

## Understanding Eicosanoids

Strange, mysterious, and almost mystical, eicosanoids are the key to our health because they control the flow of information in our Biological Internet (see Appendix C). Why are eicosanoids so important? They were the first hormones developed by living organisms more than 550 million years ago. As such they can be considered "super-hormones" because they control the hormonal actions of other hormones. Furthermore, you don't have an eicosanoid gland since every one of your 60 trillion cells can make eicosanoids.

Even though they are earliest hormones (dating from 550 million years ago), eicosanoids only were identified in the 20th century starting with the discovery of essential fatty acids in 1929. It was found that if fat in the diet was totally removed, rats would soon die. Adding back certain essential fats (then called Vitamin F) was found to enable fat-deprived rats to live. Eventually as technologies advanced, researchers realized that essential fats were composed of both Omega-6 and Omega-3 fatty acids that both needed to be obtained in the diet because the body could not synthesize them. The word eicosanoids is derived from the Greek word for 20 which is eicosa, since all of these hormones are synthesized from essential fatty acids that are 20 carbon atoms in length.

The first actual eicosanoids were discovered in 1935 by Ulf von Euler. These first eicosanoids were isolated from the prostate gland (an exceptionally rich source of eicosanoids), and were called prostaglandins (a small subset of the much larger family of eicosanoids). Since it was thought at that time that all hormones had to originate from a discrete gland, it made perfect sense to name this new hormone a prostaglandin. With time it became clear that every living cell in the body could make eicosanoids, and that there was no discrete organ or gland that was the center of eicosanoid synthesis. To date biochemists have identified more than 100 eicosanoids and are finding more each year. The breakthrough in eicosanoids research occurred in 1971 when John Vane finally discovered how aspirin (the wonder drug of the 20th century) actually worked: It changed the levels of eicosanoids. The 1982 Nobel Prize in Medicine was awarded to Vane and his colleagues Bengt Samuelsson and Sune Bergelson for their discovery of how eicosanoids play a role in human disease.

### My Journey into Eicosanoid Research

This is where my journey with eicosanoids first started twenty years ago. It was apparent to me that if certain "bad" eicosanoids were associated with chronic disease conditions (like heart disease, cancer, arthritis, and so on), then the key to wellness would be to induce the body to make more "good" eicosanoids and fewer "bad" eicosanoids. Rather than using drugs to achieve that goal, I reasoned I could use food as if it were a drug. All I needed to do was figure out the right balance of protein, carbohydrate, and fat that would turn food into this beneficial drug. After more than 20 years, I think I've come pretty close to that "drug" with the OmegaRx Zone.

Of course, my colleagues in academic medicine didn't quite share my initial enthusiasm. Almost overnight, I went from being a respected research scientist with numerous patents in the area of intravenous drug delivery systems for cancer drugs, to being called a snake-oil salesman because of my constant refrain that the appropriate diet could change the balance of eicosanoids throughout the body. Part of the problem was that very few of them even knew what an eicosanoid was.

I believe that the foundation of 21st century medicine will be the manipulation of eicosanoids. Yet ask most physicians and medical researchers what an eicosanoid is, and you will usually get a blank stare. I guess they're not familiar with the Nobel Prize winning research. As unknown as they are to the medical community, eicosanoids are the hormones that maintain the information fidelity of your Biological Internet, which means they become the key to health and longevity. Why are eicosanoids so unknown if they are so important? First, they are made, act, and self-destruct within seconds making them very difficult to study. Second, they don't circulate in the blood stream making it extremely difficult to sample them. Finally, they work at vanishingly low concentrations making it almost impossible to detect them. Despite these barriers, more than 87,000 articles on eicosanoids have been published in peer-reviewed journals. So, the basic research community is interested in eicosanoids even if your doctor never learned about them in medical school.

Eicosanoids encompass a wide array of hormones, many of which endocrinologists have never heard of. They are derived from a unique group of polyunsaturated essential fatty acids containing 20 carbon atoms. The different classes of eicosanoids are shown below

## Subgroups of Eicosanoids

- Prostaglandins
- Thromboxanes
- Leukotrienes
- Lipoxins
- Hydroxylated fatty acids
- Aspirin-triggered Epi-lipoxins
- Isoprostanooids
- Epoxyeicosatrienoic acids
- Endocannabinoids

Now if you mention the word prostaglandins to physicians, they are likely to have heard of those particular hormones. However, prostaglandins are only a small subgroup of the eicosanoid family. Some of the other subgroups have been discovered only recently. As an example, aspirin-triggered epi-lipoxins are the ones that give rise to the powerful anti-inflammatory properties described in the chapter on heart disease were discovered only a few years ago.

