

OUTSIDE THE BOX

Derrick Lonsdale

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The “box” is a traditional way of describing actions that are the acceptable norms of the day. The “box” in a given profession like medicine has been repeatedly outdated. Professionals that get outside the current “box” are invariably laughed at and ignored or persecuted, depending largely on the perceived distance from the currently acceptable. Religious persecution may be an example. There are many classic examples of this in my profession and it applies to people in other professions. It requires an unusual perception to make a jump out of a professional “box”, often intuitive and a similar perception is required of colleagues for understanding the jump. Unfortunately, colleague appreciation is extremely rare and it is often understandable. Sometimes an innovation, perhaps only later to be supported by science, will literally trash the lifework of a given individual who has been at the center of the current “box”. It sometimes takes years or decades before the originality of such an innovation is recognized, often after the innovator is dead.

The best modern example of unusual perception was an initiation speech given by the dean to a new intake of Harvard medical students. He said: “please remember that fifty percent of what we teach you here will be wrong. The only trouble is that we don’t know which fifty percent”!

Perhaps the most classic example of lack of perception is one that is well known in the medical profession. Semmelweis was a Hungarian physician who discovered in 1847 that the incidence of post delivery puerperal fever could be drastically reduced by the attending physicians washing their hands with a chlorinated lime solution. His observations were based on the concept that there was “something carried on the hands of the physicians” and this conflicted with the established medical opinions of the time, “the current box”. The theory of diseases was highly influenced by ideas of an imbalance of the basic “four humours” in the body, a theory known as dyscrasia, for which the main treatment was bloodletting

Specifically, Semmelweis's claims were thought to lack scientific basis, since he could offer no acceptable explanation for his findings. This flies in the face of the fact that there was no evidence whatsoever of scientific support for dyscrasia. Of course, we all know now that the germ theory of disease confirmed that these observations made sense and today Semmelweis is regarded as the original pioneer that led eventually to the antibiotic era. Semmelweis was subjected to an appalling state of personal rejection and died in an asylum.

Even Louis Pasteur spent twenty percent of his time in making his discoveries and eighty percent trying to make them accepted. It is now considered that he introduced the first paradigm shift in therapy, the idea of “killing the enemy”. After eventual acceptance of the fact that organisms that could only be seen with a microscope were causing disease, the obvious approach was to try to find ways and means of killing them without killing the patient. It led to years of frustrating and dangerous treatments but the discovery of penicillin partially changed that although the present antibiotic era has its own problems as we all know. It is of absorbing interest that Pasteur is said to have stated on his death bed that “I was wrong: it is the body’s defenses that matter”. The concept of killing the enemy spread to the treatment of cancer and some antibiotics that were found to be too toxic became therapies for cancer. Cancer is now gradually emerging as a disease where a vital part of the immune system has been damaged.

Another modern example of predictable rejection is the discovery of magnetic resonance imaging, now generally referred to as MRI. The initial discoveries were made by Raymond Damadian who was called

a “mad scientist” while working on this theme. Paul Lauterbur of the University of Illinois at Urbana-Champaign and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology of Medicine for their “discoveries concerning magnetic resonance imaging.”

Damadian was ignored and in an interview done later, he was asked how you can spot an innovator. His answer was “Oh that is easy; he is the guy with all the arrows in his back”

It seems to me that we are passing through an extraordinarily important example of this in modern medicine, what I think of as “the second paradigm shift” paradoxically introduced by Louis Pasteur on his death bed. If this is true, then we have to ask the question of ourselves, what is disease and how can we prevent it? Should we really be trying to assist the body defenses rather than trying to kill the enemy or should we be trying to do both at the same time in the safest manner possible?

My forecast for the immediate future is that both paradigms must be established and that is exactly what Complementary (please do not spell with an i, it is not free!) Alternative Medicine is trying to establish. I will try to address the concept as I see it. How do we approach the subject of body defense, the important correlate to killing the enemy?

It is true that I might be repeating myself, but repetition sometimes helps a message to stick. We have an estimated 70 to 100 trillion cells that make up an adult human body. Each one is genetically endowed with a program that enables them all to work together to form function. It is impossible for this to happen without proper communication, so we have a computer in the brain called the limbic system. We know that it is a computer because it regulates and controls all our defenses automatically, perhaps the best known being the fight-or-flight reflex that enables us to perform superhuman actions. A recent publication recognizes the brain’s “instructions” to the immune system. It initiates our emotions. The more recently evolved and more sophisticated brain gives what I call “advice and consent”, apart from providing intelligence. It is known that for every message that goes from the brain to the bowel, there are 9 messages that go from the bowel to the brain. In fact, the brain “talks” to all the organs in the body. They talk to each other and back to the brain. One of the most important areas of research is the study of the messengers. When we use a successful drug that eases a symptom, it is like tearing up a telegram without reading its message. It stops the message but does nothing to its underlying origin.

