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*Please note that this was written in 2001, before Vioxx was withdrawn by Merck for causing serious side effects, including death from stroke and heart attacks.

If you – or someone for whom you care – suffer with chronic **inflammation**, then by now you'll have heard of the new "**COX-2 inhibitor" drugs**. The latest painkillers to come out the pharmaceutical industry, COX-2 inhibitors – drugs with names like **celecoxib [Celebrex®] and rofecoxib [Vioxx®]**) – have become media darlings because they relieve the pain of **rheumatoid arthritis** and other diseases of chronic inflammation, without the risks to the stomach and digestive system that were associated with the older **NSAIDs (Non- Steroidal Anti-Inflammatory Drugs,** including ibuprofen [Motrin® or Advil®], naproxen [Naprosyn®], indomethacin [Indocin®]), and the old sawhorse, aspirin). All of these drugs – as well as the older **steroid drugs**, such as **cortisone** – ultimately work by interrupting the body's production of a class of local cellular "hormones" called **eicosanoids** (eye-KOSS-ah-noids). Eicosanoids are the messengers that cells use to communicate with one another, coordinating their activities. **Some ("bad") eicosanoids promote inflammation, while other ("good") eicosanoids have potent anti-inflammatory functions**. Thus, the body's inflammatory response rests in large part on the balance of "good" and "bad" eicosanoids produced by your cells when they hear the immune system's inflammatory call.

Of Saboteurs and Janus-Faced COX

When faced with the pain and inflammation of "bad" eicosanoids, one's first instinct might be to follow the example of the old French *saboteurs*. These factory workers, furious that their livelihoods – and sometimes their limbs, or even their lives – were being lost to the new machinery in the Industrial Revolution's factories, would throw their wooden shoes (in French, "*sabots*") into the offending equipment. The shoes would get stuck in the machines' wooden gears, jamming them, breaking them … bringing them to a crashing halt. The NSAID drugs – and especially aspirin – are a lot like those old wooden shoes. The cell's ability to make eicosanoids depends on the functioning of a group of key enzymes. These enzymes work much like the machines on a conveyor belt: enzymes take the materials they're given (**substrates**) and shape them into something new (**products**), before passing them down the line for further processing by other enzymes. One group of "bad" eicosanoids that are heavily involved in the short-term pain of inflammation is the **series-2 prostanoid** group. Like all the "bad" eicosanoids, series-2 prostanoids are made from an omega-6 fatty acid called **arachidonic acid (AA)**. The enzyme used to make prostanoids out of AA is called **cyclooxygenase, or COX**. Because of COX's role in creating "bad" prostanoids, the giant pharmaceutical conglomerates originally developed pain-killing drugs using a strategy just like that used by the saboteurs of the Industrial Revolution: they designed the NSAIDs to jam up the works – the more thoroughly, the better. The problem with this approach is that COX is an enzyme with two faces. While one form of COX (**COX-2**) produces

"bad" prostanoids from arachidonic acid, the other form (**COX-1**) produces prostanoids which serve so-called "housekeeping" functions – functions which are vital to health of organs like the stomach and kidneys. So totally shutting down the COX machinery – as is done by first-generation NSAIDs – amounts to a recipe for stomach ulcers and kidney damage. It's because of the safety issues with the old NSAIDs that the media has hailed the new "COX-2 inhibitor" class of NSAIDs with such enthusiasm. These drugs are a bit more targeted in their design: they strongly block the pro-inflammatory COX- 2, but only mildly inhibit the supportive functions of COX-1 alone. As a result, they seem to work as well as most NSAIDs at killing pain, but without the stomach ulcer side-effects. That doesn't mean these drugs are perfect, however. Despite theoretical expectations, Celebrex® and Vioxx® appear to be no safer for the kidneys than the older NSAIDs;[1] as well, the way these drugs are metabolized by the body can cause them to have serious interactions with other drugs.[2] And there's another reason to be wary of the synthetic COX-2 inhibitors. While they certainly provide symptomatic relief in the short term, **COX-2 inhibitors can actually** *accelerate* **the underlying inflammatory disease in the long term**.