The glory days of eicosanoid research lie ahead with new eicosanoids continually being discovered and a growing realization of the vast role these hormones play in controlling other hormonal systems. This fact has not been lost upon pharmaceutical companies, which have already spent billions of dollars trying to develop eicosanoid-based drugs. Eicosanoids as drugs, however, have a very limited role in the world of pharmaceuticals. They are not only too difficult to work with, but they are also too powerful to be used as a drug.

There does remain one way to directly manipulate eicosanoids: your diet. The reason why your diet can be successful where the largest drug companies have been unsuccessful is based on evolution. Eicosanoids were the first hormonal control system that living organisms developed. You can't have organized life unless you have cell membranes separating the internal workings of the cell from its environment. Since all cell membranes contain fatty acids (including the building blocks of eicosanoids, which are known as essential fatty acids), the cell's own membrane became the ideal reservoir for eicosanoid synthesis since you could always be certain that the raw materials for making these hormones were close by.

As autocrine hormones, eicosanoids' mission is to be secreted by the cell to test the external environment and then report back to the cell what was just outside by interacting with its receptor on the cell surface. Based on that information, the cell could then make the appropriate biological action (via the appropriate second messenger) to respond to any change in its environment.

In biotechnology, one of the hot research areas today is the field of biological response modifiers. Eicosanoids represent the first (and probably the most powerful) biological response modifiers developed by living organisms. In fact, many of the eicosanoids that we make in our bodies today are identical to ones made by sponges beginning hundreds of millions of years ago.

The reason why eicosanoids play such a central role in our physiology is due to the second messengers that certain eicosanoids generate. There are a variety of eicosanoid receptors on the surface of the cell, and depending on which eicosanoid interacts with the receptor, a specific second messenger is then synthesized by the cell. Sometimes a second messenger, such as cyclic AMP is generated, and sometimes a totally different second messenger, such as the DAG and IP3 system, is generated. If one second messenger goes up, then the other goes down. In essence, the complexity of your Biological Internet is reduced to a digital system consisting of green and red lights.

Those eicosanoids that generate increased production of cyclic AMP are your key to maintaining wellness. Why? Cyclic AMP is the same second messenger used by a number of endocrine hormones in the body to translate their biological information to the appropriate target cell. By maintaining adequate cellular levels of those eicosanoids that increase cyclic AMP levels, you are guaranteed that a certain baseline level of cyclic AMP is always present in a cell. Thus, it's far more likely that the overall cyclic AMP level in the cell will be high enough to ensure that an appropriate biological response (i.e. better hormonal communications) is generated.

### **How can you tell a "good" eicosanoid from a "bad" eicosanoid?**

An eicosanoid's effect on second messengers becomes the definition of a "good" or "bad" eicosanoid. A "good" eicosanoid will increase the levels of cyclic AMP in a cell, whereas a "bad" eicosanoid will decrease the levels of cyclic AMP through the elevation of the levels of the IP3/DAG second messengers. The table below shows a listing of the types of "good" and "bad" eicosanoids and their receptors they interact with.

### **Receptors for "Good" and "Bad" Eicosanoids**

Receptor Effect on cyclic AMP

#### **"Good" Eicosanoids**

PGE1 EP2, EP4 increase

PGI2 IP increase

PGD2 DP increase

#### **"Bad" Eicosanoids**

TXA2 TP decrease

PGE2 EP1, EP3 decrease

PGF2a FP decrease

LTB4 BLT decrease

LTC4, Cys-LTI decrease

LTD4, LTE4 Cys-LT2 decrease

Once an eicosanoid interacts with its unique receptor, a second messenger is then synthesized inside in the target cell. If a "good" eicosanoid interacts with the right receptor, then cyclic AMP is the second messenger that is formed. On the other hand, if a "bad" eicosanoid interacts with its receptor then cyclic AMP levels are decreased. Adding further to this

complexity is that some eicosanoids such as PGA and PGJ are cyclopentenone eicosanoids. These eicosanoids don't have cell receptors on the surface as they can directly enter into the cell where they can interact with the cell's nucleus to effect cellular growth and differentiation. Since there is no discrete eicosanoid "gland", there is no central site that turns "on" or "off" eicosanoid action. Nature solved this problem by developing different types of eicosanoids that have diametrically opposed physiological actions. It is the balance of these opposing actions of different eicosanoids to remain an equilibrium of biological activity. These differences in biological actions are the foundation for the eicosanoid "axis". This eicosanoid "axis" is composed of "good" eicosanoids on one side and "bad" eicosanoids on the other. In the absence of the evolutionary development of more advanced hormonal systems (like corticosteroids) to control this eicosanoid activity, this balance of "good" and "bad" eicosanoids was the best solution that could be done at the time. Obviously, there is no such thing as an absolutely "good" eicosanoid nor an absolutely "bad" eicosanoid, anymore than there is a moral attachment to "good" and "bad" cholesterol.

