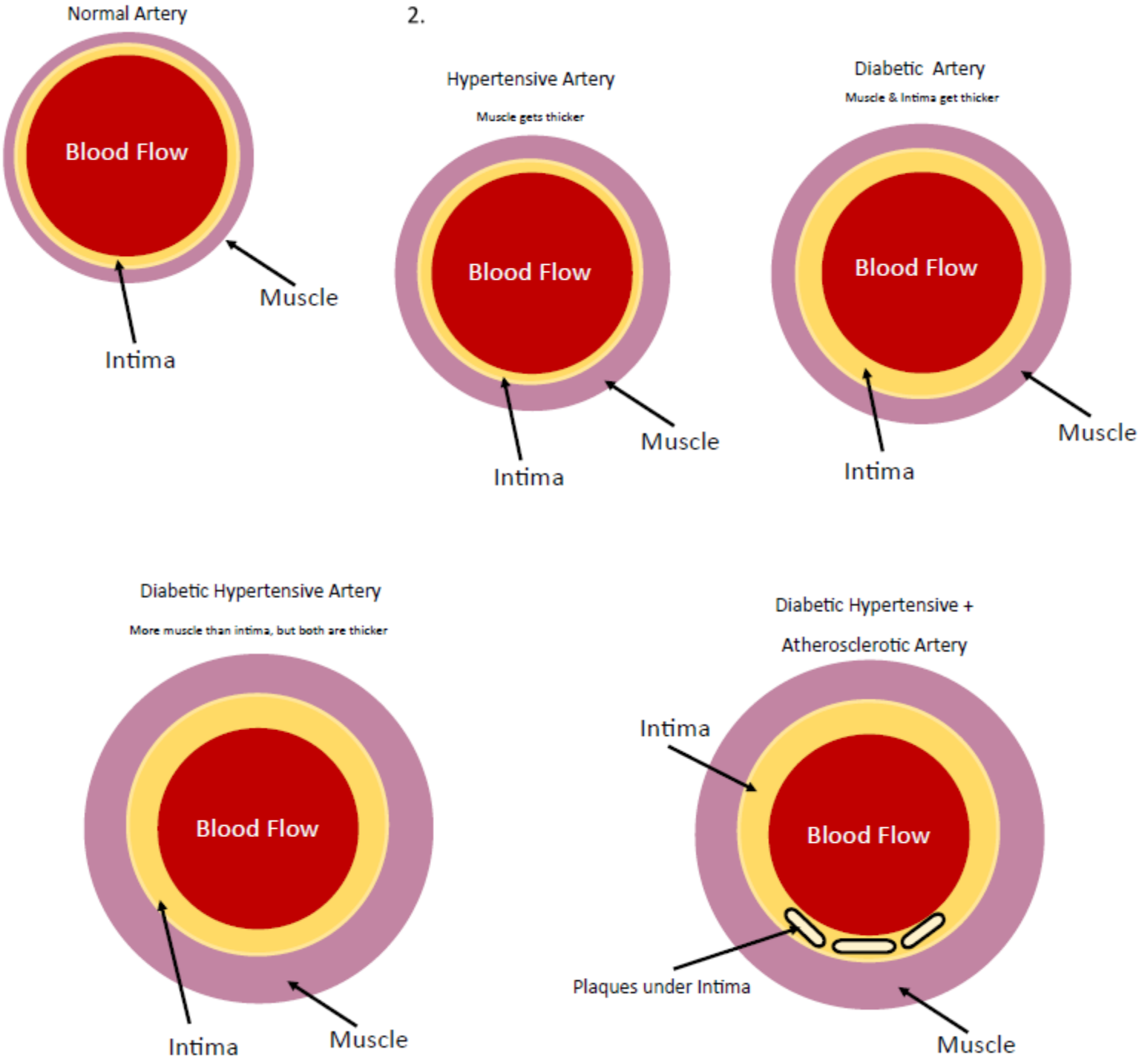
IV. BAD Outcomes of Insulin Resistance

Based upon the model from chapter 3, almost everyone with insulin resistant diabetes (or earlier insulin-resistance with high normal blood sugar) can reverse the dysfunction of the docking ports (receptors) by losing body fat, especially the fat stored in liver cells and the central abdomen. This may require very little or a great deal of fat loss, depending upon the genetics of fat storage of each individual. I have seen patients who became "non-diabetics" after 5-10 pounds of fat loss and others who required 50-100 pounds of fat loss before their blood sugar normalized. Use of DEXA scanners to assess amounts of fat stored in the abdomen and hips is helpful and a wonderful tool for those interested in body composition management. Nevertheless, the bottom line is that for most of us, until insulin resistance is gone (very low HOMA-IR), more fat loss is needed. That is why I encourage all of you who are reading this material to immerse yourselves in the labs, and textbook materials, and the accountability visits that are the substance of the Insulin Resistance Module of the Health and Nutritional Coaching Course. For most of you who have insulin resistance, fat loss may be enough for you to be totally well. For some of you, the daily need to manage blood sugar levels may be important for many weeks or months. There is certainly some crossover between what an insulin resistant diabetic must know and understand and what those who have normal blood sugar levels, but too much body fat ("non-diabetics"), must know and understand.

In fact, if we define "diabetes" as beginning when the liver cells are first overfed. – (see drawing B of Figure G), Most overweight adults need to understand this module as well as the Weight Management Module of Health and Nutritional Coaching. There are thousands and perhaps millions of adults who are insulin resistant and do not know it (because they have not measured HOMA-IR or even know what it is). Even the individual who used to have a HOMA-IR of 0.5 and now has an equally "non-diabetic" HOMA-IR of 1.5 or 2.0 is really in trouble and needs to know it and to do something about it (i.e., begin to lose body fat or "under feed" his or her cells for a while).

For those of you with insulin resistant diabetes who have to manage blood sugar daily, the rest of this chapter is for you. We should perhaps begin with a brief discussion of the cost of not managing blood sugar levels and insulin levels. As I noted above, the major pathology associated with high sugar and/or high insulin levels is damage to the inner lining of tiny arteries called arterioles.

Figure J.



The <u>first</u> artery in Figure J is that of a healthy young person. It has normal thickness of the muscle and the inner lining (intima), and has lots of room for blood to flow to

whatever organ it is supplying. The second artery is that of someone who has had elevated blood pressure for a number of years. The muscle in the artery wall has become thicker but the inner lining (intima) is still thin and healthy looking (unless blood pressure has been acutely and severely elevated). The room left for blood to flow is still pretty good, but not as good as in the first artery.

