

# New Insights and New Therapies for Insulin Resistance

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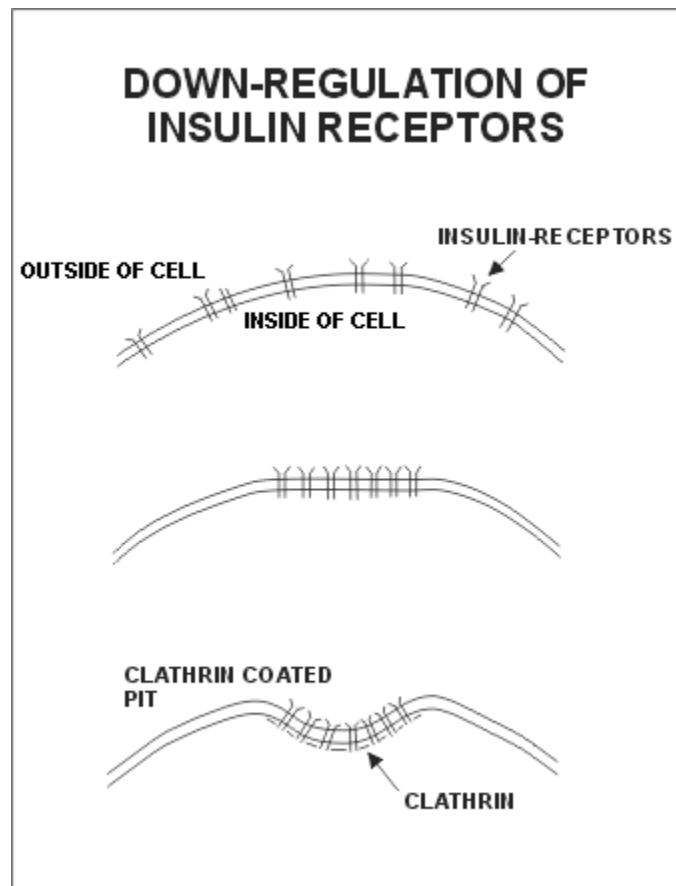
## WHAT IS UNDERSTOOD BY "INSULIN RESISTANCE"?

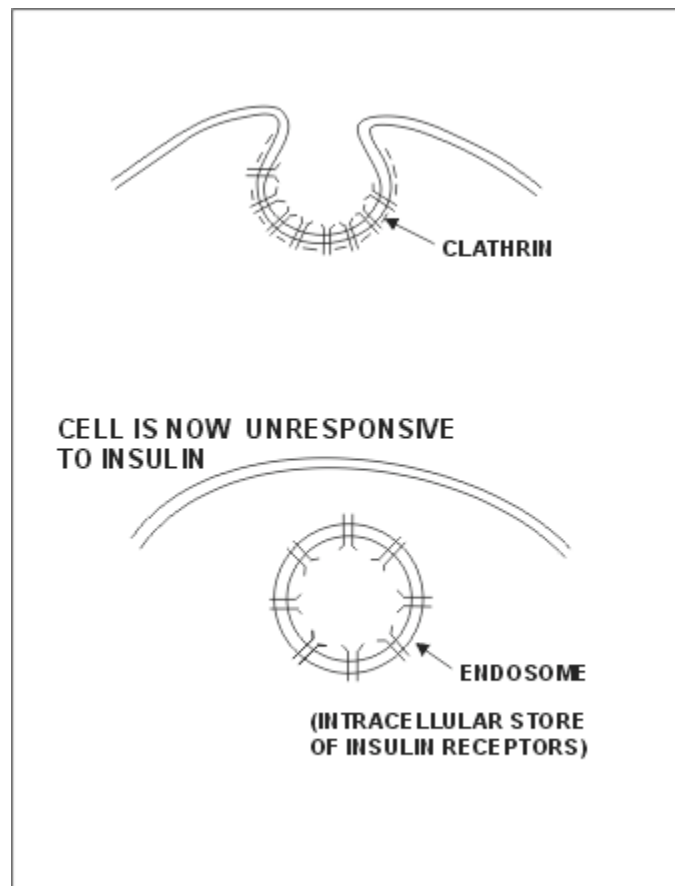
"Insulin-resistance" is the hallmark of Type 2 Diabetes Mellitus, as well as of the "Metabolic Syndrome" which is considered to be the "pre-diabetic" form of Type 2 Diabetes Mellitus. In Metabolic Syndrome the blood sugar level is normal, but the insulin level keeping it there is higher than normal. It becomes Type 2 Diabetes Mellitus when the early morning (pre-breakfast) blood sugar level is higher than normal, and sugar starts to appear in the urine at various times during the day, particularly after meals. In Type 2 Diabetes Mellitus the patient can still secrete insulin into the blood, but that insulin does not seem to be as effective as it is in normal people.