Most chronic diseases are a consequence of an imbalance of "good" and "bad" eicosanoids. I have already discussed in this book the role of eicosanoids in heart disease, cancer, diabetes, arthritis, and depression among others. The 1982 Nobel Prize in Medicine provided me an insight into the molecular nature of chronic disease since it could be seen as an imbalance in eicosanoid levels. It became apparent to me at the same time that the appropriate balance of eicosanoids could be used to provide a molecular definition of wellness. In essence, the more the balance of eicosanoids is tilted toward "bad" eicosanoids, the more likely you are to develop chronic disease. Conversely, the more the balance is tilted toward "good" eicosanoids, the greater the chance that you'll achieve wellness and longevity. The AA/EPA ratio will indicate where you stand in terms of such a balance.

If you are skeptical about the statement that eicosanoids play such a fundamental role in a such number of diverse disease conditions, then ask any physician what happens when they give a high dose of corticosteroids to a patient for more than 30 days. The answer will be physiological devastation, if not death. This occurs because corticosteroids have only one mode of action, they knock out all eicosanoid production -- "good" and "bad" by inhibiting the release of essential fatty acids from cell membrane. This chokes off all supply of precursors to make any type of eicosanoid. Without eicosanoids, you can't survive.

### **How Eicosanoids are Synthesized**

Since eicosanoids are produced in every cell-not one specific gland-- it's as you have 60 trillion separate eicosanoid glands capable of making these exceptionally powerful hormones. Unlike the endocrine hormones, which are under control of the hypothalamus, there is no such central control on eicosanoids. Rather than responding to some master signal, each cell responds to changes in its immediate environment. The first step in generating a cellular response is the actual release of an essential fatty acid from the phospholipids in the cell membrane. The enzyme responsible for the release of the essential fatty acid is called phospholipase A2.

Since there is no feedback loop to stop the production of eicosanoids, the only way to inhibit their release from the membrane is by the production of corticosteroids (such as cortisol) from the adrenal gland, which causes the synthesis of a protein (lipocortin) that inhibits the action of phospholipase A2. By inhibiting this enzyme, which releases essential fatty acids from the cell membranes, you choke off the supply of a substrate required for all eicosanoid synthesis. Obviously, if you are overproducing corticosteroids (or taking corticosteroid drugs), you will bring all eicosanoid synthesis to a crashing halt, which can cause the shut down of your immune system.

The most powerful eicosanoid modulating drugs are corticosteroids. As I mentioned above, they inhibit the release any essential fatty acid so that no eicosanoids can be synthesized. Obviously, if you have intense pain or inflammation, this may be your only course of action on a short-term basis. Over the long term, corticosteroid therapy lowers the response of your immune system, decreases cognitive function, increases fat stores, thins the skin, and accelerates osteoporosis. In fact, if you give a single injection of corticosteroids to healthy individuals, their lymphocytes will be very similar to those in AIDS patients within 24 hours.

### **Enzymes that Make Eicosanoids**

There are three primary pathways an essential fatty acid (composed of a string of 20 carbon atoms), once released from the cell membrane, can follow. The first is via the cyclo-oxygenase system (i.e. COX) that make prostaglandins and thromboxanes. In this pathway the highly contorted essential fatty acid is closed upon itself to form a prostanoid ring. The second is through the 5-lipo-oxygenase (5-LIPO) pathway that makes leukotrienes. There is a third pathway in which the 20-carbon essential fatty acid is simply modified via either the 12 or 15-lipoxygenase (12 or 15-LIPO) enzymes as in the case of hydroxylated essential fatty acids. It is via this third pathway that many of the newly discovered eicosanoids are made. These pathways are shown below.

## **Types of Eicosanoid Synthesizing Enzymes**

### **Long-chain Essential Fatty Acids**

#### **COX 5-LOX 12 and 15 LOX**

## Prostaglandins Leukotrienes Lipoxins and and Thromboxanes Hydroxylated Fatty Acids

Certain drugs can inhibit the cyclo-oxygenase pathway of this eicosanoid formation. The most well known is aspirin which literally destroys a cyclo-oxygenase enzyme on a one-on-one basis. This is what is known as a suicide inhibitor. When you are suffering from a headache or arthritic pain, you are overproducing "bad" eicosanoids, but in particular "bad" prostaglandins. The aspirin temporarily shuts down all prostaglandin formation (but not leukotriene formation), until the cell can make more of the cyclo-oxygenase enzyme to replace the ones destroyed by the aspirin. However, you can't be using these suicidal soldiers forever, as aspirin also shuts down the synthesis of "good" prostaglandins, especially those that protect the stomach from dissolving itself. When that happens, you get internal bleeding. This is why there are more than 10,000 deaths per year associated with the over-use of aspirin. Other drugs known as non-steroidal anti-inflammatory drugs (NSAID's) also inhibit the cyclo-oxygenase enzyme but not the lipo-oxygenase enzyme that makes leukotrienes. The common names for these NSAID's are Motrin, Advil, Aleve, and others. Continued use of these NSAID's generates the same problems as does long-term aspirin use.