The third artery is that of someone who has had elevated blood sugar (and probably insulin as well) for many years. The muscle in the artery is still pretty normal in thickness, but the internal inner lining has become thickened and sometimes inflamed because of high insulin and/or sugar levels. No one knows for sure how this happens or whether the problem is high insulin or high sugar or both. Insulin in addition to its role in fitting into and opening the docking ports (receptors) also has the capability of causing some cells to grow and multiply. This might be okay in some places in the body, but not in the lining cells of the artery. Sugar itself appears to damage the artery lining cells (intima) by causing accumulation of fat and sugar byproducts (glycerol) in the artery lining cells. Regardless of whether the intima lining is damaged by sugar or insulin, the result is a thicker lining that is vulnerable to accumulation of inflammatory products and fat. This accumulation may ultimately develop the plaques that rupture and cause heart attacks, gangrene, and strokes. As you can see, the third artery still has pretty good central opening (diameter) to allow blood to flow to whichever organ the artery is supplying with blood.

The fourth artery is obviously in trouble and does not have a lot of room left for blood to flow. This is the artery of a person who has had both high blood pressure and high sugar and insulin levels (diabetes) for a long time. As you can see, the muscle is thick from the high blood pressure, and the inner lining is thick from the insulin and sugar damage – leaving not much room for blood to flow.

The last artery is one like the previous artery, but in addition there are several areas in which the intima lining has become inflamed and has developed “plaques” under the lining. These plaques are full of damaged, oxidized cholesterol, and other fats. The exact cause of these accumulations remains a mystery at present, but high levels of insulin, sugar and cholesterol are the biochemical background for this arterial damage in many individuals.. There are many individuals who develop atherosclerotic plaques in their arteries and do not have high sugar and insulin levels, so causes of atherosclerosis are probably many. Nevertheless, high glucose (sugar) and insulin levels in the blood are the background for the fourth and, in many cases, the fifth artery shown on the previous page. With progressive narrowing of small arteries going to all organs of the body, blood supply to vital tissues in many diabetics slowly decreases. This is why individuals with years of diabetes develop signs of disease in so many organs. Blood flow may be lost to nerves (neuropathy), eyes (retinopathy), kidneys (nephropathy), heart (cardiomyopathy), skin (ulcers), toes, fingers, and a host of other places. Sudden clotting of larger arteries may occur due to poor blood flow or rupturing of plaques shown in artery number 5 above.