Insulin-resistance is defined as any condition in which the plasma insulin concentration is higher than the blood sugar level suggests it should be. It is therefore, not unreasonably, interpreted to mean that insulin is not as effective at lowering the blood sugar level as it should be, i.e. there is "resistance" to its action. The nature of this "resistance" is a major unsolved problem in medicine and physiology, although recent insights have dispelled much of the mystery, and therefore opened the way for new and highly promising therapeutic possibilities.

## HOW DOES "INSULIN RESISTANCE" COME ABOUT?

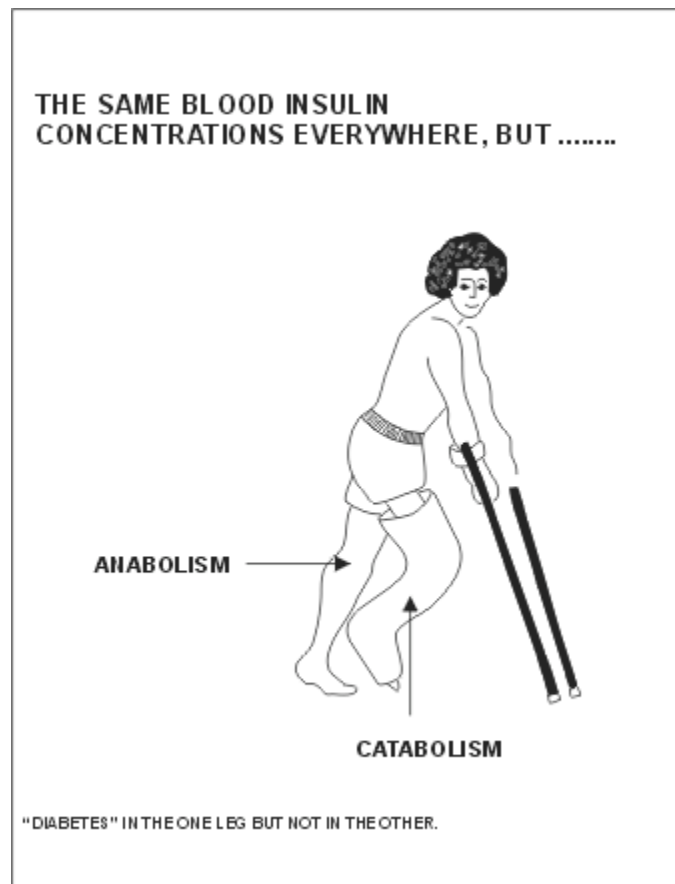
One way in which the tissues can become truly "resistant" to insulin's actions results from the removal of insulin receptors from the surfaces of their cells (so-called "down regulation" of insulin receptors).





Insulin is a protein hormone which is secreted into the blood by the beta cells of the pancreatic islets when the blood sugar level is high. It is spread throughout the body by the blood stream. It then affects only those cells which have receptors on their outside surfaces for insulin. Insulin receptors are molecules into which insulin, and only insulin, can fit in the manner of a hand into a tailor made glove. A cell without insulin receptors on its outside surface cannot respond to the presence of insulin in the blood. Conversely a cell with plentiful insulin receptors on its surface will respond vigorously to the presence of insulin in the blood, usually by removing glucose from the blood and turning it into glycogen or into fat. These are then stored within the cell (or, sometimes, the fat is exported to the adipose tissue, where it is then stored inside the fat cells).