This discussion is about to lead us outside the “box” because the brain/body relationship is not generally thought to be as important as I am implying here. Everything above the neck is thought of as mental and everything below it physical, or organic. I began to look over the side of the “box” when I was a resident in my teaching hospital. It was before the antibiotic era had become standard procedure and all we had was M&B, a code name for sulfonamide. One night, I admitted a middle aged man to hospital with pneumonia. It was also known that he had tuberculosis. In the morning, my chief was standing behind me in the ward entrance and said quietly, “I see that you have a dying patient”. He pointed out that the man was extending an arm toward the ceiling and “picking at thin air”, a sign, he said, of toxic brain. When he died, autopsy showed that his entire body was riddled with small staphylococcal abscesses. He never had a raised temperature and the laboratory reports were all normal. He did not have the slightest sign of a defensive reaction to his overwhelming infections. He did indeed have a sick brain! I began to understand that the brain was of the utmost importance in the brain/body exercise of survival, but which part of the brain was involved?

In the 60s I had to leap out of the “box” when I was confronted with a 6-year old boy with intermittent episodes of cerebellar ataxia. The cerebellum governs balance and when one of these episodes struck him, it was always in association with a mild infection, a mild head injury or even after an inoculation. He would lose his balance, develop slurred speech and behave as though he was affected by alcohol. Each of these illnesses would last about 10 days and he would recover spontaneously without any treatment. All the conventional studies had been performed and were negative. By studying his body

chemistry it turned out that he had a defect in a vital enzyme that governs the processing of sugar in the synthesis of cellular energy. The curious feature was that urinary metabolites that reflected the defect were higher during the day and lower at night, rising to a climax at the beginning of his spontaneous gradual improvement. It strongly suggested that circadian rhythm, the 24-hour brain cycle, was involved, for our hormones are released and controlled by this rhythm and the autonomic nervous system is cycled also.

The defective enzyme is enormously complex, enabling cells to synthesize energy from glucose for functional activity. It is particularly vital in the brain where oxygen utilization is the highest of all our organs. It only works properly with vitamins and minerals that include B1 and magnesium, two agents derived from diet that act as cofactors to many important enzymes. He had an inherited condition involving difficulty in using thiamine, vitamin B1, so it exactly imitated the classic nutritional disease scourge that has existed for thousands of years and known as beriberi. I wrote a short letter to the editor of the New England Journal about the case and a researcher by the name of John Blass at the National Institutes of Health was studying a similar case, read my letter and we collaborated. Blass subsequently was able to show that this boy's defect and that of his own patient was in the vitamin B1 component of the enzyme complex. John later became a well known investigator into the complex metabolism of thiamine and is now retired. He and his colleagues have reported that therapeutic thiamine does have a mild beneficial effect in Alzheimer disease and I would be surprised if anyone here has even heard of this fact. My patient required enormous doses of the vitamin, a condition known as vitamin dependency, a relatively rare genetically determined phenomenon. When he was given 600 milligrams of vitamin B1 (the normal requirement is 1.5 mg/day) his episodes ceased. Whenever he began a cold or minor infection he would double this dose. A similar condition has been described called Maple Syrup Urine Disease because the urine smells exactly like that of the best Vermont variety of syrup. It is also thiamine dependent in some cases. An intermittent Maple Syrup disease has been reported where each episode of metabolic breakdown is precipitated by a simple infection such as a cold. My patient's case was published in a pediatric journal in the 60s. The concept of a minor injury precipitating a metabolic breakdown is extremely important in considering the sometimes mysterious effects of some form of physical or mental stress. Diabetes sometimes begins after a cold or "flu" and even after receiving a telegram that delivers bad news.

It is instructive to report what happened when this boy had a minor head injury and was taken unconscious to the nearest emergency room. The mother tried to tell the doctor that he required an injection of thiamine and that he had a special case of thiamine requirement. Unfortunately it fell on deaf ears. The mother called me for help and I was unable to persuade the emergency room doctor about the details of his problem. Outside the box is like being stuck far from civilization in a car that is out of gas and with no telephone. It always reminds me of the story of Rip van Winkle.

