Chapter 9

Type II and Type III Diabetes

We shall begin here with a few introductory remarks of certain human physiology, particularly its development and aging that relate to many common disorders and syndromes. Much of the body's functions can be grouped into tissues and related cells, and the most common cellular uptake is the glucose whose metabolism with oxygen mediated by insulin provides energy for the cells. Lacking insulin at a young age, or the Type I diabetes, the body must be provided with exogenous insulin dose to survive. Similarly, those adults who have grown into a reduced level of insulin or its utilization later in life would also need an exogenous source of insulin or an insulin-related stimulus for glucose metabolism. They are classified as the Type II diabetes. Since a substantial fraction of the glucose metabolism can be traced to the central nervous system (CNS) as being memory-related, as indicated by some recent experiments related to the cumulation of beta-amyloid formation in the CNS, we simply group this syndrome here as the Type III diabetes as they seem to share certain similar therapeutic procedures as for the Type II diabetes considered in this chapter.

The formation of a healthy CNS structure can generally be considered in two distinct stages, with the first stage, the growth of neurons that peaked at a very early age, age 3, and the second stage, the growth of neural shields that largely terminate much of the random useless neural connections at approximately age 25, an age at which automobile insurance companies would deem the driver to be a responsible adult. Many well-known childhood behavior disorders or syndromes specific to young persons could often be traced to the delayed formation of the neural shields and as the shield structures become established later in life, the random neural communications would cease, and the disorder or syndrome reduced or disappeared. The use of functional MRI could help identify more specifically many of the physical locations and related neutral functions and neural stresses associated with the brain disorders.

As one gets into advanced ages, many youthful events can clearly be remembered while those occurring recently often cannot be recalled. Those youthful events are generally organized into the neural network well before the

age of 25 with a primary neural shield structures and have been re-enforced over and over into multiple neural pathways. They become firmly embedded into the memory bank. But the formation of new neural connections without much stress hormone over recent neural connections and shields are composed at a much shallower level over an aging process, and, without a set of exercise to enforce neural shield formations, new neural connections can easily be digested by proteolytic enzymes in the CNS into reusable oligo peptides, etc. whose imbalance or cumulation in the CNS, in fact, seems to be largely responsible for the excess formation of the beta-amyloid plaques that are toxic to the neurons and therefore the Alzheimer's disease. These introductory remarks present perhaps a much too simplified perspective, nevertheless, they will provide, hopefully, a useful outline for therapeutic procedures.

A note on recent experimental evidence of the brain's memory registration and its recall. The set of brain cells responsible for certain memory registration apparently are the same set of neurons that would deliver the vivid memory recall as ordered by a separate set of cells to initiate the recall functions over a duration of one second or so. Since this recall function is triggered by an activation mechanism similar to muscle functions, they can be enhanced through exercise. That is, without exercise, this activation function will atrophy. "Use it or lose it" is the statement which has often been the theme stressed by many rehabilitation centers.

Diabetes Mellitus, or DM, with Type I for those young patients without proper insulin production to metabolize the glucose, the Type II for adults who develop into reduced level of insulin is a common disease occurring for 5% of U.S. population. Insulin is produced by the islet cells of the pancreas necessary to metabolize glucose, a source of energy for many tissues, particularly the liver, the brain, and the muscle. The insulin molecule is a highly conserved peptide for mammals with the pig and cow's version differing from the human's by only one or two amino acids out of 41, and can generally be used by humans without an immune reaction. The management of blood sugar levels by insulin injection is a tedious affair. There are several insulin types on the market, rapid acting, intermediate acting, or long acting, and can usually best be selected by the user. The key here is not the insulin, but the blood sugar level. If a high sugar level is allowed to persist in the body fluid for a long time, it will polymerize and form harmful polysaccharide (polysa) that can no longer be metabolized and must be removed by antibodies. The accumulation of somewhat randomly produced polysa can overwhelm the immune system. I often use the example of a popular dish "soft shell crabs" to illustrate the problem. The crabs can be kept in a jar without exogenous mineral to shed and grow their shells, they would grow new

shells with structured polysa, which has no sweetness at all in taste. Imagine if such a polysa material is allowed to continuously to grow in our organs, it would interfere with various organ functions such as the eyes, kidneys, and blood supply of the foot. Obesity with a heavy load to the heart and hypertension are also typical for Type II diabetes.