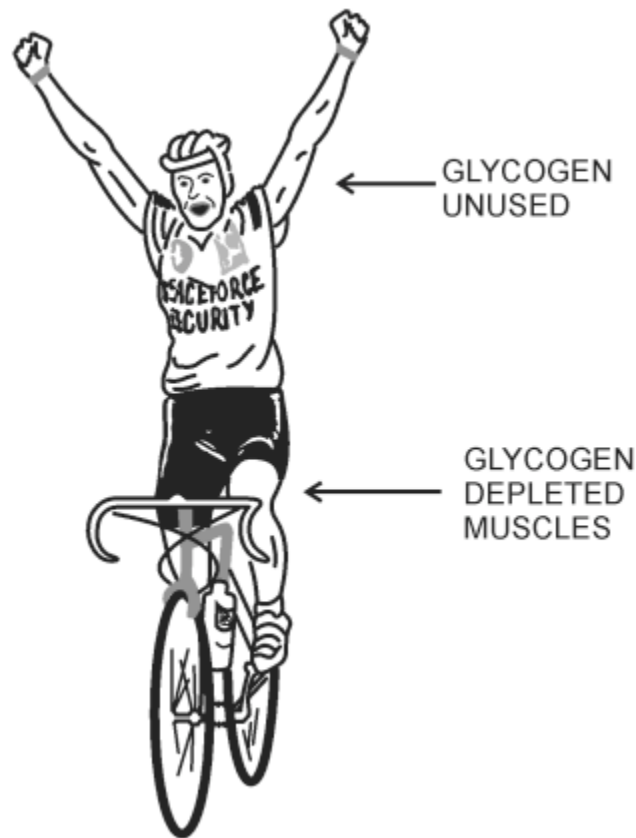
The cells which store glycogen (especially muscle cells) or fat (fat cells) have the ability to remove the insulin receptors from their surfaces, and store them inside "endosomes" within the cell. This is called the "down regulation" of the insulin receptors. They do this when the cell is full of glycogen or fat, or if it has not been active for a long time. Thus, the muscles of a leg which has been splinted (in the treatment of, for example, a fracture) remove insulin receptors from their surfaces, with the result that they store very little glycogen, and become atrophied, i.e. they become thinner.



In addition to stimulating cells to take up glucose for storage as glycogen or fat, insulin is also essential for stimulating or maintaining protein synthesis in many cells.

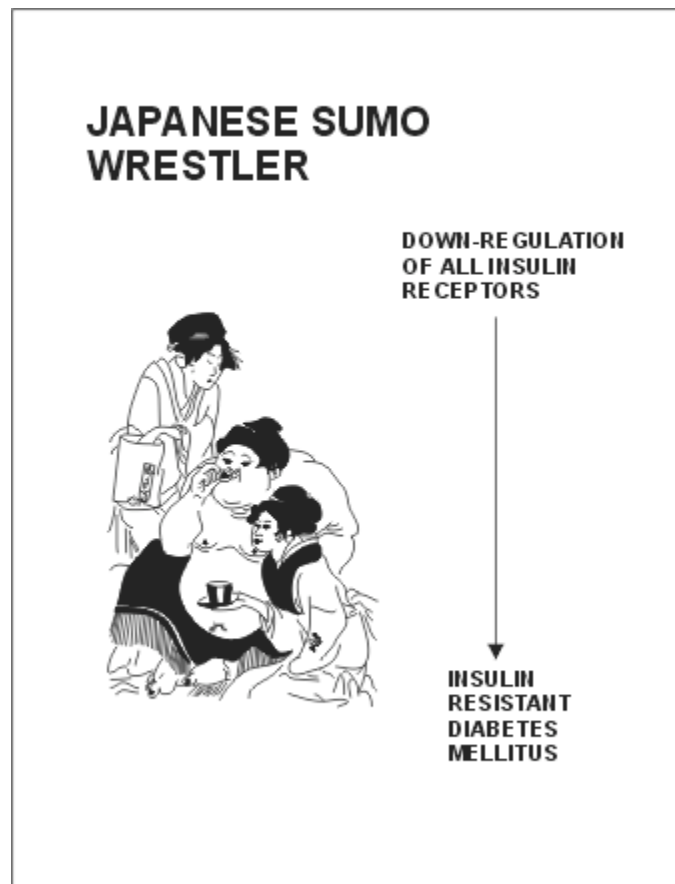
A muscle cell that is full of glycogen or an adipose tissue cell that is full of fat will also down regulate its insulin receptors, thus becoming resistant or unresponsive to insulin's presence in the blood. Conversely cells whose glycogen or fat stores have been depleted by starvation or exercise return the insulin receptors to their surfaces. This makes them hypersensitive to the presence of insulin in the blood.

The importance of this mechanism can be seen, for instance, after a cycle race. At the end of the race the cyclist will have used up most, if not all, of the glycogen in his leg muscles, but his arm muscles which have hardly been used, still retain most of their glycogen.