### COX Enzymes

The most common types of anti-inflammatory drugs are those that can only affect those eicosanoids that are synthesized via the cyclo-oxygenase enzyme or COX. It was recently discovered there are two forms of this enzyme known as COX-1 and COX-2. COX-1 enzymes are a constant fixture of the vascular cells that line the bloodstream or in stomach cells that secrete bicarbonate to neutralize stomach acid. COX-2 appears to be an enzyme that is synthesized only in response to inflammation. Standard drugs like aspirin and NSAID's (like Advil) don't discriminate between these specific forms of the COX enzyme, which is why they have side-effects associated with their long-term use.

For example, it appears that the anti-cancer benefits of aspirin may stem from its inhibition of COX-2, whereas the side-effects (like an increased risk of internal bleeding) come from its simultaneous inhibition of COX-1. However, this same inhibition of the COX-1 enzyme appears to convey the cardiovascular benefits associated with aspirin. This may explain why long-term use of COX-2 inhibitors may not work to decrease heart attack rates: They don't target the COX-1 enzyme. Weighing the risks against the benefits presents a dilemma associated with all drugs that affect eicosanoid synthesis.

### LOX Enzymes

Unlike inhibitors of the COX enzymes, there are very few inhibitors of the LOX enzymes. Since leukotrienes (particular LTB<sub>4</sub>) represent a primary mediator of pain, then the only way to affect their production is to use corticosteroids with all of their associated side effects. However, the leukotrienes synthesized from EPA are physiologically neuter compared to those derived from arachidonic acid. This is why the AA/EPA ratio is a very good indicator of the body's potential to prevent the over-production of leukotrienes without using resorting to the use of corticosteroids.

Drug companies are racing to develop new patentable drugs--ones that affect the downstream enzymes that control eicosanoid production from arachidonic acid. Overlooked in this frenzy by the drug companies seeking new and more expensive drugs to go downstream to modify eicosanoid synthesis, is that there is an existing "drug" that can achieve all of these benefits without any side effects. This is because it goes upstream to modify eicosanoid production by reducing arachidonic acid levels. That "drug" is high-dose fish oil since the elevated levels of EPA will reduce the production of "bad" eicosanoids (such as PGE<sub>2</sub> and LTB<sub>4</sub>) derived from arachidonic acid.

### Synthesis of Essential Fatty Acids

To understand the importance of diet in controlling these eicosanoids and re-establishing an appropriate eicosanoid balance, we have to understand how the actual precursors of eicosanoids are made. To begin with, all eicosanoids ultimately are produced from essential fatty acids that the body cannot make, and therefore must be part of the diet. These essential fatty acids are classified as either Omega-3 or Omega-6 depending upon the position of the double bonds within them. However, typical essential fatty acids are only 18 carbons in length and must be further elongated to 20-carbon fatty acids by the body before eicosanoids can be made. Remember, all eicosanoids come from essential fatty acids that are 20 carbon atoms in length. It is just not the number of carbon atoms that count, but also their configuration. Eicosanoid precursors must have a certain spatial configuration with at least three conjugated double bonds in order to be converted into an eicosanoid. How your diet controls the formation of dietary essential fatty acids into the actual 20-carbon atom precursors of eicosanoids is a complex story.

The discovery of essential fatty acids was first reported in 1929. At that time essential fatty acids were called Vitamin F. But Vitamin F was useless unless transformed into an eicosanoid. Thus began a continuing 70-year journey to understand how your diet does three things: controls eicosanoid formation; alters eicosanoid balance in the body; and determines how eicosanoids become a central players in your health.

The differences between the two classes of essential fatty acids, Omega-6 and Omega-3, are based on the position of the double bonds within the fatty acid molecule. This is important since it is the positioning of these double bonds that dictates their three-dimensional structure in space that ultimately determines how they interact with their appropriate receptors. Although the synthesis of essential fatty acids use the same enzymes, their metabolic pathways are quite

different. The metabolism of long-chain Omega-3 fatty acids are more complex, so let's start with the simpler pathway to make Omega-6 fatty acids.

### Omega-6 Fatty Acids

There are two key steps in this process that determine the amount of eicosanoid building blocks that will be made. These are known in biochemistry as "rate-limiting steps". The first rate-limiting step is controlled by the enzyme delta-6-desaturase. This enzyme inserts a necessary third double bond in the essential fatty acid in just the right position to begin bending inward and forms gamma linolenic acid (GLA) from linoleic acid as shown in the figure below.