Obviously, everyone with diabetes or diabetes and high blood pressure does not get these so-called vascular complications, but many do have tremendous amounts of pain, suffering, and health care costs.

The moral of the story is that, if high sugar levels and high insulin levels – singly or together – can cause arteries like number 3, 4 or 5 above, we need to do whatever we can to control blood levels of both of them. The best long-term management and chance for normalizing sugar and insulin levels comes with consistent depletion of fat from the cells as discussed above – and in more detail in our Weight Management Module of the Health & Nutritional Coaching Program. The shorter term management of blood sugar levels and insulin levels on a daily basis falls into the two general categories of pharmacologic and behavioral.

PREVENTION OF INSULIN RESISTANT DIABETES
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V. Pharmacologic Management of Diabetes

The pharmacologic management of insulin resistant diabetes (Type II diabetes) has been going on for the past 60 years, and has been in a continual state of change over that time. It is likely that whatever I say is the current best drug therapy will likely be wrong ten years from now because new agents that influence blood sugar and insulin levels are forever being developed by researchers and pharmaceutical companies. Nevertheless, with that disclaimer, I will try to give you an idea of where we have been and where we seem to be going with drug therapy.

As noted earlier, the first efforts at lowering blood sugar levels in "Type II or Adult Onset Diabetes" occurred without the knowledge that blood insulin levels were actually high or elevated in these individuals. The first commonly used agents arose from sulfa antibiotic research after World War II and were known as "sulfonylureas". These agents worked by stimulating release of bigger amounts of insulin from the beta cells in the islets of the pancreas. They then lowered blood sugar by "flooding the market" with insulin and "pushing open" some of the insulin docking ports (which were likely "gummed up" with fat) to let sugar into the cells. I personally wrote hundreds of prescriptions for many of these including Orinase, Tolinase, Diabinase, and others. I thought that I was helping my patients, but may (if insulin causes vascular damage), have been hurting them while I was "controlling" blood sugar levels. In fact, one very large study done at many university academic medical centers with thousands of patients enrolled, showed that those who received sugar lowering drugs had many more heart attacks over a ten-year period than those who managed their sugar with diet and exercise. This study (UDG study) made many enemies in the academic community, and many "flaws" in the study left us all not knowing what to believe. "Safer and newer" sulfonylureas replaced many of the older ones, and we proceeded on stimulating the pancreas to make more insulin.

The knowledge that insulin resistance and not insulin deficiency caused diabetes (during the 1980s) gradually led to a change in pharmaceutical agents available to doctors and their patients. The first of these agents was metformin (glucophage), which seemed to work by modifying the docking port or insulin receptor and allowing insulin to "fit into the dock" more easily (in spite of the fat still in the cell). This drug has now been around for over 20 years and has become a mainstay of therapy for insulin-resistant diabetics (because it lowers insulin needs and blood levels while it lowers sugar levels).

Another group of agents (glitazones) entered the market in the 1990s. They also work by decreasing insulin resistance, and are used in patients who cannot control sugar with metformin alone (and dietary and activity changes discussed below). Unfortunately, these agents have had some serious side-effects (liver failure) in some patients, and at least one of these agents had to be taken off the market for this reason. The glitazones have some very positive benefits, however, and they will likely continue with metformin for some time in the future.

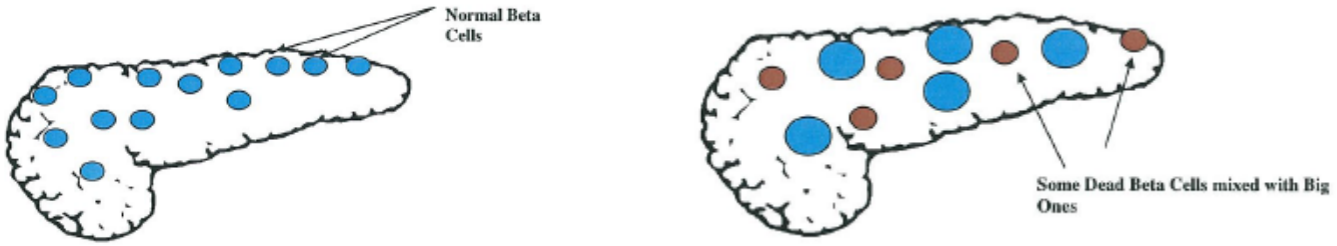
In recent years, a third group of sugar lowering, insulin-resistance reducing agents have become available. These are derived from saliva of lizards (Januvia and Byetta) and are being added as a "third agent" to try to get blood sugar levels lower in patients who cannot be "controlled" with the first two groups of drugs.