If there were no way of down- or up-regulating insulin receptors, the next pasta meal that the cyclist consumes would end up equally in his leg and arm muscles. The arm muscles would therefore become bloated (and functionally impaired) with grotesquely large glycogen stores, while the leg muscles remained inadequately stocked with glycogen. In practice, however, the glycogen depleted muscles of the legs up-regulate their insulin receptors after the race, and become exquisitely sensitive to minute quantities of insulin in the blood, while the arm muscles are relatively "insulin resistant". The carbohydrate in the post-exercise pasta meal therefore preferentially ends up in the leg muscles, with almost none being taken up by the arm muscles, despite both sets of muscles being perfused by the identical blood (and therefore identical blood insulin and glucose levels).

Over-eating, as occurs in Sumo Wrestlers during competition rallies, will also result in the down regulation of insulin receptors in, particularly, adipose tissue, but also in muscle.



Champion Sumo Wrestlers therefore nearly always become insulin-resistant and diabetic during the competition season. After the competitions, when they are no longer force-feeding themselves, the insulin resistance lessens, and the diabetes disappears. The insulin resistance mechanism limits the body size they can attain. At a certain point, no amount of over-eating will induce any further weight gain because the tissues are too insulin-resistant to allow further deposition of fat or other material in the cells.

### **"INSULIN RESISTANCE" IN TYPE 2 DIABETES MELLITUS AND METABOLIC SYNDROME IS PROBABLY A MISNOMER**

The form of "insulin resistance" described above, though easy to understand, is probably not the most common form encountered in older persons with Metabolic Syndrome or frank Type 2 Diabetes Mellitus. Many of these patients are not obese, and are not over-eating (certainly not in the manner of the Sumo Wrestlers). Being older, they are by nature less active than the average 20 year-old, but not so inactive that their "insulin resistance" can easily be ascribed to their inactivity. Indeed, most 60 year-olds with Metabolic Syndrome and Type 2 Diabetes Mellitus do not eat more than their healthy age and gender peers, nor are they more obese.

Part of the problem arises from the definition of "insulin-resistance". The inherent assumption in the definition is that a normal blood sugar level should evoke a "normal" insulin response from the pancreas. The higher the blood sugar level rises above the normal level, the greater the amount of insulin that is secreted. A simple relationship is therefore assumed to exist between the blood sugar level and the amount of insulin found in the same sample of blood. If there is more insulin in the blood than is predicted by this relationship, the person must be suffering from "insulin-resistance".

However, it is very unlikely that this apparently obvious relationship exists. During exercise the blood sugar level remains normal (or might even rise above normal, particularly in trained athletes), but the insulin concentration falls drastically. Similarly in starvation. Here too the blood sugar level

is within the normal range, but the insulin level in the blood is very low. Conversely, after a meal, the blood sugar level does rise slightly, but the insulin concentration in the blood rises dramatically. Thus to picture a simple relationship between the blood glucose level and the resulting insulin level is erroneous: a normal blood sugar level can be associated with a very high or very low blood insulin level.