It was this case that set me off on an exploratory journey into the library to ascertain all that I could find about vitamins, particularly vitamin B1. That interest continues to this day and Rick Rickards, who introduced me to the Club, used to send me articles from veterinary medicine for years. It became increasingly obvious that the brain/body relationship is vital to our understanding of disease. I liken the body to a fortress that has to be defended against a multitude of microscopic foes, toxic agents, psychological and physical trauma. I think of microorganisms making their point by attacking us to ascertain whether we are fit "experimental" subjects in the "Grand Plan" of evolution, wherever that leads us. The "command post" is in the limbic brain computer and its activity depends on its heavy consumption of oxygen that is the prime nutrient in the manufacture of cellular energy. The oxygen that we inhale is delivered to the tissues where it must be used in the complex machinery that governs the life-giving process of oxidation. The first tissues in the entire body to be affected first are the brain

computer and the heart, both of which work 24 hours a day and are avid consumers of oxygen. A defective limbic system affects our ability to adapt to the stresses and strains of survival. That is why the classic disease known as beriberi affects the brain, nervous system and heart. Thiamine governs the use of oxygen that is called oxidation and can be compared with a spark plug in a car engine.

The vital importance of energy synthesis and utilization was the essential message that was given to us by the great Hans Selye who called modern diseases “the diseases of adaptation”. His entire thesis depended on how much energy was required to meet the functions of daily life and that any form of stress automatically increases energy consumption. Selye was a Hungarian who, as a medical student, observed that sick patients always “looked alike” in their facial expression and body habitus, no matter what name the professor gave to the disease. He concluded that the thing that they all had in common was the stress of the disease itself. He immigrated to Canada and set up his “Stress Institute” in Montreal. He did thousands of experiments on animals that he stressed in various cruel ways in order to study the details of how their physical systems responded. It is absolutely amazing to read his report in a 1946 issue of the Journal of Endocrinology when he reported the General Adaptation Syndrome. The detailed biochemistry should educate us in reading the laboratory reports of human patients. Unfortunately the “antivivisectionist league” did their best to destroy his reputation and that has influenced the appreciation of the significance of his work. I think that it prevented him from receiving a Nobel prize that he dearly wished for.

I am proud to say that I had the privilege of visiting him at his Institute many years ago. I was first introduced to one of his graduate students and at 4.0 clock a bell rang and we literally ran down the corridor to have tea with the great man. Selye sat at one end of a long table and I was placed at the other. His staff sat on both sides of the table and when I asked a question of Selye they all turned their eyes on me in unison. When he answered they all turned to him and none of them participated in the dialogue. It reminded me of an audience watching a game of tennis or ping pong. After tea Selye took me into his office, lined with books, each of which had little paper stickers protruding from their pages. Each sticker marked a reference to Selye in the book. Then he took down a large book that fell open automatically at a double page showing photographs of about six or seven of the most important modern medical researchers. He passed his hand over the double page and said “this represents the medicine of the 21st century”. Guess whose photograph was there. I happen to agree with him for I believe that he really did open a Pandora Box that could influence our thinking of disease significantly.

His work is still largely unrecognized and very few physicians know much about it, but I predict that it will become increasingly important to our understanding of disease as the years roll on. My belief is that Canadians should be very proud of Selye’s Canadian association and his formulation of the General Adaptation Syndrome. He was, like Linus Pauling, outside the “box”. If he is not vindicated yet, he certainly will be!

I had the great pleasure also of visiting Linus Pauling at his Institute in California. On the first day I was introduced to an office and requested to read the pamphlets and literature that was abundant. The next morning I was in the same office and there was a knock on the door. I said “come in” and Dr Pauling popped his head around the door and said, “I understand that you wish to talk to me”. I was deeply impressed by the humble nature of this man, the greatest chemist of the 20th century. I spent the whole morning with him and after lunch I was privileged to present my own research to him and his staff. Afterwards I asked him what he thought I was accomplishing and he answered that he thought that I was stimulating brain enzymes. You may not be aware of how Pauling’s work was rejected by the medical profession and how his name became vilified. When I wrote my first book I called the late Mildred Seelig, famous for her work with magnesium, for a foreword but she was too busy. I asked her whether

Linus Pauling would be a good one to ask since I had met him. She said “Oh I would not do that for it might hurt your own reputation”.