For a mild diabetes mellitus and with proper kidney functions, the drug Metformin, derived from a plant called the French lilac that has been used over the centuries, can be very effective. By enhancing the liver's use of insulin, Metformin is effective in reducing LDL cholesterol and triglyceride levels without causing hypoglycemia as those engaging the usual insulin injections may face. Prescriptions for Metformin have reached 40 million worldwide, or more than twice the population of type II diabetics in the U.S. at 18.6 million.

In a normal body, islet cells would produce insulin after a meal in a pulsed delivery over every six minutes, and the liver would respond to the insulin pulse, not the background insulin level, and utilize up to 90% of the insulin to produce various enzymes such as bile etc. Much of the insulin would be used by the liver after a heavy meal, depriving the brain of insulin and rendering one to sleepiness, as well as to the muscle for tiresome. The insulin and the blood sugar molecules have a rather short half-life of several hours in the body fluid. That is, most blood sugars are new and have not stayed long enough to polymerize into polysa and are harmless. For diabetics, however, the insulin must be injected, and without a pulsed delivery to trigger the liver uptake, mostly only muscle could utilize the imbalance. Therefore the muscle must work an order of magnitude harder in order to make up for what the liver would have used. Nevertheless, it is still possible to do so. Those patients who swim often to purge (not just use) the body with all available blood sugar, can still lead a normal life, eat sweet cakes etc., because without their blood sugar polymerizing into old sugar residues, there is little chance to form polysa to do the damages. In addition to swimming, long walks at the golf course, for example, can also help as long as the patient can purge the blood sugar several times each week.

Smart Insulin

A simple pump for pulsed insulin injection every six minutes into the veins in order to mimic the natural delivery of the islet cells can be very useful, and several States have already approved its use for diabetics. It is particularly useful to recover kidney functions that depend on certain enzymes produced by the liver. Using more gadgets such as the insulin pump pulsing into the vein means that the patient must be able to avoid infections at the point of insulin injection.

While there are many kinds of insulin shots; fact, intermediate and long release, I wonder if the insulin uptake can be designed for a "smart insulin" with its releases at 6-minutes intervals in order to trigger the necessary insulin uptake of the liver after the meal without the use of insulin pump.

The excess of randomly formed polysa interferes with the blood supply of various organs, and may result in blindness, reduced kidney functions and skin ulceration of the foot, etc. This condition is generally irreversible. The situation becomes more savior as the patient gets older. An inventor friend Zhou Lin, has a heat-lamp-like BFS (bio-frequency spectrum) stimulator that is very popular for wound-healing used in most hospitals in China. Both my former secretary's father and a technician's father had diabetes with ulcerated foot. Prior to the usual surgical removal of the ulcerated section, their respective feet healed completely by using the BPS lamp. In fact, one of them even had his kidney function improved from 20-30% to 80%. Unfortunately, this smart lamp, or "magic lamp", is not FDA approved in the U.S. It maybe qualified for clinical trials under the deemed statistics (Chapter 7).

There is some statistical evidence that diabetics have a much higher incident rate of Alzheimer's disease. In fact, some call this disease "Type III diabetes", which we shall address below. An article from the 2009 Feb. 10 issue of PNAS seems to confirm also this insulin-related function common to both of the diseases.

Our laser-like monoenergetic X-ray instrument considered in Chapter 6 was designed for an X-ray microscope, but whose applications now include X-ray diagnostic imaging, low dose mammography, radiochemotherapy (Chapter 10), and the mega-Gray Auger dose useful for localized cracking of the β-amyloid ligands as well as the polysa, and thereby may provide therapeutic value for Alzheimer's disease and diabetes mellitus. Our shoebox-sized X-ray instrument can indeed serve a great variety of applications beyond the conventional X-rays, but the high cost of market entry has so far inhibited its introduction in commercial use. There have been some occasional odd applications that did help support the instrument development. For example, an agency of the Defense Department once announced a proposal solicitation for a portable field X-ray system with a digital imager to be mounted beneath a soldier's stretcher. I thought that our light and efficient X-ray generator could serve very well there, without realizing that the program was "pre-wired" for a major vendor. While working out the project details, the director of the agency told me that he would support us if we could deliver the entire system at 15 pounds. We were able to design the X-ray generator, including the battery, the electronic control, the high

voltage power supply and the X-ray tube at only 12½ pounds. But the imager, which was combined from 4 digital mammography imagers by the major vendor for $25M, would already weigh 45 pounds. Our light generator, therefore, became a non-starter. The director then commented that proposals like ours tried to serve the needs of the last war, while he wanted to anticipate the needs of the next war, where there would be no wounded soldier on a stretcher. For our demonstration, we did receive a token compensation, which occurred a decade ago. What a difference from the post cold war needs of the Army in the Mideast!