### "INTEGRAL CONTROL" OF THE BLOOD SUGAR LEVEL

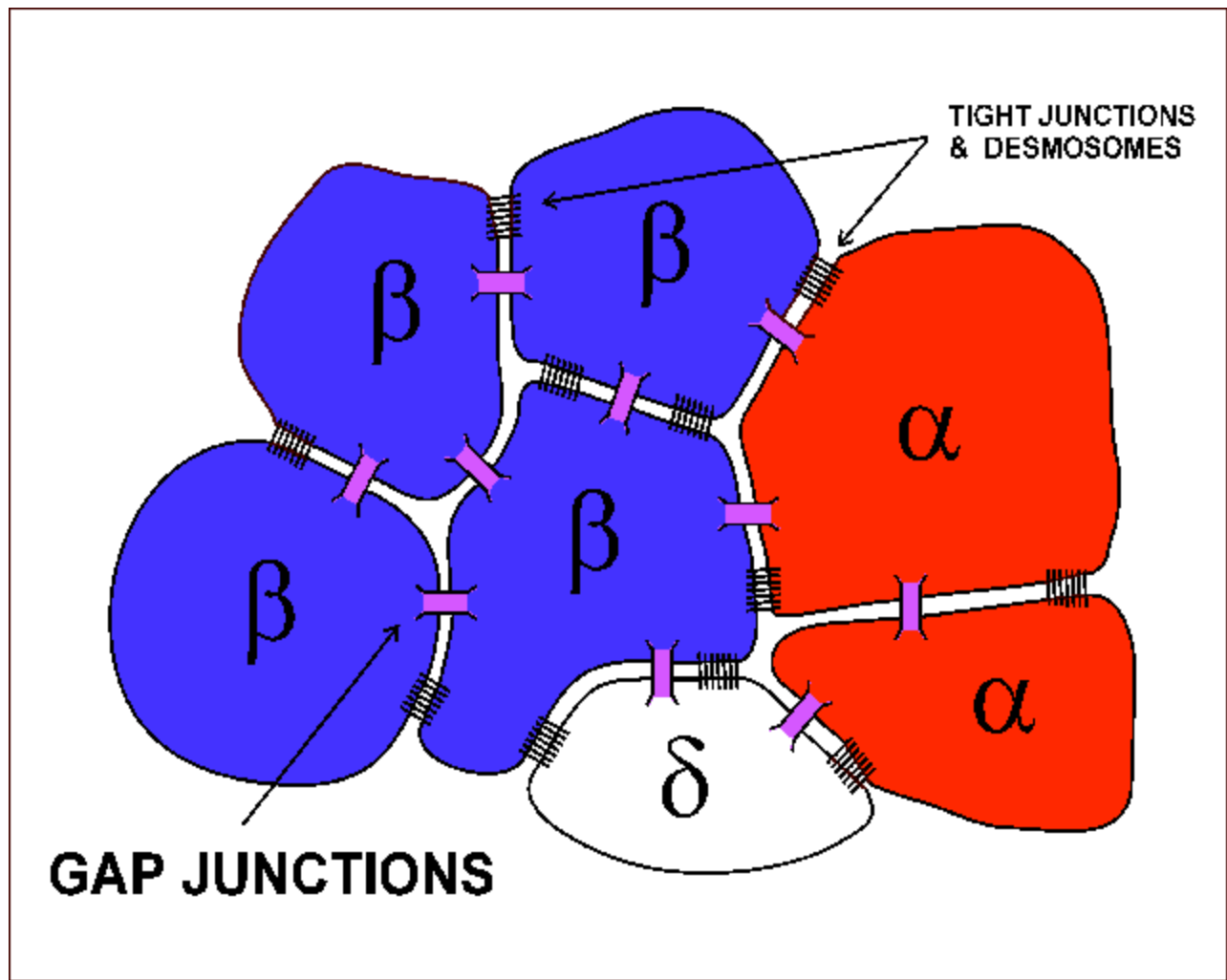
The blood sugar level is probably regulated in the same way that a motorist keeps a car's speed constant at, say, 120 km/hr, while driving along an undulating country road. The motorist does this by depressing the accelerator whenever the speedometer is slightly below 120 km/hr, and continuing to depress it further and further until the speedometer reads 120 km/hr again. Similarly, on a down-hill gradient, the motorist closes the throttle more and more until once again the speed is exactly 120 km/hr. The position of the accelerator when going uphill is very different from the position of the accelerator when going downhill, even though the speed of the car is the same in both cases. One could use the term "petrol-resistance" for the car's performance going uphill, and "petrol-hypersensitivity" for its performance going downhill, but the terms are not very useful. Nor do they represent the real state of affairs; there is nothing wrong with the car's engine, or its sensitivity to petrol.

The glucose homeostat probably operates on a similar principle. Vastly different insulin levels can be found associated with the same (normal) blood sugar level, depending on whether glucose is being used up at a high rate (during exercise) or entering the body at a high rate (after a meal). Such a regulator (whether a motorist, or a beta cell in the pancreas) is called an "integral controller" after the mathematical operation that is used to achieve the constant speed (in the case of the motorist) or the constant blood sugar level (in the case of the beta cell). With "integral control" there is no simple relationship between, say, the blood sugar level and the blood insulin level. With a properly working integral controller a normal blood sugar level can - and should - be associated with any of the possible insulin levels the system is capable of producing, in the same way that a speed of 120 km/hr can be associated, in a perfectly normal car, with both the pedal-to-the-metal and the foot-off-the-pedal situations, as well as everything in between. If this is so, then "insulin-resistance" requires urgent redefinition. In fact, except in the case of the Sumo Wrestlers and in certain mutations, it might not have any sensible meaning.