In 1971 Pauling published a seminal paper in *Science* describing his concept of orthomolecular therapy. He argued that the body only functioned properly when the required molecules, many of which come from nutritional elements, were in place at their proper concentration. It led to the formation of an Orthomolecular Society in the West and another one in the East that was led by Dr Carl Pfeiffer, a psychiatrist who treated schizophrenia with vitamin therapy. I was privileged to be asked to speak at one of the Eastern meetings to address my work on Sudden Infant Death Syndrome, known as SIDS. In the wake of the drug cartel these efforts have had little impact as yet on the way that we practice medicine.

I want to expand a little on my own efforts to leave the “box”. My experience with patients at the Cleveland Clinic insisted that the present method of treatment only treated symptoms, but did not address the underlying cause. My interest in vitamin B1 led me to a series of papers in the prestigious journal named the *New York Academy of Sciences*. Each paper was written to give credit to Williams who had synthesized the vitamin in 1936. One of them reported that a thiamine supplement had been moderately successful in treating as many as 132 diseases. If this were really true, it would trash the current “box”. It was not only surprising, it was clearly in defiance of the current disease model that claims that each disease has its own cure”. Being inquisitive and because I had gained so much information from my reading, I started to try using thiamine for some of the children for whom treatment had been either unknown or where the drugs had failed to help. To my surprise and satisfaction, I found that some of them had dramatic improvement. It only encouraged my interest, but it was becoming clear that my colleagues were becoming increasingly suspicious of my actions. .

One day a child was admitted with a classic form of Reye’s disease. Some of you may remember that this tended to come in waves or epidemics associated with the flu season, so it was natural that research had focused on the virus. The disease produced a creeping paralysis of the brainstem where all the automatic life reflexes were managed, so death was a common outcome. The treatment, performed under the direction of a neurologist was ponderous and of little or no value, but this child was alive after it. The neurologist had a colleague visiting him and I was present when he discussed the case with his visitor. She was on a respirator and unconscious and the neurologist told his colleague that she had no hope of recovery and that she was brain dead.

I took this child into my care and loaded her with a form of thiamine that occurs naturally in garlic but has for years been synthesized in Japan. Because of my current interest in the vitamin, I had taken out an Independent Investigator License for this derivative of thiamine. It is called TTFD that stands for its biochemical name. Since there is no known toxicity, I gave her huge doses, at first intravenously and later by mouth. The first thing that we noted was that the cheeks became rosy instead of deathly pale and the vermilion color returned to her lips. This suggested that oxygen was being picked up by the blood and being conveyed to the tissues where its use was required. We know that the arterial oxygen concentration in beriberi is very low while it is high in the venous blood, so thiamin has much to do with the unloading of oxygen from blood to cells. She began to respond to the nurses and started to accept food from a spoon and developed a return of eye contact, yet she was still not conscious. This is a state called “coma vigilum”, the twixt and between unconsciousness and consciousness. She eventually walked out of the hospital although the residual damage ultimately affected her behavior. It was later found that Reye’s disease was caused by giving a child aspirin to bring the fever down when suffering from the flu. It was not the infection that killed the child, it was the treatment, an important offense of the rules set by Hippocrates who said that we should assist healing and that the worst thing we could do was to cause harm.

In my reading I discovered a paper in a prestigious British medical journal, written in 1942 by a Dr Fehily. She was an officer in the British Public Health Service and was sent out to Hong Kong, then still under British protection, to study a form of sudden infant death that was occurring there in the Chinese mothers. It occurred usually in a breast fed 3 month old male infant during the night. It was locally known as “breast milk toxicity”, but Fehily discovered that it was due to a deficiency of thiamine in the mother’s milk. It had the exact epidemiology of modern SIDS. Investigators at that time who were studying beriberi noted that the infantile form of the disease produced this kind of sudden death. and published the fact that “sudden death in infants is pathognomonic of beriberi.

You may remember that the Japanese invaded Hong Kong and the Chinese people, which of course included the breast feeding mothers, were put on starvation terms. Although their infants were also starving and failing to thrive, the incidence of sudden death disappeared, only to reappear after the Japanese left and the rice intake was unrestricted.

This became for me a revelation that has given me the idea of what I call the “Choked Engine Syndrome” If you try to run a car engine with gasoline without a sufficiency of oxygen, or an inefficient spark plug, the engine suffers and its power is diminished. You ingest an excess of carbohydrate with insufficient thiamine, you develop beriberi. The presence of oxygen in the blood is useless unless it is consumed in the complex mechanisms of oxidation. My good friend Dick Wooley suggested to me at a PCC meeting that I thought of nothing else but oxidation. He was pretty close to the truth.