A few words on the Auger electrons. Electrons in an atom orbit in shells, with each shell having a precise set of energy levels. When an X-ray photon has energy just above that of the inner shell of an atom, the photon would resonantly scatter with an eight-fold enhanced cross-section, or being resonantly absorbed by the atom. Having generated a monochromatic X-ray beam, we can select the end-window target material to produce X-rays to react with most elements in the periodic table and initiate their inner shell ionization in order to reach an Auger cascade and deliver a very high dose *in situ* to the neighboring molecules, as described in chapter 6. Most chemical and biochemical reactions deal with bond energies below the one eV level, but Auger electrons at 12-18 eV are an order of magnitude or more higher, therefore they can easily disrupt all known chemical and biochemical bonds. We have positioned some moderately heavy atoms like Gadolinium (Gd) into some of the tightly structured molecules like benzene or biological units like plasmid, and they all underwent disintegration upon receiving the localized super-ionizing dose initiated from the resonant X-ray photons that triggered the inner shell ionization of Gd. This mega-Gray dose should be useful for the saccharolytic or the depolymerization of beta-amyloid structures.

After President Reagan died, there was much news coverage on Alzheimer's disease. A pathologist from Pittsburgh showed a diagnostic procedure that caught my attention. Usually the autopsy of an Alzheimer's brain involves the use of a dye with a high affinity to the Alzheimer's plaque, the beta-amyloid ligands. This pathologist altered the dye molecule somewhat by making it more polar (the Pittsburgh molecule) so that the dye would cross the blood-brain barrier, thus allowing the molecule to be injected *in vivo* for healthy persons. He further attached a radioactive methyl ($^{11}CH_3$) to the dye for positron generation using PET (positron emission tomography) for imaging. He found that the ligand in question exists even in normal healthy persons without the disease. Apparently the formation and digestion of the amyloid ligands in the central nerves system (CNS) is a dynamic process, and as metabolic rate slows with age the formation of beta-amyloid ligand increase because there is more amyloid

created than digested and thus the accumulation and polymerization leading to the formation of the toxic Alzheimer's plaques.

Current etiology of the Alzheimer's peptide seems to suggest that it is really a "tombstone" of a complicated series of polymerization processes. Nevertheless, the plaque is certainly neurologically toxic in animal models, and once formed, the digestive proteolytic enzymes can no longer penetrate the polymerized ligands to get in and breakdown the amyloid structure, thus making the process dynamically irreversible. As plaque formation becomes sufficiently thick, it not only blocks the proteolytic enzymes from reaching and accelerating the accumulation, but also brings toxicity to the neurons and etchs out holes in the brain tissue. We need to break into the polymerized structures and allow the proteolytic enzymes to reach into the amyloid structure in order to reverse the process. We need to link the above mentioned Pittsburgh dye with the well known Gd-DTPA, a molecule with Gd caged in the DTPA which is FDA approved and commonly used in MRI (magnetic resonance imaging). That is, instead of displaying the Pittsburgh molecule with $^{11}CH_3$, we could display it with Gd-DTPA using MRI. MRI at ~$750 per scan is less expensive than a PET scan at $3,000. More importantly, with Gd tagging to the ligands we can now use our novel X-rays to help break into the polymerized plaque and allow the existing proteolytic digestive enzymes in the CNS to penetrate the plaques *in vivo*. Note that there are already good animal models of the beta-amyloid ligands using mice as well as biologically active plaques *in vitro*. Similarly, there are good polysa samples for both *in vivo* and *in vitro* models. With our laser-like X-ray system using a Tm target to deliver the Gd-specific Auger dose *in situ*, this combination could be a good start to crack and reduce the toxic plaque and the polysa as a method to manage Alzheimer's disease and diabetes mellitus.

Since both the beta-amyloid and the polysa are a polymerized structure, perhaps both are related to insulin functions. Would the Pittsburgh molecule provide high affinity to them both? I am asking this question because we know so little about the polymerization processes *in vivo* of the amyloid ligands. Are there similar attachment molecules to polysa? Because we already have the X-ray system that can deliver a high ionizing dose *in situ* to the Gd atoms, Gd-DTPA can be chemically attached to almost any molecule that has high affinity to the targeted polysa, and thereby allow our X-ray system to deliver the high dose *in situ* to help reverse the polymerization process.