### AMYLOID IN TYPE 2 DIABETES MELLITUS

In the most common form of Type 2 Diabetes Mellitus (of the elderly), the most consistent abnormality seen in the pancreatic islets is deposits of "amyloid" (a sort of clotted or congealed egg white) between the cells, and especially surrounding the beta cells. It seems to originate from a protein which normal beta cells secrete together with insulin. Its normal function is unknown. Why it clots round the beta cells in Metabolic Syndrome and Type 2 Diabetes Mellitus is also unknown.

One of the effects of these amyloid deposits is that it disrupt the connections between the alpha and beta cells in the islets of the pancreas.

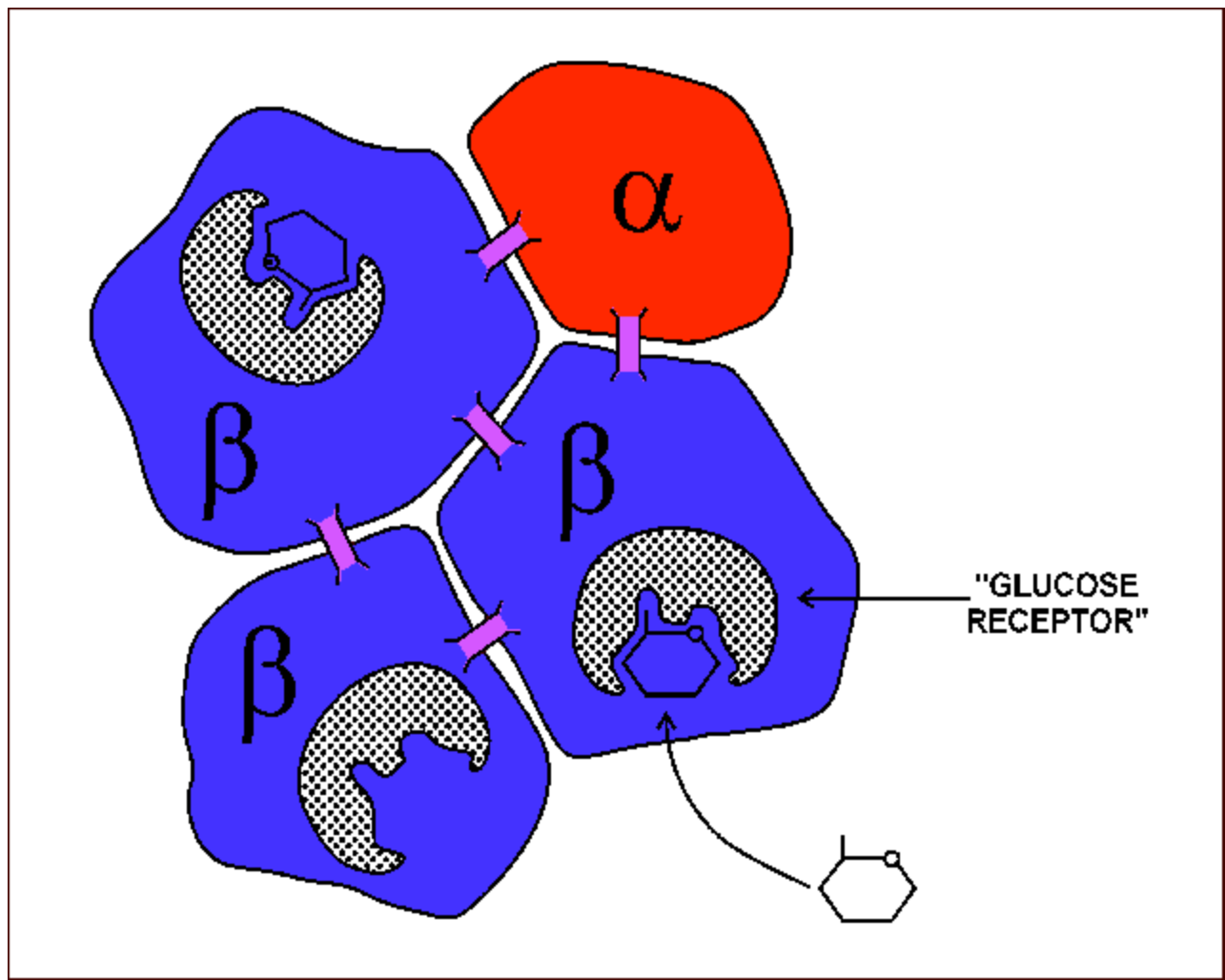


A diagrammatic representation of a normal pancreatic islet, showing the connections, via gap junctions, between the different types of cells.