Synthesis of Omega-6 essential fatty acids into eicosanoid precursors

Linoleic Acid (C18:2)

Delta-6 desaturase

Gamma Linolenic Acid (GLA) (C18:3)

Elongase

Dihomo Gamma Linolenic Acid (DGLA) (C20:3)

Delta 5-desaturase

Arachidonic Acid (AA) (C20:4)

"Good" Eicosanoids "Bad" Eicosanoids

(The number after the C tells how many carbon atoms the essential fatty acid contains, and the number after the colon tells how many double bonds there are in the essential fatty acid)

I define an activated essential fatty acid as any essential fatty acid that has this new double bond inserted by the delta-6-desaturase enzyme. This is because this new double bond starts bending the essential fatty acid to get the appropriate spatial configuration required to make an eicosanoid. Once this new double bond has been inserted into a short-chain essential fatty acid, then very small amounts of these activated essential fatty acids can profoundly affect eicosanoid balance in your body.

However, there are many factors that can decrease the activity of delta-6-desaturase enzyme. The most important factor is age itself. There are two times in your life during which this enzyme is relatively inactive. The first is at birth. For the first six months of life, the activity of this key enzyme in the newborn is relatively low. But this is also the time at which maximum amounts of long-chain essential fatty acids are required by the child since the brain is growing at the fastest possible rate, and these long-chain essential fatty acids are the key structural building blocks for the brain. Nature has developed a unique solution to this problem: mother's breast milk. Breast milk is very rich in GLA and other long-chain essential fatty acids such as the EPA and DHA. By supplying these activated essential fatty acids through the diet, this early inactivity of the delta-6-desaturase enzyme is overcome.

The second time in your life during which the activity of this enzyme begins to decrease is after the age of 30.

Eicosanoids are critical for successful reproduction. Since the primary child-bearing years for women are between the ages of 18 and 30, it makes good evolutionary sense to start turning down the activity of a key enzyme needed to make the precursors of eicosanoids required for fertility after age 30.

The delta-6-desaturase enzyme can also be inhibited by viral infection. The only known anti-viral agents are "good" eicosanoids such as PGA1 because of their ability to increase cyclic AMP levels that keep viral replication under control. On the other hand, if you are a virus, then your number-one goal is to inhibit the formation of this type of eicosanoid. This is exactly what many viruses do by inhibiting the delta-6-desaturase enzyme. By doing so, the virus has devised an incredibly clever way to circumvent the body's primary anti-viral drug (i.e. PGA1).

The final factor that can decrease the activity of delta-6-desaturase is the presence of two types of fatty acids in your diet; trans fats and Omega-3 fats. Trans fatty acids don't exist naturally but are produced by food manufacturers. They are essential Omega-6 fatty acids that have been transformed by a commercial process (known as hydrogenation) into a new spatial configuration that is more stable to prevent oxidation. The increased stability of these fatty acids makes them ideal for processed foods, but also makes trans fatty acids strong inhibitors of the delta-6-desaturase enzyme. Trans fatty acids occupy the active site of the delta-6-desaturase enzyme, thus preventing the formation of the activated essential fatty acids required for eicosanoid synthesis. In essence, trans fatty acids can be viewed as anti-essential fatty acids because of their inhibition of eicosanoid synthesis. This may be the reason why they are strongly implicated in the development of heart disease. How do you know if a food product you're consuming contains trans fatty acids? Look for the word "partially hydrogenated vegetable oil" on the label. If it is there, then you know the food contains trans fatty acids.

Surprisingly, Omega-3 fats can also inhibit the delta-6-desaturase enzyme activity in producing GLA since short-chain Omega-3 fatty acids such as alpha linolenic acid (ALA) preferentially bind to the enzyme thus decreasing GLA synthesis, and long-chain Omega-3 fatty acids such as DHA act as feedback inhibitors of the enzyme.

The journey toward becoming an eicosanoid is still far from over after passing this first hurdle of making GLA. Once GLA is formed, it is rapidly elongated into dihomo gamma linolenic acid (DGLA), which is the precursor to many of the "good" eicosanoids. However, DGLA is also the substrate for the other rate-limiting enzyme in essential fatty acid cascade in the chart above. That enzyme is called delta-5-desaturase. The activity of this enzyme ultimately controls the balance of "good" and "bad" eicosanoids thus making it the primary target to alter its activity by your diet if your goal is to treat chronic disease and promote wellness.

This is because the end product that the delta-5-desaturase enzyme that produces from DGLA is arachidonic acid (AA). DGLA is the building block of many of the "good" eicosanoids, whereas AA is the building block of "bad" eicosanoids. Thus excess amounts of AA can be one of your worst hormonal nightmares. Ultimately, it is the balance between DGLA and AA in every one of your 60 trillion cells that determines which types of eicosanoids you will produce. You need some AA to produce some "bad" eicosanoids, but in the case of excess production of AA, the balance of eicosanoids will shift toward accelerated aging and chronic disease.