The Ticking Timebomb

Drugs that work by only inhibiting COX-2 prevent the formation of the series-2 prostanoids, which are *one* family of "bad" eicosanoids. But there's *another* family of "bad" eicosanoids: the **series-4 leukotrienes**. Like "bad" prostanoids, "bad" leukotrienes are made from arachidonic acid. However, cells use different "machinery" to make leukotrienes: an enzyme called **lipoxygenase (LOX)** enzyme pathway. That is, the body uses two different enzymes to make two different finished products from the same raw material – sort of like starting with pasta dough, but using one machine to make manicotti and another to make ravioli. Both the prostanoids (made by COX-2) and the leukotrienes (made by LOX) play important roles in the inflammation process – but in different places, in different ways, and on different time schedules. Prostanoids are usually elevated in the inflamed tissue *itself,* and are more strongly involved in the *short-term* pain of inflammation. In rheumatoid arthritis, for instance, series-2 prostanoids are at work in the thick lubricating material (**synovial fluid**) that bathes the joint. By contrast, **leukotrienes are the eicosanoids released by** *immune cells* **involved in the body's inflammatory responses, and are more responsible for the** *long-term* **consequences** of inflammation, which can result when a deranged immune system attacks the very body which it was designed to defend. And that's where you run into danger if you're *only* blocking COX-2. When COX- 2 is blocked, the arachidonic acid doesn't just disappear. Instead, **inhibiting COX-2** *alone* **merely puts more arachidonic acid to work in making leukotrienes**[3-5] (see **Figure** 1). Think of the flow of water in a river with two arms. If you dam up just one arm, then *that* arm's water levels will run down to a trickle …but *the other arm's shores will flood*. This effect has serious ramifications if your inflammation is caused by a dysfunctional immune system, as is the case in **rheumatoid arthritis,** in **psoriasis,** and in most **inflammatory bowel disease** (**IBD)** cases (including **Chron's disease** and **ulcerative colitis**) and **asthma**. Thus, for instance, even though people suffering with IBD have high levels of prostanoids from COX-2 as part of their disease, the drugs that work by **inhibiting COX** *exclusively* **can not only permanently worsen IBD,**[6] **but can also** *create* **an artificial form of the disease,**[7] reactivate the disease when it had been dormant,[8] or worsen intestinal permeability ("leaky gut") in otherwise healthy relatives of Chron's victims.[9] Moreover, evidence exists to suggest that this may apply to new COX-2 inhibitors just as it applied to older NSAID drugs, although the effect is likely to be much milder.[10] Likewise, there is the phenomenon of **"aspirin-induced asthma,"** seen in about 10-20% of asthma sufferers, in which **COX-inhibiting drugs (including older NSAIDs**[11] **and to some extent the new COX-2 inhibitors**[12,13]**) can exacerbate existing asthma and trigger flareups** – precisely because of increased leukotriene