Unfortunately, there is one other complication of having high sustained insulin production that I have not discussed previously. As you have seen, our pancreatic beta cells respond to the challenge of a fatty liver and sick insulin receptors by making more insulin. The islet cells actually get larger in size as they are asked to "step up to the plate" and increase production. This process of overproduction of insulin may go on quite well for a long time, but apparently is not without a cost. In laboratory animals – and likely in humans as well – over-worked beta cells seem to "burn out" and become scarred and die. The exact time course of this beta cell death syndrome is probably quite variable from person to person, but the final result is a pancreas that looks more like the pancreas of a type I insulin-deficient diabetic – i.e., one with fewer than normal beta cells and decreased capacity to make insulin. The above data would suggest, however, that the best time to manage insulin resistance is when it begins – and not when the pancreatic beta cells are half dead from being overworked. Figure K shows the process of overworked hypertrophied beta cells dying. We can actually measure how much "beta cell reserve" is present at any time in a person with type II diabetes by measuring blood insulin levels serially – (or one of insulin's pieces called C-peptide). When insulin levels come down in a patient who has not lost weight, the process of beta cell death is probably well established. The "word to the wise" for all of us is to reverse the problem early before the pancreas has been damaged so much that even good behaviors cannot cure the problem.

Figure K.

Healthy Pancreatic Beta Cells

Later Type 2 Diabetes



Using insulin injections does have one bright side; however, giving injected insulin decreases the amount of insulin that the pancreatic beta cells have to make. As discussed above, the beta cells are chronically "overworked" in insulin-resistant diabetics, and there is considerable evidence accumulating that chronic over-stimulation

of the beta cells to make more insulin (because of docking port disease and secondary elevated blood sugar levels) causes slow but steady burnout and death of the beta cells. If this is true, many individuals who begin in their 30s with insulin resistance end up in their 50s with insulin deficiency (or relative insulin deficiency). If beta cell burnout occurs after some period of insulin over-production (and I believe from my literature review that it does), we need to intervene much earlier in the insulin resistance process (see Figure G, drawings 2 and 3 on page 16). In other words, if we can underfeed the cells and get rid of fat from the cells, we can improve docking port function (insulin-resistance), decrease blood sugar levels, decrease insulin need, and prevent burnout and overuse dysfunction and death of beta cells.

As you can tell by now, I am grateful that we have drugs and injected insulin to lower sugar levels, but I prefer behavioral management of sugar if it is enough to do the job. Even if drugs and insulin are needed to control sugar levels, there are obviously very important behaviors involving nutrition and activity that can make drug management easier and more effective. The remainder of this chapter will discuss these behaviors.

PREVENTION OF INSULIN RESISTANT DIABETES
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VI. Behavioral Management of Blood Sugar Levels

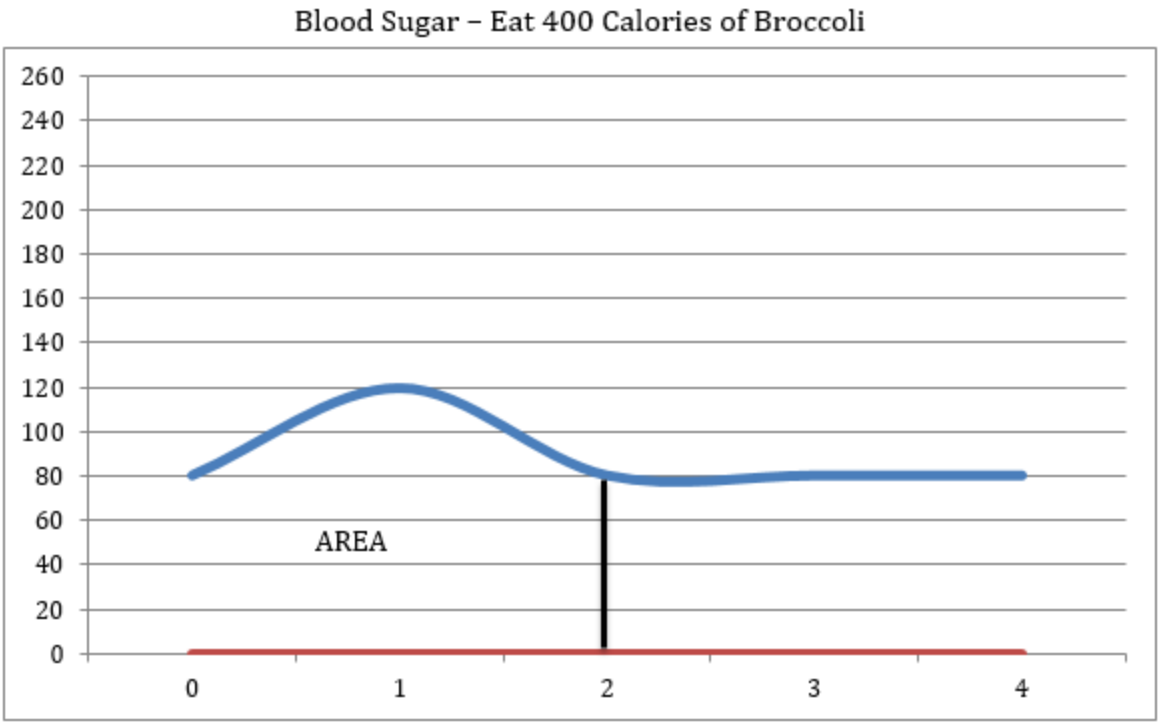
There are two principle behavioral areas that influence blood sugar on an hour by hour and day by day basis. Whereas, loss of body fat through activity and dietary change may eventually "cure" insulin resistance, there are clearly activities and dietary behaviors that can cause acute changes in blood sugar and insulin right now – today.

