A STORY of CROHN’S DISEASE

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Review Edition
DEDICATION

PREFACE

“Science is driven by the desire for answers that, in turn, demands answers. Our world is long on intelligence, but short on creative imagination. What makes a scientist is the same element that distinguishes the poet from the writer. Like the poet, the scientist must dedicate in order to perfect his or her art. The creativity of a scientist is not in the answer, but in the question asked”

Donald Barron
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Part 1
CROHN’S DISEASE

WHAT IS CROHN’S DISEASE?

• Crohn’s disease is an inflammatory disease of the human gastrointestinal tract. The primary regions affected are the small bowel and the first portion of the large bowel.

• The disease causes affected individuals to precipitously seek a bathroom many times a day.

• One in four afflicted individuals will have one or more surgery’s to remove diseased bowel.

• The characteristic time of onset is between 11-24 years of age. A second, smaller disease group occurs at a time of waning immunity late in life.

• The early onset of Crohn’s disease now tends to involve more children.

• For most afflicted individuals, Crohn’s disease is a lifelong affliction.

• In 2002, the CDC had placed the number of US cases of Crohn’s disease at 200,000. By 2012 there were over 800,000 cases of Crohn’s disease in the United States and over 1.5 million cases in Western countries.

• Certain ethnic populations appear to have a greater predisposition to disease than do other ethnic groups.

• Western countries are in the midst of a growing Crohn’s disease epidemic.
• As the economies of third world countries have improved, the prevalence of Crohn’s disease in these populations has dramatically increased.

• In the United States, the medical costs to an individual afflicted with Crohn’s disease are $12,000-$18,000 a year.

• The United States’ annual medical and indirect costs from Crohn’s disease are estimated to be over $10 billion and $4.2 billion respectively.

• Crohn’s disease causes a significant number of afflicted individuals, in the midst of their most important earning years, to prematurely leave the work force or change employment to accommodate the demands of the disease. The progressively increasing medical costs of Crohn’s disease are being assumed by the federal government.

• The number of new cases of Crohn’s disease a year is increasing worldwide.

Simply stated, Crohn’s disease is a destroyer of lives and life itself.
MILK’S ZOONOTIC BRIDGE

Dorland’s Medical Dictionary defines zoonosis (zoo plus the Greek nosos meaning disease) as a disease of animals that may be transmitted to man under natural conditions. The term, zoonotic, means being able to be transmitted an infection from animals to man under natural conditions.

Historically, the United States Department of Agriculture (USDA) has given special attention to micro-organisms that have negative effects on agriculture and agriculture-dependent businesses. When agriculture-based, zoonotic pathogens threaten a significant element within agribusiness, USDA has been prompt to act to destroy the transmission bridge between the source and man.

Two prime examples of USDA’s interventions when the public health had been threatened are brucellosis and bovine tuberculosis due to *Brucella abortus* and *Mycobacterium bovis*, respectively. The brucella organism was transmitted to humans through wool and animal contact. USDA instituted a policy (test-and-cull) in which each animal within the herd was tested and those that tested positive for brucella antigens were removed from the herd and destroyed. Cows infected with *M. bovis* had the potential to shed viable organisms into unpasteurized milk. When ingested in sufficient quantity, this mycobacterium produces chronic enteritis that is not dissimilar to that characteristic of Crohn’s disease. Again, the policy of test-and-cull was implemented. The threat to agriculture was deemed so significant that when an animal was documented to be infected, not only was it destroyed, but so were all of its herd mates.
MILK

Milk is critical in conveying nutrition and, in some cases immunity, from a female to its offspring. In nutritionally stressed countries, survival of an infant is largely influenced by the age the child is taken off the mother’s nipples in order to feed the next baby.

Perception of the nutritional value of milk has resulted in the rearing of animals (cows, goats, sheep, camels etc.) for the express purpose of providing a food source for human consumption.

In 1863, Louis Pasteur found that if he heated the local grapes to about 50-80 degrees Centigrade for a brief period of time, he could prevent the wine from souring. Heating the wine eliminated contaminating microbes. The occasional presence of pathogenic microbes in milk extended the utilization of pasteurization.