production.[4] In fact, to say that blocking the COX pathway simply *diverts* the arachidonic acid floodwaters into the LOX channels may underestimate the seriousness of the effect. The reason: ironically, despite their role in the *short-term* pain of inflammation, **prostanoids derived from COX-2 may actually help to** *shield* **the body from the** *long-term* **ravages of leukotrienes!** For one thing, **some prostanoids directly put the brakes on overproduction of leukotrienes**.[14,15] On top of this, some prostanoids help **keep tumor necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1) under control**.[19] TNF-alpha and IL-1 are rampaging **cytokines** (a kind of messenger chemical in the immune system) which give the orders that unleash the body's immune cell arsenal. This is great when you have a cold, but disastrous in autoimmune disorders. In rheumatoid arthritis, for instance, **TNFalpha and IL-1 give the command for immune cells to attack the affected joints**,[20a] and stimulate the production of **collagenase** enzymes which tear down joint tissue.[21] **Etanercept (Enbrel®)**, a hot drug for rheumatoid arthritis just approved by Health Canada this March, reduces the pain of the disease, while actually slowing down the long-term joint destruction, ***precisely*** because it soaks up excess TNF-alpha, preventing it from wreaking its havoc. The cost? Biweekly injections cost the average American user $12 000 US a year. But if TNF-alpha gives the orders, it's the leukotrienes that make sure they're carried out. **If TNF-alpha is the general, then leukotrienes are the platoon leaders in the field, and the body's immune cells are the "grunts."** Because some prostanoids from COX-2 can help to keep a lid on the hazards of leukotrienes, a synthetic version of **the prostanoid PGE1 actually** *protects joint tissue* **against damage from these cytokines**,[18] and NSAID **drugs, which block COX-1** *as well as* **COX-2, are known to cause long-term joint damage**.[22,23] Does this mean that series-2 prostanoids are "good" after all? Not exactly. But few things in the body serve ***exclusively*** negative functions: for example, although having too much LDL ("bad") cholesterol in your blood will increase your long-term risk of heart disease, some amount of LDL is needed day-to-day for making the membranes to your cells. So when you block the prostanoids ***alone***, you get rid of their directly hurtful effects, but you also lose their *counterbalancing* effects on leukotrienes. **Blocking the COX pathway without** *also* **dealing with leukotrienes creates an** *imbalance* **– an imbalance which ultimately trades short-term gain for long-term pain**. Therefore, we don't just want a supplement which blocks COX: we want a supplement which will defend us against ***both*** short-term suffering caused by series-2 prostanoids, ***and*** long-term damage from series-4 leukotrienes. To put it another way: **what people suffering with autoimmune disorders most need is a "dual pathway inhibitor:"**[24] **a molecule which will shut down COX-2 and LOX alike**, preventing the formation of *all* "bad" eicosanoids (see **Figure 1**). That's a pretty hard position to fill. Our dream molecule must be at once broad-spectrum ***and*** carefully focused, addressing both immediate suffering and long-term risk. Like NSAIDs, this molecule would inhibit COX-2. Like the COX-2 inhibitors, it would leave the essential housekeeping functions of COX-1 alone. And like the asthma drug zileuton (Zyflo ®), it would block the LOX pathway. But unlike ***any*** of these drugs, our miracle molecule would do all of these things at once, with negligible side-effects. From the perspective of the medical establishment, this doubtless sounds like a job for some pharmaceutical giant. The transnational drug lords would be delighted to invest in a small army of specialized scientists, a billion-dollar research budget, and a decade of development time, if it were to culminate in a patent-protected, monopoly pharmaceutical with the potential of a true dual-pathway inhibitor. But Nature has once again beaten the pharmaceutical transnationals to the finish line. An obscure, hard-to-find omega-3 fatty acid already fits the bill.