One day I was confronted with an infant whose parents had heard him gasp and stop breathing while he was asleep. They had rushed to an emergency room where this very healthy looking infant was found to be quite normal in the examination and was sent home. The parents were so scared that one of them would watch the infant at night while the other slept and they took shifts. When it happened repeatedly the parent would lift the infant from his crib and he would start breathing again. I admitted him to the hospital but could find no cause. So, extracting my knowledge from Fehily, I started thiamine and there were no more incidents. Well, finding a dime on the ground does not mean that there is a fortune underneath so two of my colleagues joined me in investigating this further. One was running the pediatric intensive care unit and the other was an audiologist who was an expert at using a tool that examines the electrical waves that occur in the brainstem with an auditory stimulus. Not only did we show some abnormalities that improved with the administration of thiamine, we found that there was asymmetry in the wave patterns that were produced in some of these infants who by then had been recognized as Threatened Infant Death Syndrome.

Can you imagine the horror of finding your 3-month old infant dead in his crib in the morning? We got to the point that we should get this information out to the public as an urgent message and gave a press release, hoping to stimulate further interest and study. That was a mistake! We became aware of the evils of attempting innovative communication. We felt that we could actually predict the possibility of SIDS and treated many of these infants with thiamine. A researcher also published her work on the use of magnesium, a mineral that is essential to the role of thiamine. No matter that positioning the infant in the crib has become the accepted preventive method, it still occurs and it is the disadvantaged, low income family where appropriate nutrition is difficult. We found ourselves again outside the “box”. However, I want to mention a case that arose from this work since it tends to illustrate the point of my presentation. Early in my career at Cleveland Clinic I knew every physician on the staff by first name. I was number 52 when I joined the staff in 1962 and I believe that there are now over 500 physicians and researchers there now. Even that may well be an underestimate. One day I was having lunch with an Ear Nose Throat surgeon. He said “you know Derrick, you should go up to the medical intensive care unit and see the case of Mrs M. She was unconscious and stopped breathing. I had to put a tracheostomy tube in. It reminded me” he said “of your work on SIDS”. Believe it or not, she was the most obvious case of

beriberi that I had ever seen. When given large doses of thiamine she recovered, except for permanent damage that made her wheel chair bound. The massive edema that is the hallmark of the disease disappeared and she turned out to be an extremely intelligent woman with whom I became a friend.

Here is the odd thing about this case: I was a pediatrician, a doctor who is generally regarded as looking after small people and adults are not supposed to be within their province, even though the biochemistry is the same. So she was under the care of an internist who never accepted the diagnosis and refused to bring the case for discussion at Grand Rounds where odd cases are normally brought out and discussed for the benefit of all. This was in spite of the fact that the patient confessed to years of beer drinking and she was a heavy smoker, both of which injure the ability of our cells to use oxygen efficiently, one because of the high calorie intake and the other because of carbon monoxide and other toxic agents. Although a number of physicians observed the clinical changes in this woman I was never asked a single question by any of them and no discussion took place concerning what was to say the least an unusual recovery in a patient that had remained an undiagnosed problem for some time. I can only presume that they considered it to be a “spontaneous remission” that is often used as a term to cover our ignorance. There is no doubt that being outside the “box” has much the same connotation as the “whistle blower”. Often intuitive, it can ruin a career but often results in advances with which science sometimes catches up years later.

There were just one or two physicians and researchers in Cleveland in the 70s who were thinking along the same lines as I was and we met in each other’s houses like the early Christians. At that time it was dangerous to talk about nutrition and vitamins because it was considered to be a return to the so-called “snake-oil era”

In closing, I want to mention two fairly typical cases that I have dealt with in my present practice. One spring day, a fourteen-year old boy came into my office on crutches with a diagnosis of rheumatoid arthritis. He went out for football in the subsequent fall. Naturally the question that might be asked is “was it the right diagnosis or are you kidding yourself”? Well, I didn’t make the diagnosis but the use of crutches suggests severe incapacitation. I treated a young girl with the same diagnosis and after her recovery her father went to the rheumatologist to tell him that there was perhaps another way and that he might like to hear about it. The rheumatologist turned his back on the father and left the room without a word. I am sincerely confident that Complementary Alternative Medicine will ultimately become more accepted and I was not particularly surprised to see that the Cleveland Clinic hosted a seminar on this very subject in Chicago in November 2010. Perspectives that have long been accepted as the paradigm can change dramatically and history has demonstrated this repeatedly.