Pasteurization does not kill all the microbes present in milk. What it does is reduce the number of organisms, thereby allowing the taste of the milk not to be impaired until after a calculated expiration date. High-temperature, short-time (HTST) pasteurized milk typically has a refrigerated shelf life of two-three weeks. Ultra-pasteurized milk can last longer. HTST pasteurization is designed to achieve a five-log reduction, killing 99.999% of bacteria such as Salmonella, Listeria, Campylobacter, Staphylococcus aureus, pathogenic Escherichia coli, and Mycobacterium bovis among others.

The set point for temperature and duration of pasteurization is determined by the potential pathogenic micro-organism that can potentially contaminate or be shed into milk. The most important milk-related pathogen had been Mycobacterium bovis.

Modern day mycobacterium groupings are the result of their divergence through an apparent evolutionary bottleneck into two interrelated, but distinct families. One subgroup is thought
to have evolved from *Mycobacterium bovis*. The other is derived from *Mycobacterium avium* or possibly *Mycobacterium hominissuis*. 
**MYOCOBACTERIUM BOVIS**

*Mycobacterium. bovis* is a main cause of tuberculosis in cattle and other mammals. Infection/disease is most frequently acquired by oral ingestion of the organism resulting in gastrointestinal disease as its primary clinical manifestation. In the Middle Ages, the fashion of very high collars covering the entire neck was due to tuberculous and non-tuberculous mycobacterial infection of the regional lymph nodes causing disfiguring masses and fistulae (scrofula). In children, scrofula was due primarily to non-tuberculous mycobacteria.

It has been theorized that human *Mycobacterium tuberculosis* evolved from *Mycobacterium bovis*. The Calmette-Guerin strain of *M. bovis* is used to produce the human BCG tuberculosis vaccine.

U.S. figures for deaths (pre-pasteurization) due to *M. bovis* have been difficult to obtain. Between 1912 and 1937, an estimated 65,000 individuals in England and Wales died from the disease of the gastrointestinal tract disease contracted from consuming milk containing *M. bovis*.

To address that threat to the public health and to protect milk’s importance within the national economy, the United States Department of Agriculture (USDA) embarked on a successful “test-and-cull” campaign to eradicate *M. bovis* from the nation’s domestic herds.

This threat to dairy and dairy-related industries was ultimately resolved when it was demonstrated that *M. bovis* could be destroyed by proper pasteurization.
MYCOBACTERIUM AVIUM
SUBSPECIES PARATUBERCULOSIS

*Mycobacterium avium* subspecies *paratuberculosis* (MAP) belongs to the group of mycobacteria that are theorized to have evolved from *M. avium*. MAP, being a relatively newer strain, exhibits greater disease producing potential than *M. avium*.

MAP has a near global presence in soil. The microbe’s reservoir is in soil and contaminated water. Not surprisingly, MAP can become embedded in the food supply of animals that eat grass and plants. MAP infection has been identified in almost every herbivore studied in depth: cows, sheep, goats, deer, elk, buffalo, camels etc. Animals such as rabbits that share pasture with infected animals can also become infected and disseminate the organism beyond the confines of fixed boundaries.

Animals become infected primarily by consuming plant material or water containing MAP. Grass-feeding animals, both wild and domestic, ingesting the organism become infected. When certain conditions are met, a small number of infected animals develop a chronic granulomatous infection of their gastrointestinal tract. In cattle, the resultant disease is called paratuberculosis or *Johne’s disease*. Diseased animals develop soft stools that eventually progress to profuse diarrhea. If allowed to run its course, the disease is usually terminal.

Like *Mycobacterium tuberculosis* in humans, MAP has been shown in rare cases to cross both the placental and blood-brain barriers in cattle, causing mother-to-fetus congenital infection to occur.

In milk production animals whose immune systems are not able to inhibit continued MAP reproduction, infection progresses to disease. Animals with active infection produce less milk, have poorer reproductive outcomes, and lower slaughter weight.

On a global level, MAP infection/disease of domesticated milk producing animals is a multi-billion dollar problem for producers.
The primary concern of the veterinary world has been reducing the economic cost to producers from MAP induced disease.

Once MAP is introduced into the pasture environment, elimination of the organism is extraordinarily difficult. Even if elimination of MAP could be achieved, the ultimate reservoirs of infection cannot be easily eradicated. MAP infection in dairy herds acts much like *Mycobacterium tuberculosis* in humans: disease is a small percentage of infection. Within a confined herd, once a resident animal develops clinical signs, a significant number of animals within the herd will have already been infected.