### **Some of the Eicosanoids Derived from Arachidonic Acid**

Arachidonic Acid (AA)

COX 5-LOX 12 and 15 LOX

PGH2 TXA2 LTB4 12-HETE Lipoxin

PGD2 PGI2

LTB4 15-HETE

PGJ2 PGF2a PGE2

PGB2 LTBD4

PGA2

LTBE4

Many of these eicosanoids derived from arachidonic acid can be considered to be "bad" because they promote inflammation (PGE2 and LTB4) and decrease blood flow (TXA2). In addition, the inflammatory "bad" eicosanoids can also promote the release of other pro-inflammatory cytokines.

While there is bewildering complexity of eicosanoids from arachidonic acid, there are a very limited number of eicosanoids that come from dihomo gamma linolenic acid (DGLA) as shown below

Eicosanoids from DGLA

Dihomo Gamma Linolenic Acid (DGLA)

COX LOX

PGH1 15-OH Triene

PGE1

PGA1

The primary eicosanoid derived from DGLA is PGE1, one of the most highly studied "good" eicosanoids as it a very powerful vasodilator and inhibitor of platelet aggregation. It also reduces the secretion of insulin and increases the synthesis of wide variety hormones that normally decrease during the aging process. PGE1 is able to achieve these diverse functions because it causes an increase in cyclic AMP production. PGA1 is the most powerful suppressor of viral replication, especially HIV transcription, as well as inhibiting nuclear transcription factor NFkappaB necessary for synthesis of a wide variety of pro-inflammatory cytokines. And finally the 15-LOX enzyme can convert DGLA into a powerful inhibitor of the 5-LOX enzyme that decreases leukotriene synthesis. You can see that having higher levels of DGLA compared to AA which play an important factor for decreasing inflammation and increasing blood flow.

So how do you help your body block excess AA formation and tilt the balance back toward a favorable DGLA/AA ratio? By making sure your diet has adequate amounts of EPA. The importance of EPA is that it acts as a feedback inhibitor of

the delta-5-desaturase enzyme. The higher the concentration of EPA in the diet, the more the delta-5-desaturase enzyme is inhibited, and the less AA is produced. As a result, the presence of EPA in the diet allows you to control the rate of AA production derived from DGLA, and thus generate a favorable DGLA to AA ratio in each cell membrane. This is why the AA/EPA ratio in the blood is such a powerful predictor of chronic disease.

### **Omega-3 Fatty Acids**

The synthesis of long-chain Omega-3 fatty acids is much more complex as shown below.  
Synthesis of Long-Chain Omega-3 Fatty Acids

Alpha Linolenic Acid (ALA) (C18:3)  
Delta-6 desaturase  
Arachidonic Acid (C18:4)  
Elongase  
Eicosatetraenoic Acid (C20:4)  
Delta 5-desaturase  
Eicosapentaenoic Acid (EPA) (C20:5)  
Elongase  
C22:5  
Elongase  
C24:5  
Delta-6 desaturase  
C24:6  
Peroxisomal degradation  
Docosahexaenoic Acid (DHA) (C22:6)  
Peroxisomal degradation  
Eicosapentaenoic Acid (EPA) (C20:5)

The synthesis of EPA is seemingly relatively straight-forward from the short-chain Omega-3 fatty acid, alpha linolenic acid (ALA), just as the synthesis of arachidonic acid is from its short-chain precursor, linoleic acid. However, alpha linolenic acid is an inhibitor of the delta-6-desaturase enzyme, just as EPA is a feedback inhibitor of the delta-5-desaturase enzyme. This feedback inhibition makes the formation of EPA much more difficult than it should be. This is why studies comparing dietary intake of ALA versus EPA have indicated that the efficiency of making EPA from ALA is extremely limited. Therefore if you want to get the greatest benefit of EPA, it will have to come from eating fish oil as opposed to vegetable sources rich in ALA (such as flaxseed).

Now it gets even more complex when going further on to make the DHA that is critical for the brain. The EPA must be elongated and then converted again by the delta-6-desaturase enzyme to the precursor of DHA which then must be shortened by peroxisomal enzymes into DHA. The result is that the synthesis of DHA from ALA is even more difficult than the synthesis of EPA (which isn't very good to begin with). Furthermore, DHA acts as a feedback inhibitor of the delta-6-desaturase enzyme that further reduces the flow of ALA to EPA and DHA. You can begin to see why until modern man starting eating shellfish some 150,000 years ago, that his ability to have adequate levels of long-chain Omega-3 fatty acids for his brain was highly compromised.

DHA can also be retro-converted into EPA by the same peroxisomal enzymes used necessary to make DHA in the first place. Although the process is not that efficient, but at least it provides a mechanism by which vegetarian sources (genetically modified algae) of DHA can provide EPA. This retroconversion process appears to be a more efficient way of making EPA for someone following a vegetarian diet than is its synthesis from ALA.