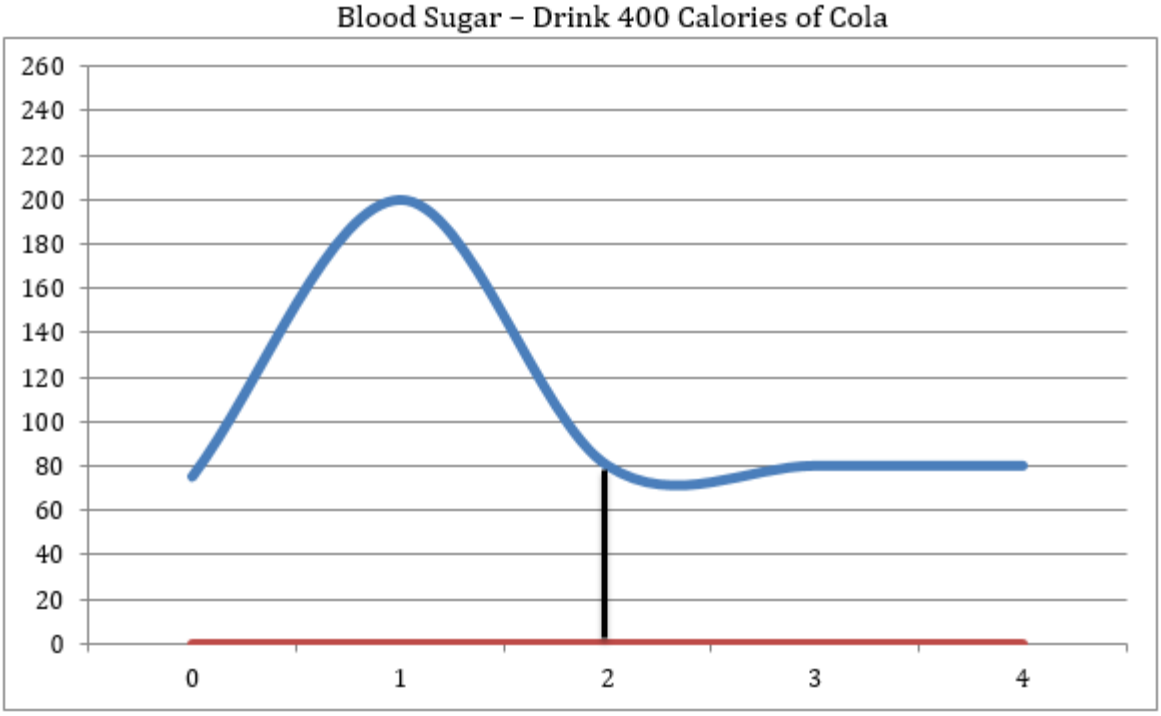
In fact, physical activity of all types causes an increase in sugar usage in the heart and muscle cells – regardless of insulin resistance – and can cause blood sugar levels to drop acutely. This by itself will decrease how much insulin needs to be produced daily in the pancreas and is, of course, necessary (in most of us who eat food) to allow us to lose body fat. The majority of people with insulin resistant diabetes do not do enough exercise to totally control blood sugar, but in a great many, activity alone in high amounts would likely keep blood sugar and insulin levels in a normal or near normal range.