The gastrointestinal tract of animals, as well as humans, contains complementary receptor sites that allow MAP to attach to the mucosa. Human MAP isolates have been demonstrated to have similar genetic markers to animal MAP isolates, making it, more probable than not, that MAP isolates cultured from human beings could produce disease in susceptible animals and vice versa. The universal presence of these receptor sites has explained the ease with which MAP can cross species barriers. The MAP of a goat or an elk can infect cows and humans vice versa.
CROHN’s DISEASE

Crohn’s disease is a chronic granulomatous inflammation of the human gastrointestinal tract. The primary areas affected are the small and large bowel. In the United States, an estimated 800,000 individuals are currently afflicted. Individuals with Crohn’s disease experience the sudden, often explosive, need to defecate many times a day. One in four affected individuals will have one or more surgery’s to remove diseased bowel. The characteristic time for the onset of multiple bowel movements or diarrhea is between ages 11-24. A second smaller disease group occurs at a time of waning immunity late in life.

For most individuals, Crohn’s disease is a lifelong affliction. It causes a significant number of afflicted individuals in the midst of their most productive earning years to prematurely leave the work force or change their employment to accommodate the demands of the disease.

The United States is in the midst of a Crohn’s disease epidemic. According to the National Association for Colitis and Crohn’s disease, in 2001, Crohn’s disease affected about one in every 1,600 individuals: In 2002, the Center of Diseases Control and Prevention estimated the number of afflicted individuals to be 200,000. By 2010, the estimated number of cases of Crohn’s disease in the United States was said to number 800,000. Along with the increase in the number of cases, there has been a shift in the demographics of the age at which individuals first develop symptoms of the disease. Onset of disease is becoming more common in early childhood.

In the United States, the annual medical cost for Crohn’s disease therapy has been reported to be conservatively between $12-18,000. The overall annual medical cost is estimated to be over $10 billion. No indirect or societal costs of Crohn’s disease have been published to date. Owing to the disease’s debilitating effects, the burden of payment is increasingly being borne by the federal government.
The United States is not alone in experiencing an epidemic. The industrialized nations in Europe are similarly in the midst of similar epidemics of Crohn’s disease. There are between 1.5-2.0 million cases of Crohn’s disease in westernized countries. As the economies of third world countries have shifted to Western style living, the incidence of Crohn’s disease has dramatically increased.
THE CAUSATION HYPOTHESIS

Hypothesis is little more than an upscale word for a thought out guess. In medicine, most sophisticated guesses are derived from observations derived from experiments in nature.

Medicine is not a pure science. Being pure sciences, the laws within mathematics or physics always render the same answer. Medicine is a pseudo-science. Its facts are never identical. The foundations of its so-called “scientific truths”, more often than not, are the residues of coinciding probabilities. Much of medicine is conjectural science, based upon statistics which serve as empirical enumeration of observations.

The French physiologist, Claude Bernard, wrote “the application of mathematics to natural phenomena is the aim of all science”. He went on to state that attempts to apply mathematics to medical problems were flawed because the empirical data would always be insufficient. He therefore held that the most useful pathway for medicine to follow was to seek to discover new facts instead of trying to reduce to equations the facts that science already possesses. In his classical work, *The Study of Experimental Medicine*, Professor Bernard describes the guidelines by which conjecture becomes a “scientific truth”.

To translate an observation in nature to a pseudo-scientific fact, involves four steps:

- Gather all the information relevant to the observation under analysis.
- Construct a hypothesis to account for the proposed postulate relating to the observation.
- Construct an experimental design to, not support the hypothesis, but challenge the hypothesis.
- Reinterpret the hypothesis in light of the data.
An unwritten part of Claude Bernard’s scientific method is that the exceptions must prove the prevailing “scientific truth”.

A brilliant physician and scientist, John Hermon-Taylor, described a case of a young boy with scrofula from which MAP was recovered. Subsequently, the boy went on to develop Crohn’s disease. Seizing upon his observation, Hermon-Taylor and his collaborators have gone on and produced an impressive body of work in support of his hypothesis of causality.


A major difference between the histopathology of Johne’s disease in cattle and Crohn’s disease in humans is that, while MAP DNA could be demonstrated and MAP could be cultured from diseased human tissues, special stains did not demonstrate the presence of acid-fast bacilli. This disconnect between DNA observation, culture and histological demonstration of a mycobacterium was ultimately addressed when it was demonstrated that, in feces, MAP lost its stainable outer covering and persisted as a spheroclast.