Introducing ETA

Eicosatetraenoic acid (ETA) is an omega-3 fatty acid you probably haven't heard much about. Because ETA is so rare in food sources, there's been little study of its role in the effects of diet on chronic disease – unlike the well-known **eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)**, which are easily in fatty fish and in regular fish-oil supplements). The rarity of ETA has also meant that it's been hard to make a commercial supplement based on ETA. It's also meant that, until recently, little research had been performed on it in supplement form, as compared with the extensive research on readily-available fish oil supplements. The rule has been: *you go with what you've got.* Yet there *has* been research done on ETA in the past– it's just that the researchers didn't know what it was that they were studying. While ETA is very rare in the normal Western diet, it *is* found in significant amounts in the fatty acids of the green-lipped mussel (*Perna canaliculus*), a food used since time immemorial by the coastal Maoris, the aboriginal peoples of New Zealand. And, indeed, statistics show that those Maoris who live near the shore (whose diet contains a significant amount of green-lipped mussel) have a very low reported incidence of arthritis – whereas their inland cousins, who eat little of this sea-sourced food, have the same rates of arthritis as Europeans living on the islands.[25] After first being alerted to the traditional use and some anecdotal evidence, a group of researchers at the Victoria Infirmary in Glasgow, Scotland performed a preliminary, open study of the crude extract of the green-lipped mussel in people with arthritis (55 cases of rheumatoid arthritis and 31 osteoarthritis victims).[26] In this study, patients were treated with the crude extract for anywhere from six months to over four years; **over two-thirds of those suffering with rheumatoid arthritis, and over one third of those with osteoarthritis, were reported to benefit from the crude extract**. Encouraged by their preliminary findings, these scientists initiated a placebo- controlled, double-blind , study.[27] Sixty-six patients on a waiting list for joint surgery at the Infirmary (28 rheumatoid arthritis sufferers and 38 people with osteoarthritis), who did not have an allergy to fish or shellfish, were randomly placed into one of two groups, receiving either 1050 mg of the crude extract of *Perna canaliculus* or the same amount of an inactive fish preparation . Then *all* patients were assigned to receive the active treatment for a further three months. During the initial, placebo-controlled phase, **59% of the people with rheumatoid arthritis improved while receiving the crude extract,** compared with only 27% of the people receiving the dummy pill; and **in the osteoarthritis group, 37.5% of people receiving the crude extract improved, versus only 13.6% of the fish-pill stand-ins**. But when other investigators tried to confirm the results of this study, the results were contradictory. While the effectiveness of the crude extract was confirmed by French investigators in a double-blind, placebo-controlled trial,[28] two *other* such trials using the crude extract reported that it had no effect.[29,30] The same contradictions turned up in animal experiments.[31-35] What was going on?

The Missing Ingredient

For a decade or so, the contradictory results led most scientists to conclude that the green-lipped mussel was a dead end for research, and virtually no new work was done. Then, in 1995, scientists at Australia's Royal Melbourne Institute of Technology resolved the contradiction in the previous studies, providing the key that explained the inconsistent results of previous studies. These researchers hypothesized that the anti-inflammatory properties of the green-lipped mussel were most likely due to some specific ingredient, which might have been present in some crude extracts and not in others. Studies performed by this group proved the hypothesis correct. Specifically, **it was the free fatty acids – and, in particular, the ETA-rich omega-3 content – which was responsible for the anti-inflammatory effects of** *Perna canaliculus*.[36-39] Tellingly, a test which compared seven commercially available crude green mussel products with the a stable fatty extract rich in ETA revealed strong anti-inflammatory powers in the

ETA extract, while the crude extracts were found to vary wildly in strength.[38] More tellingly, when the inflammation fighting powers of a stable ETA-rich extract were compared with crude *Perna canaliculus* extracts whose fatty acid content had been deliberately removed, the fatty acid extract of the mussel exhibited potent anti-inflammatory effects, while the ETA depleted preparation was found to be completely ineffective. [39] And studies using highly purified sub-fractions of the fatty acid extract demonstrated **that by far the most potent fraction of the fatty acid extract was not the portion with the *common* omega-3s (EPA and DHA), but the fraction rich in ETA**.[36,37] Now the reason for the controversy over green-lipped mussel extracts began to make sense. The crude extracts were not created in a way which would consistently deliver a rich dose of ETA. The products used in these studies did not contain a defined quantity of free fatty acids, nor was the extract processed or stabilized with the care required to protect what ETA was present in the material. Thus, "The mussel powder used in the original trial was freshly prepared for [the investigators] along with the fish-based placebo. Stability … may well have been a problem with the material used in [unsuccessful] studies."[40] The contradictory results, then, were not the fault of the various research groups, but were almost certainly caused by batch-to-batch variations in the ETA content of crude extracts.