Obviously, we all have to eat, and as long as we absorb what we eat from our intestines, blood sugar levels will rise whenever we eat. In people with "docking port disease" (insulin-resistance or Type II diabetes), eating will cause the blood sugar to rise higher than it would in someone who has no insulin resistance – regardless of the food consumed. The interesting point, however, is that "what" is consumed has a tremendous effect upon how high the blood sugar rises after eating and how long the sugar stays elevated. This phenomenon is now known as the "Glycemic Index of Food," and it is becoming increasingly accepted as an important dietary management tool in the management of blood sugar. The glycemic index is important for both insulin deficient and insulin resistant diabetics. For the insulin deficient patient, how high the sugar rises after eating a food and how long it stays up determines how much insulin needs to be injected with an insulin pump or by syringe. For the insulin-resistant patient, how high the sugar rises after eating food and how long it stays up after it rises is important in determining how high his insulin level has to rise to get sugar to go into the cells. If the high insulin levels and high sugar levels likely are "toxic" to his or her arteries, it would be much better to eat a food with a low glycemic index than a high one. Figure L below shows a graph of blood sugar levels recorded following consumption of the same number of total calories (400) of broccoli and a cola drink by the same patient.

See Figure L. (next page)

Figure L.





As you can see, in this normal non-diabetic patient, the blood sugar was much higher following the coke than it was after the broccoli, because the sugar from the 400

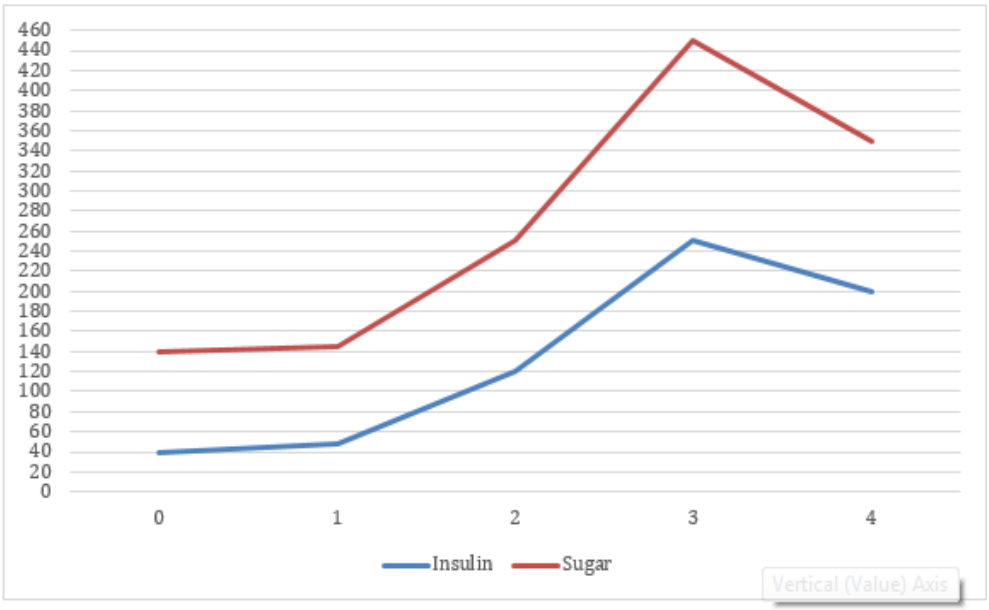
calories of cola was absorbed much more rapidly than the same amount of sugar (400 calories) coming from the broccoli. The blood sugar dropped back to normal by two hours past consumption for both foods, but the "area under the curve" is much greater for the cola than for the broccoli. The cola is said, therefore, to have a higher glycemic index than the broccoli. We have supplied glycemic indices for many common foods in the handouts section of your Insulin Resistance Management Notebook. An internet site is available at (www.glycemicindex.com) and covers indices of even more foods. However, not all foods have been tested to determine their glycemic indices. As you can see, there is a very broad range of glycemic indices for common foods that we all consume. Why is the index important? A glance at Figure M below will give you a clue. As you can see, I have now added insulin levels to the cola and broccoli graphs. The amount of insulin needed to normalize the blood sugar for the cola is much greater than that required to normalize sugar after the broccoli. In other words, foods with high glycemic indices necessitate release of more insulin from the beta cells of the pancreas than foods with low indices (for normal people or for the patient with insulin resistant diabetes). For the patient with insulin deficiency, more insulin must be injected after consumption of a high glycemic index food than a low one.