This is why long-chain Omega-3 fatty acids, like EPA, are so important in my dietary program. They inhibit the delta-5-desaturase enzyme thereby restricting the flow of any Omega-6 fatty acids into arachidonic acid, which therefore decreases the production of "bad" eicosanoids. As long as you are consuming very moderate amounts of Omega-6 fatty acids with equal amounts of EPA, then those dietary Omega-6 fatty acids in your diet tend to accumulate at the level of DGLA (because of the inhibition of delta-5-desaturase by the EPA), which increases the production of "good" eicosanoids. However, the total amount of Omega-3 and Omega-6 fatty acid you need is relatively low. This means you still have to add some extra fat to your diet to help slow the rate of entry of carbohydrate to control insulin secretion. And the fat should be primarily monounsaturated fat. Monounsaturated fats can't be made into eicosanoids ("good" or "bad"). Thus by having no effect on eicosanoids nor insulin, monounsaturated fats can provide the necessary amount of fat for controlling the entry rate of carbohydrates into the bloodstream without disturbing the hormonal balances that you are trying to achieve through the OmegaRx Zone.

### **The Spillover Effect**

In the early days, I thought that simply controlling the ratio of EPA and adding the right amount of GLA would be all that I needed to control eicosanoids. Taking all the data into account, including the increasingly massive over-consumption of Omega-6 fatty acids in general, I believed that a 4:1 ratio of EPA to GLA should do the trick. I thought one ratio would

work for everyone. This was obviously flawed thinking in retrospect, but since I was coming from my background in pharmaceutical drug delivery, it seemed logical at the time. So I started out with this ratio, made some soft gelatin capsules containing both fish oil (the source of EPA) and borage oil (the source of GLA), and found some friends who were willing to be guinea pigs. I gave them my standard phrase, "Trust me".

Since I was only working with changing fatty acid levels during this early phase of my research, my initial observations on eicosanoids were not confounded by other potentially hormonally modulating approaches, like controlling insulin or restoring endocrine hormone levels. I had a very targeted approach to focus solely on manipulating eicosanoid levels through dietary supplementation with defined amounts of activated essential fatty acids. And many of the physiological changes I observed occurred within weeks, if not days.

The time frame for these physiological actions was important because it was much faster than the reported responses for treatments that focus on the restoration of endocrine hormones. Those changes usually take weeks, if not months, to see measurable effects.

After several months, however, I noticed that strange things seemed to be happening. Virtually everyone who took the combinations of EPA and GLA felt much better initially. After all, they were now making more "good" and fewer "bad" eicosanoids since I was changing the DGLA/AA balance in the cells. With time, some individuals mentioned that they seemed to have stabilized or that they even saw a drop-off in the early benefits they first experienced. Nonetheless, they still felt better than before they started. However, there was another smaller group, who saw their initial benefits erode completely and actually began to feel worse than when they started. Some of my friends were no longer quite so friendly, until I figured out what was happening. I called it the "spillover" effect.

Initially, as the ratio of DGLA to AA improves, the person begins making more "good" eicosanoids and fewer "bad" ones. Everything just keeps getting better. But there will be some point in time, depending on your biochemistry and gender, that the DGLA to AA ratio begins to degrade as more of the DGLA gets converted into AA. They still feel better than when they started, but not quite as good as they first did. For some individuals, this degradation of the DGLA/AA ratio continues to the point that they begin to feel worse than when they first started the program because they are now making many more "bad" eicosanoids. This is shown in the figure below.

These particular individuals developed a buildup of DGLA in their cells. The increased levels of DGLA were providing more substrate for the delta-5-desaturase enzyme to make more AA. The increase in DGLA was overwhelming the amount of EPA being supplied to inhibit the delta-5-desaturase enzyme. This spillover effect seemed to occur more often in females than in males. So much for the "one size fits all" ratio of GLA to EPA.

So I decided that if one size does not fit all, I had better start making a wide array of different EPA and GLA combinations and fine-tune them for each individual. But how could I do this? Fortunately eicosanoids do leave a biochemical audit trail that gives an insight into their actual balance in different organs in the body. That's what led me to develop the Eicosanoid Status Report to provide me with information on how to alter the amounts and ratios of activated essential fatty acids to fine-tune these exceptionally powerful hormones. (Now the AA/EPA test makes it even more precise.)

By 1989, I thought I had finally gotten this concept down to a science. A more complex science than I had originally thought, but one still governed by some basic biochemical rules. However what finally gave me the insight for the OmegaRx Zone was my work with elite athletes.

I began to notice that some of the elite athletes I was working with would have great training sessions, but then not do as well during competition. Others would do extremely well. When I started to ask them if they were doing anything different from a dietary standpoint prior to competition, it turned out that those who were carbohydrate-loading prior to a competition always appeared to do worse than those who maintained a consistent diet. I racked my brain trying to understand what had gone wrong or what had changed to explain this sudden shift in their eicosanoid status. Then it struck me. It was carbohydrate-loading that was increasing their insulin levels. This also explained the rapid decrease in the performance of the Stanford University swimmers who switched off my dietary recommendations and went back to eating dorm food composed primarily of high-density carbohydrates.