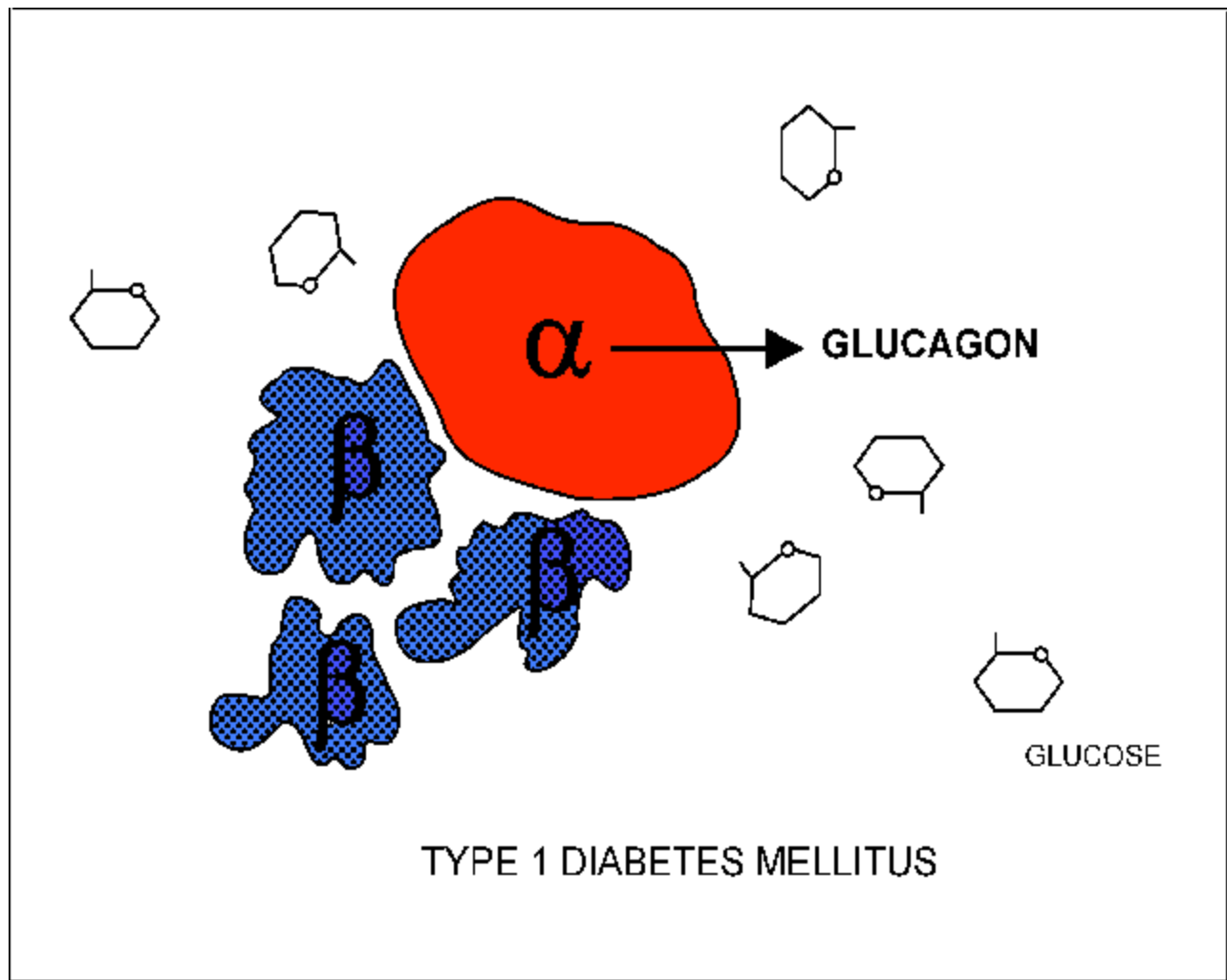
The alpha cells secrete glucagon into the blood when the blood sugar level is low. Glucagon, like insulin, circulates throughout the body, but it is particularly the liver cells which have glucagon receptors on their surfaces. Should these receptors be stimulated by circulating glucagon, the liver rapidly converts its glycogen into sugar which it secretes into the blood. The liver also converts amino acids it extracts from the blood into sugar which it then also releases into the blood stream together with the sugar derived from glycogen. Insulin and glucagon between them, in a normal person, can, therefore, convert the liver from an absorber of glucose from the blood to a secretor of glucose into the blood, and vice versa, depending on the body's needs.