Figure M.

In figure N, we see the same graphs for a patient who has insulin resistant diabetes. As you can see, this patient's fasting blood sugars and insulin levels are higher at baseline than those of the non-diabetic patient in Figure M. In addition, the sugar and insulin

levels rise to a much higher level with the cola and a somewhat higher level with the broccoli, than with the non-diabetic in Figure M. Obviously, the person with insulin resistance should try to avoid high glycemic index foods.

Figure N.



In summary, every food that contains carbohydrate

has a glycemic index, and foods with high glycemic indices elevate blood sugar, keep the sugar levels high longer, and keep already elevated insulin levels even higher for longer periods of time after food consumption. The overfeeding syndrome that begins the process of insulin resistance (Figure G – drawing 2) is obviously aggravated by high glycemic index foods. Some individuals are genetically more likely than others to respond to the overfeeding with accumulation of fat in their liver cells and the sickness of the insulin docking ports (receptors) that follow.

Body weight and fat stores are controlled by energy balance – total calories in and total calories out – whether from broccoli or colas. The insulin resistance syndrome, however, while ultimately related to abnormal fat stores, is triggered more rapidly in genetically-at-risk people by their consumption of high glycemic index foods.

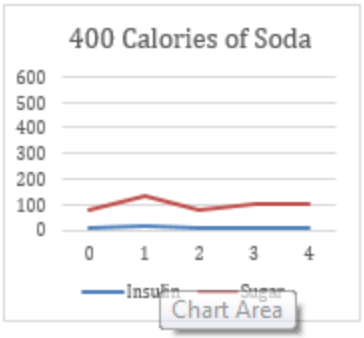
All of us, whether we have insulin resistance or not, need to be familiar with the glycemic index of foods to which we are frequently exposed. For this reason, we have created a number of food laboratories committed to the concept of teaching the glycemic index. In a diverse universe with a multitude of foods available, we need to have a good understanding of both concepts if we are to maintain optimal health.

I would like to finish this chapter by feeding a cola drink of 400 calories to our patient back in Figure G as she progresses from age 25 to age 55. Since by now you have all become adept at reading glucose and insulin graphs, you should be able to understand what is going on.

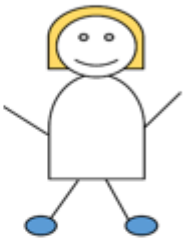
See Figure O. (next page)

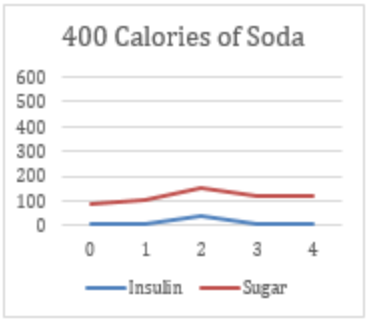
Figure O.

Age: 25
Weight: 125lbs
Fasting Sugar: 80 mg/dL
Fasting Insulin Level: <2
HOMA IR: 0.4

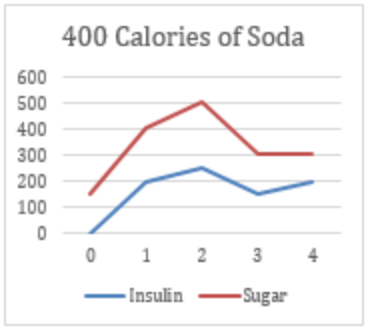


Age: 35
Weight: 135lbs
Fasting Sugar: 90 mg/dL
Fasting Insulin Level: 4
HOMA IR: 0.8

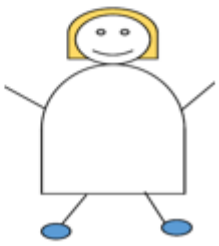


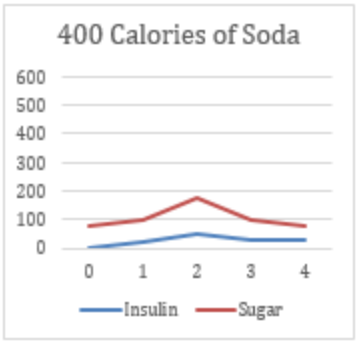


Age: 45
Weight: 145lbs
Fasting Sugar: 105 mg/dL
Fasting Insulin Level: 12
HOMA IR: 3.2