ETA Beats Out the Other Omega-3s

Once we see that the anti-inflammatory powers of the green-lipped mussel were due to its unique, ETA-rich blend of fatty acids, the next logical question is: how does ETA stack up in comparison to other omega-3 sources, such as fish oils and flaxseed oil? Two direct comparison studies have been performed to answer this question, weighing the anti-inflammatory effects of the ETA-rich oil of *Perna canaliculus* against those of salmon, cod liver, flaxseed, and two mixed fish oils.[39, 41] In these studies, the powers of the various omega-3 supplements were tested in animals who were given an inflammation inducing substance – the same sort of test which had given such contradictory results in tests on the crude green mussel extracts of the previous generation. The various omega-3 supplements (and some other products) were tested by looking at the amount of swelling in the wrist and digits, as well as through the use of a standardized "arthritis" score, looking at things like how sensitive the animals' feet were to handling, how thoroughly the animals groomed their inflamed paws, and how mobile the animals were. These studies clearly show that **the ETA rich fatty acid extract of *Perna canaliculus* is far superior to other omega-3 sources at quenching the fires of inflammation**, giving more potent anti-inflammatory benefits at significantly lower doses. Using the series of tests discussed above, **ETA supplementation lowered arthritis scores by 42[39] to 75[41]%, vs. 0 to 31% using conventional omega-3 sources.** Likewise, **rear paw swelling was reduced by 96- 98% by the ETA-rich oil, while swelling was only lowered by 7 to 38% with common omega-3s**! These results are all the more remarkable because **the dose of ETA-rich *Perna canaliculus* oil was only about 1% of that used for the standard omega-3 oils**. Several studies have also compared the ETA omega-3 supplement to *drugs* used to fight pain and inflammation – the NSAIDs ibuprofen,[38] naproxen,[38] and indomethacin, [38,39] two new drugs which work by inhibiting the action of leukotrienes.[41] Remarkably, **ETA performed similarly to, or better than, any of these pharmaceuticals** in inhibiting inflammation and in arthritis scoring.

A New Human Trial

With the new understanding that the fragile fatty acid component of the green-lipped mussel was the key to its inflammation cooling abilities, the lipid extract was put to the real test: a new randomized, double-blind, controlled trial, following essentially the same design as the original controlled study, but using 30 patients in each group (rheumatoid or osteoarthritis sufferers) and with modifications approved by the West Ethical ommittee.[40] The results:

among rheumatoid arthritis sufferers taking the *Perna canaliculus* oil, **significant improvements were reported in morning stiffness and measures of joint functionality during the double-blinded phase; further, night pain was "much improved" in 40% of subjects, and vanished in an additional 26.7%**. Improvements were also seen in some patients' grip strength and overall visual-scale pain scores, but these results were not found statistically meaningful. Assessment by doctors and patients concluded that **73% of the persons with rheumatoid arthritis had experienced a good response – including 20% who became completely symptom-free** by the end of the double-blind phase. **The results were similar in the osteoarthritis victims**, with significant improvements in morning stiffness and measures of joint functionality reported for the patient group which had taken the *Perna canaliculus* oil supplement, though grip strength was not significantly improved. With surprising consistency, 40% of OA patients taking the green-lipped mussel oil supplement saw their night pains improve considerably, including total disappearances in 26.7%. Doctor/patient assessments again judged 73% of people with osteoarthritis to have been improved, though none were symptom-free. No side-effects were seen except for mild water-retention in some patients. Similar results have been reported in an unpublished pilot trial[42] and in case reports.[43]

Breathe Easy

A supplement which blocks both the COX and the LOX pathways would also be a godsend for people who suffer with **asthma**. In an unpublished double-blind, placebo-controlled study,[44] **asthma sufferers who took the stable oil of *Perna canaliculus* experienced significant reductions in the frequency of chest tightness and night waking, cut down on their use of beta-agonist drugs, and saw improvements in their peak airflow**. No improvements were seen in the placebo group. A report in the *Medical Journal of Australia*[45] supports this finding. It details the case of a 69-year-old patient suffering with both osteoarthritis and asthma. This woman – who was originally taking 100 milligrams of the stable *Perna canaliculus* oil daily for her osteoarthritis – found that the supplement also dramatically improved her asthma**: using the ETA-rich oil led to an 80% cut in the use of the steroid drug prednisone, and an increase in peak airflow from 250 liters per minute to 350** over the course of two years.