A trip to the bowels of the MIT library confirmed my suspicion. There I found previously published research that demonstrated that high levels of insulin activate the delta-5-desaturase enzyme, whereas glucagon inhibits this enzyme's activity. All the hormonal benefits I had carefully crafted for each athlete to manipulate their ratios of DGLA to AA were being undermined by the surge of insulin caused by their elevated carbohydrate intake. This increase in insulin stimulated the delta-5-desaturase enzyme to increase the production of AA at the expense of DGLA. For these athletes, the result was that a highly favorable DGLA to AA ratio created during training quickly became a very undesirable ratio at the time competition. It was the same spillover effect that I had observed in the early days of learning how to fine-tune eicosanoid levels. It was at that point I knew that I would never be able to control eicosanoid levels without controlling insulin first. It was back to the drawing board.

Was there any confirming evidence that high levels of insulin would affect the DGLA to AA ratio in humans? Fortunately, that information was published in 1991. The goal of that research was to maintain a high level of insulin for six hours in both normal subjects and patients with Type 2 diabetes (who are characterized by excessive insulin levels). After only six hours of exposure to elevated insulin levels, the ratio of DGLA to AA in the bloodstream in both healthy individuals and



Type 2 diabetics had dropped by nearly 50 percent. The elite athletes who were carbo-loading prior to competition were suffering the same decrease in DGLA/AA ratios by eating more high-density carbohydrates (grains, pasta, and starches), thus increasing insulin, which caused a rapid deterioration of their DGLA/AA ratios.

So now the metabolism of activated essential fatty acids had to be modified to take into account the role of insulin and glucagon on the delta-5-desaturase enzyme. This is shown below.

### **Effect of Elevated Insulin on the Metabolism of Activated Essential Fatty Acids**

Dihomo Gamma Linolenic Acid (DGLA)

Delta-5 Desaturase  
Activated by Insulin  
Inhibited by EPA

Arachidonic Acid (AA)

Insulin was an activator of the delta-5-desaturase enzyme. The role of excess insulin in negatively affecting eicosanoid balance also explained why excess insulin was highly associated with heart disease. It wasn't that insulin was a cause, but that it drove the metabolism of essential fatty acids to make more arachidonic acid, and therefore more "bad" eicosanoids. The more "bad" eicosanoids you make, the more likely you will promote platelet aggregation and increased vasoconstriction, the underlying factors for a heart attack.

I knew the only way to control insulin required controlling the protein-to-carbohydrate ratio at every meal. Again I was confronted by what the optimal ratio of protein-to-carbohydrate ratio should be? A good beginning was to attempt to estimate the ratio of protein-to-carbohydrate ratio consumed by neo-Paleolithic man some 10-40,000 years ago, since our genes haven't changed that much since then.

Fortunately, such an estimate did exist in research published in an 1985 issue of The New England Journal of Medicine. Using anthropological data and comparing a large number of existing hunter-gatherer tribes, these researchers estimated the average protein-to-carbohydrate ratio in neo-Paleolithic diets to be approximately 3 grams of protein for every 4 grams of carbohydrate, or a protein-to-carbohydrate ratio of 0.75. Using this research as a starting point, I began developing a diet that would control the protein-to-carbohydrate ratio in a range between 0.5 and 1.0 at every meal so that the balance of insulin and glucagon would be maintained from meal to meal. This is the foundation of the insulin control component of my dietary recommendations.

Thus, my dietary program controls both the ratio of long-chain Omega-3 fatty acids to Omega-6 fatty acids as well as the balance of protein-to-carbohydrate at every meal while restricting total calories. This dietary strategy maintains the dynamic balance of eicosanoids by controlling the levels of the actual precursors and the hormones responsible for activating the critical enzymes in essential fatty acid metabolism. By keeping the balance of eicosanoid precursors in an appropriate zone (after all, you need some "bad" eicosanoids to survive), you also control the information flow of your Biological Internet. Control that flow and avoid hormonal miscommunication, and you have begun to reverse the aging process.

The development of chronic diseases (heart disease, diabetes, cancer, and arthritis) associated with aging does not occur overnight but is the result of constant hormonal insults to your body. But by the time they do appear, significant (and potentially irreversible) organ damage may have occurred. So if eicosanoids act as master hormones that control this complex hormonal communication system, is there some way we can continue to monitor and fine-tune this ultimate mechanism of aging before chronic disease conditions appear? If so, then you could tell when you are moving out of the appropriate eicosanoid zone and then take immediate dietary steps to restore that balance? There are very few direct diagnostic tests for eicosanoids. However, the ratio of AA/EPA will provide a remarkably good insight into your eicosanoid status. More importantly, this is a blood parameter that can be changed rapidly within 30 days by getting into the OmegaRx Zone