Age: 55
Weight: 155lbs
Fasting Sugar: 139 mg/dL
Fasting Insulin Level: 26
HOMA IR: 8.5

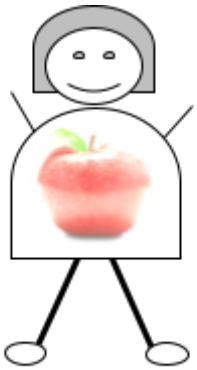




Please note: All graphs display levels after drinking 400 calories of soda

As you can see, the patient's fasting sugar levels and insulin levels have slowly risen over the years as body weight and fat content have risen. The big jump in both sugar and insulin did not occur with the first 10 pounds of hip fat (pear appearance) but rather with the next 10 pounds when she gained abdominal fat (apple appearance). As her weight has increased to 155 pounds with more abdominal fat, she has developed marked insulin resistance and frank "insulin resistant or Type II diabetes."
Figure P below shows the same patient five years later in two separate scenarios.

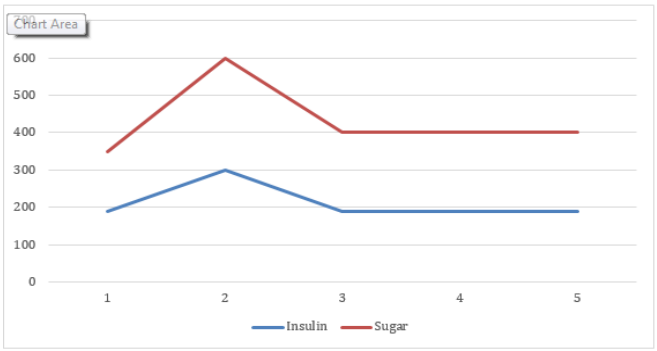
Figure P.

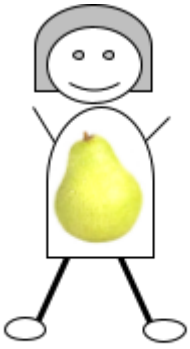


60 Years Old
Weight: 180 pounds

Fasting Sugar – 180 mg/dL
Fasting Insulin – 25
HOMA IR – 10.2

"Apple" Shaped

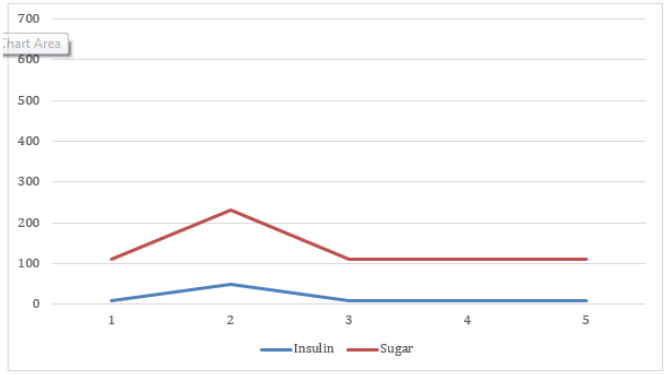




60 Years Old
Weight: 138 pounds

Fasting Sugar – 95 mg/dL
Fasting Insulin – 5
HOMA IR – 1.2

"Pear" Shaped



Please note: Graphs indicate levels after drinking 400 calories of soda

HOMA IR = Insulin Resistance Factor
Fasting Sugar x Fasting Insulin / 405 = HOMA IR

In scenario number one, the patient has gained 25 more pounds in five years. She now is truly diabetic and is taking metformin, pioglitazone, and Januvia to "control" blood sugar. Even on these medicines her sugar is too high, and she likely will need insulin injections shortly. Interestingly, her insulin blood levels are actually a little lower than they were five years earlier – evidence that her pancreatic beta cells are wearing out and dying off due to the chronic need to overproduce insulin. She likely is developing damage to the inner lining of her arteries and is increasingly vulnerable to all of the terrible complications of this process.

The patient in part 2 of Figure P has participated in all of the modules of Health by Design's Health and Nutritional Coaching Program. Having learned at age 55 the story of insulin resistance and its complications, she has been making major changes in her diet, her activity level, her body composition, and her health screening. She has lost all of the abdominal fat gained between ages 35 and 55.

Hopefully patient number 2 above is you. As you read this material, and do the nutrition labs, I trust you are embracing health, working on improving body composition and decreasing insulin resistance if you have already developed it. Hopefully also the glycemic index food labs have been stimulating to you and enhanced what you have learned in this course. I wish you all Health by Design.

David M. Player, MD