Stopping the Monthly Rollercoaster?

Many women taking stable fatty acid extracts of *Perna canaliculus* oil for their arthritis, have also reported that they experience relief from their **premenstrual syndrome (PMS)** symptoms.[41] This makes sense: the extreme contractions of the uterus which underlie much of the cramping of PMS are ultimately *caused* by wild hormonal tides, but the increase in contraction is largely *delivered* through "bad" eicosanoid signals – eicosanoids from both the COX and the LOX pathways.[46] Furthermore, "bad" eicosanoids actually heighten the pain sensitivity of the uterus, increasing the *suffering* associated with the physical contractions.[46] In a recent study,[41] female lab animals were administered the key women's hormones estrogen, progesterone, and oxytocin in a way that mimics the normal monthly menstrual cycle, and given either the ETA rich green-lipped mussel oil or an olive oil dummy supplement. Scientists then examined the force and frequency of their isolated uterus' contractions as a model of menstrual cramping. While a single treatment with the *Perna canaliculus* oil had no effect on uterine contractions, **giving the animals the ETA-rich oil for three consecutive days reduced the cramping of the uterus** when stimulated by the hormone **oxytocin**. The olive oil treatment had no effect.

How Does It Work?

The answer to this question is a little bit technical. To fully explain the effects of ETA on inflammation, and its superiority to common omega-3 supplements, in a way that's clear to any intelligent person with no background in the biochemistry, would occupy more space than is available for this article *as a whole* – and we've already had to skim quickly through results which deserve much more detailed reporting. So it'll take bit more effort to understand this section. Read it carefully if you're interested – or skip it if you're not. There won't be a quiz. The fact is that *all* omega-3s have some degree of "dual pathway inhibitor" action, blocking both the short-term pain and inflammation of the prostanoids (from COX-2) and the longer-term immune attacks which are the danger of the leukotrienes (from LOX). These abilities are based on several aspects of the body's processing of fatty acids. For one thing, **the same COX and LOX enzymes which make "bad" eicosanoids from arachidonic acid, can make "neutral" eicosanoids from specific omega-3s**. Omega-3s can thus put the brakes on inflammation by tying up the enzymes which would otherwise be put to work making "bad" eicosanoids – thereby preventing those eicosanoids from being formed.[47] Furthermore, like other omega-3s, **ETA is a natural COX-2 inhibitor,** which ties up the inflammatory form of the enzyme without affecting the "housekeeping" function of COX-1.[48] Remarkably, omega-3s accomplish this feat not *only* by binding up COX-2, but *also* by **actually working at the** *gene level* **to reduce the production of COX-2** from the DNA code.[48] And, at the same time, omega-3s like **ETA also block the formation of leukotrienes**[47] **and of ETA stop TNF alpha and IL-1 from being produced** *in the first place*[49] (unlike Enbrel,® which works *after the fact* as a TNF "sponge"), cutting levels of these cytokines by as much as *90%*[47] – and again, by working right down at the gene level.[48] Omega-3s such as ETA also work their magic one step further up the chain, by **reducing the body's formation of arachidonic acid** *in the first place*. This effect, again, is the result of tying up an enzyme – in this case, the enzyme which the body uses to *make* arachidonic acid (an enzyme called **delta-5-desaturase (d5d)**). Remember that, when it comes to eicosanoids, **arachidonic acid is the "root of all evil:"** all "bad" eicosanoids – both the series-2 prostanoids and the series-4 leukotrienes – are formed from this omega- 6 fatty acid. Every molecule of arachidonic can be used to make a "bad" eicosanoid … and thus, every AA molecule not made is a potential "bad" eicosanoid nipped in the bud. So if all omega-3s have these effects, why is it that ETA works so much better than its more common cousins? Simply put, **ETA does a better job than other omega-3s of binding up the key enzymes involved in making "bad" eicosanoids**. At this point matters become even more complicated, so you're forgiven if your eyes start to glaze over. One key point is **ETA is an alternative "substrate" for delta-5 desaturase, the enzyme that also makes arachidonic acid**: that is, ETA is a *raw material,* from which d5d can make a *product*. If you feed d5d the omega-6 fatty acid **dihommo gamma-linolenic acid (DGLA)**, it will churn out arachidonic acid. From arachidonic acid come the "bad" eicosanoids. But **if you instead feed ETA to d5d, it will make EPA**, the omega-3 found in common fish oil products (see **Figure 2**). And as long as d5d is busy making EPA, it can't make arachidonic acid. It can't take on both jobs at the same time. Though it's not immediately obvious, this series of relationships actually explains why ETA can tie up d5d more powerfully than can EPA, and thus more effectively prevent the production of arachidonic acid. That's because **enzymes always bind more strongly to their** *substrates* **than to their** *products*. So while both EPA and ETA can inhibit the arachidonic acid-producing activity of d5d, ETA has the edge, delivering a much stronger effect. And that edge yields double dividends. Not *only* does keeping arachidonic acid under control prevent the formation of *"bad"* eicosanoids … it also leaves the cell with extra DGLA, which can then to go on to make *"good"* eicosanoids, which have potent anti- inflammatory effects (see **Figure 2**). As a result, **ETA-based supplements are believed to actually increase production of "good" eicosanoids from DGLA**.[50] On top of this, substances made directly