While the beta cells are capable of measuring the blood sugar level, the alpha cells are not.





A diagrammatic illustration of a group of a normal beta cells, each capable of measuring the blood glucose concentration. (The precise nature of the glucose sensor is known in great detail, but is schematically represented here by means of a speckled glucose mould.)



In Type 1 Diabetes Mellitus the beta cells in the islets of Langerhans are destroyed by an autoimmune process. The alpha cells survive, but having no beta cell connections, they produce glucagon at an inappropriately high rate, regardless of the blood sugar level. This indicates that they do not possess glucose sensors of their own, relying, under normal circumstances, on signals from the beta cells to inform them of prevailing the blood sugar level. Thus, in Type 2 Diabetes Mellitus, when amyloid separates the alpha cells from their companion beta cells, the alpha cells also produce persistently high and inappropriate glucagon levels in the blood.

The high levels of glucagon in the blood, in the Metabolic Syndrome and Type 2 Diabetes Mellitus, stimulate the liver to produce unnecessary amounts of glucose. The integral controller responds to this by putting out more and more insulin till the blood sugar concentration returns to normal. This is typically the situation in Metabolic Syndrome: a normal blood sugar level associated with a high plasma insulin level.

Is that "insulin resistance"? It is, according to the definition commonly used for "insulin resistance", but the term is misleading. There is no resistance to the action of insulin; it is just that insulin is responding appropriately to a persistent outpouring of glucose from the liver.

For a fuller discussion of the precise nature of the "insulin resistance" in Metabolic Syndrome, click [here](#).

#### TREATMENT OF TYPE 2 DIABETES MELLITUS

Exercise and a reduction in food intake appear to reduce the severity of the "insulin-resistance" (as

commonly defined) in the Metabolic Syndrome and Type 2 Diabetes Mellitus. But this is only because the high glucose output by the liver is now appropriate. The normal response to exercise or starvation is a high plasma glucagon level. Since the exercising muscles are taking up the resulting extra glucose, the integral controller ceases to secrete insulin. The sugar is then no longer diverted to the fat cells to be disposed of as fat, nor are the muscles converting it to glycogen.

During exercise the blood sugar stays normal with far less insulin in the blood, but there is no more, or less, "insulin-resistance" than at rest.

Hence exercise and weight reduction do not address the central problem of Metabolic Syndrome or Type 2 Diabetes Mellitus. They address an incorrect conclusion drawn from an inappropriate definition. Drugs which stimulate insulin secretion, and insulin administration, similarly do not address the central problem, and are associated with weight gain, and the aggravation of many of the problems in Type 2 Diabetes Mellitus.

At present there is no cure or treatment that will remove the amyloid in the islets of the pancreas.

However, there is hope.....

### **GLP-1 and DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITION IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS**

GLP-1 and DPP-4 inhibitors are currently under investigation as new generation drugs in treatment of Type 2 Diabetes mellitus, capable of powerfully suppressing glucagon secretion. GLP-1 is a hormone secreted by the gut, best known for its ability to stimulate insulin secretion in response to food in the duodenum. However, it has proved to be a powerful inhibitor of glucagon secretion. Thus, when used in the treatment of experimental Type 2 Diabetes Mellitus, it corrects the high plasma glucagon levels, thereby normalising of the blood glucose level and, interestingly (but not unexpectedly), *lowering* of the plasma insulin level. It therefore addresses the root of the problem, causing the so-called "insulin resistance" to disappear, together with all its metabolic consequences. It does so without putting the patient at risk of hypoglycaemia (too low blood sugar levels).

Since GLP-1 is broken down very quickly in the blood, it is not very practical to administer it on a long term basis. However, a number of drugs have been developed which inhibit the enzyme which breaks GLP-1 down in the blood. These DPP-4 inhibitors are proving to be very effective in raising the natural blood GLP-1 levels, and thus curing Type 2 Diabetes Mellitus, and the Metabolic Syndrome.

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Click [here](#) for a PDF version of this JOURNAL OF PHYSIOLOGY article.

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