This cracking of the amyloid ligands may also work in the eye, which is perhaps one of the most complex and important outposts of the CNS. While the body develops, the size of the eyeball grows, and certain speculation states that

the peripheral vision being in-focus is the checkpoint to stop the eye's growth. That is, if peripheral vision is out of focus, the eyeball will continue to grow. The result of the eyeball being too large for its lens is called myopia and can readily be corrected by corrective glasses. But the frame of the glasses would largely block peripheral vision, and during teenage years as the body is growing fast, those with corrective glasses suffer typically an enhanced level of eye-growth and deeper myopia. In fact, this enhanced growing will stop as soon as contact lenses are used or the cornea are flattened by laser surgery, as the cornea is responsible for more than 80% of the focusing power of the eye.

For elderly persons, vision impairment can be attributed to the cornea, the lenses, the ocular tension and blood supply, macula detachment, macula degeneration, transmission of the optical neural paths, etc. I was surprised to learn that for the eye lens, the cataract condition can be linked to the coating of the beta-amyloid ligands.

A common vision impairment of elderly persons is cataracts, the clouding of the eye's lens that may result in blindness. A cataract lens can readily be replaced with a plastic one under a key-hole surgical procedure. The procedure includes the use of a super-cooled rod to attach to the lens, pull out the lens, and insert a plastic one with springs that would readily position the lens into the lens cavity properly upon insertion. The polymerized peptide or ligands that cloud the lens have been reported to be the same beta-amyloid. After all, eyes and optical nerves are a part of the same CNS so that what can be accumulated in the brain could also be accumulated in the eye lens. A Boston group had used the $^{11}CH_3$ attached Pittsburgh molecule to evaluate the presence of beta-amyloid at the eye lens using PET. As the eye lens tissue would continuously grow thicker, if the attached amyloid material has already been grown over and covered by the lens tissue, it could probably no longer be reached by the Pittsburgh molecule. But if the surface layer of the lens has shown positively the presence of amyloid using PET, it should also positively indicate the presence of amyloid by Gd-DPTA, which could even be administered under an eye-drop, and thereby allow the Gd-specific X-rays to deliver the Auger dose to help reduce amyloid accumulation.

Replacing the cataract lens with a plastic one has become a rather routine procedure. But in many countries, such a simple surgical procedure is not available. If an eye drop containing the Pittsburgh molecule with Gd-DTPA can reach the eye lens coated with amyloid ligands, and if our novel X-ray can indeed crack the said ligands, this shoebox X-ray system plus the Gd-based eye drop can perhaps reach more cataract patients than surgical procedures. Another

procedure for the deemed statistics?

CHAPTER NINE FOOTNOTES

9.1) While the pathology of Alzheimer's brain is the toxic plaque composed of beta-Amyloid peptides, and as described in Chapter 9, a nearly mono-energetic X-ray beam is proposed to generate a high dose of ionizing radiation *in situ* with Auger electrons to help disrupt and dissolve the plaque, on the other hand, Tsai *et.al*. has shown that the memory development in animal studies can readily reverse the memory loss with certain chemical treatments as described by what announced under the Howard Hughes Medical Institute of MIT.

Memory of the brain is related to neuronal movements, to their positioning, to axon generations, and to dendrite development. Tsai's team has shown that the cycline-dependant kinase 5 with the protein of gene p25 would regulate not only the neuronal migration in the brain, but also correlate the excessive presence of p25 with the formation of beta-Amyloid plaque, and such an excess in a special mouse brain can be reversed with chemical means.

9.2) There was a 10-hour series (September 2010) describing the Brain by Charlie Rose at the TV Channels for Public Broadcasting Corporation. Rose, together with co-host Professor Eric R. Kandel of the Columbia University, a Nobel Laureate on the brain functions, invited researchers and physicians of various aspects of the brain, in functions as well as in disorders, for an open discussion of the current knowledge. It is rather informative and may soon be available as an educational package.

In the 10-hour series, various brain specialists correlated the brain functions, or its lack of, with fMRI as well as with surgical interventions in an anatomical point of view. They considered also psychological and social aspects of behavior, in human as well as in lower form of animals and insets. They did not, however, consider the brain from a cell biology point of view, the view for which I anticipate certain most pronounced discoveries in the coming decades.

CHAPTER NINE REFERNCES

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KEYWORDS

Alzheimer's Disease
Auger *in situ* MegaGray Ionization
Auger Therapeutic Disruption
Beta-Amyloid
Poly-Saccura
Type II Diabetes
Type III Diabetes