from DGLA also inhibit the ability of COX and LOX machinery to make bad" eicosanoids.[51,52] It's a virtuous circle, with the end result being that **the more thoroughly you bind up d5d, the more you will inhibit "bad" eicosanoids …** *and* **the more you will support the formation of "good" ones**. Another factor in ETA's unique anti-inflammatory power is the fact that its chemical structure is so close to that of arachidonic acid (see **Figure 3**). Scientists believe that this similarity may allow ETA to "fool" the LOX enzyme into thinking that it *is* arachidonic acid, thereby again outdoing other omega-3s in keeping the inflammatory enzymes safely occupied, instead of busily making "bad" eicosanoids from arachidonic acid itself.[36,37] Certainly, studies in human immune cells consistently show that *Perna canaliculus*' **ETA-rich oil potently blocks formation of "bad" eicosanoids by both LOX[39,37,53] and COX.[39]**

Knowing It ... and Living It

In the end, what matters to users of ETA based omega-3 supplements is not learning technical terms from biochemistry, or understanding the fascinating underlying enzymology. What matters is relief from suffering, and restored functionality. **ETA based omega-3 supplements deliver what no other natural supplement can**: an orthomolecular substance, naturally present in the body and required for its health, which provides powerful support against inflammation in a way that other natural supplements can't match. In short: the biochemistry *explains* the results seen in animal studies and clinical trials. But only you can *experience* them … for yourself.

The Bottom Line

NSAID drugs like aspirin and ibuprofen work by tying up an enzyme which makes a family of micro-hormones called **prostanoids**. •The main **side-effects of NSAID drugs** are created because they keep the body from making both "good" and "bad" prostanoids. •The new **"COX-2" inhibitor drugs have fewer side-effects**, because they don't interfere with "good" prostanoids. •However, **COX-2 inhibitors may create long-term problems** by increasing the formation of another class of joint-damaging micro-hormones called **leukotrienes**. •Omega-3 fatty acids, such as the EPA and DHA in **common fish oils, can reduce the formation of both "bad" prostanoids and leukotrienes.** •Studies show that **ETA**, a rare omega-3 fatty acid, **has much greater anti-inflammatory powers than conventional fish oils**.

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