In 1996, Chiodini and Rossiter isolated MAP from the feces of 26 out of 135 patients with Crohn’s disease, but from only one of 121 control individuals.

Chiodini and Rossiter’s experimental design was to compare the presence of MAP in the stool of individuals with and without Crohn’s disease. The results, while circumstantially supporting the hypothesis of causality, were far from incriminating. Changes induced by a disease process will significant alter the gastrointestinal tract’s microbial flora. In theory, the tissue destruction observed in Crohn’s disease could independently
select for the retention as MAP within the resident micro-flora. Guilt by association is at best an invitation for further investigation. What was important is that MAP was isolated from the stool of one individual without Crohn’s disease. A **scientific truth** must address its exceptions. The 1996 isolation of MAP from a non-diseased individual was the exception that demanded an answer.

The embers of the MAP/Crohn’s disease hypothesis simmer until scientific publications documented the presence of viable MAP organisms in pasteurized milk. Confirmation of a potential zoonotic pathogen in milk had the potential to be the opening of a Pandora’s Box.

When a possible issue concerning food safety is identified, the advocated societal response is spelt out in the Rio Declaration on Food Safety and then again in Sanitary and Phytosanitary Measures of the World Trade Organization.

The 1992 United Nations Conference on Environment and Development issued The Rio Declaration on Food Safety. Principle 15 of the Rio Declaration states: “In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full knowledge shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.”

In 1994, The World Trade Organization published its Agreement on Sanitary and Phytosanitary Measures. Article 5.7 allowed regulatory measures “where relevant scientific evidence is insufficient to demonstrate the safety of a product or commodity”.

The fires of controversy received a bucket of cold water by a 1997 publication from a group of USDA scientists headed by Judith Stabel. The paper showed that the high temperature, short duration pasteurization used in the United States destroyed MAP that had been seeded into milk. Irene Grant, among others,
criticized the methodology. The USDA scientists had taken frozen MAP organisms and then sonicated them, thereby allowing for a predictable outcome. Subsequently, when milk was taken from regional grocery stores in the five most important dairy states, over 2% of the containers contained viable MAP organisms. Despite scientific criticism, USDA never issued a retraction of their findings. This paper was later used in congressional testimony by the Food and Drug Administration (FDA) to reassure Congress that pasteurized milk in the United States was safe.

MAP was long considered to be but an opportunistic zoonotic pathogen for humans: causing disease in, primarily but not exclusively, individuals whose immune system had been impaired by retro-viruses (AIDS). In May of 1999, the National Institute of Allergy and Infectious Diseases (NIAID) published its research agenda in which it targeted seeking an infectious cause of Crohn’s disease as a possible research objective. This topic went unfunded.

In 2000, Naser and co-workers isolated MAP from the milk of two lactating women with Crohn’s disease and none from samples from five normal control women. The number of critical observations would have been ridiculously small were it not for the source from which MAP was recovered. MAP in feces is one thing, MAP in breast milk identifies systemic invasion.

Responding in part to this new piece of information, the Centers for Disease Control and Prevention (CDC) reputedly explored the possibility of funding to identify risk factors for zoonotic human disease due to MAP. This too went unfunded.
RESPONSES TO A HYPOTHECTICAL RISK

Lord Justice Phillips’ 2001 report to Her Majesty’s Government states “Where the likelihood of a risk to human life may appear remote, where there is uncertainty, all reasonably practical precautions should be taken …… The importance of precautionary measures should not be played down on the grounds that the risk is unproven.”

In 2001, the Office International des Epizooties (OIE) listed paratuberculosis (the disease caused by MAP) as a disease of major global importance. Paratuberculosis was categorized as a List B pathogen in terms of its socioeconomic and/or public health importance.

In June 2001, the United Kingdom Food Standard Agency issued its report for food standards. The conclusion statement contained the following language “There is undoubtedly sufficient cause for concern (relative to MAP as being the cause of Crohn’s disease) for further action to be taken urgently to determine what the available data means …… This question can be divided into two areas: What action should be taken to reduce exposure to MAP even though the causal link is not established; and what action can be taken to increase the knowledge base so that future decisions may be based upon more information.”

In 2001, the Office International des Epizooties (OIE) listed paratuberculosis (the disease caused by MAP) as a disease of major global importance. Paratuberculosis was categorized as a List B pathogen in term of its socioeconomic and/or public health importance.

In 2001, the United States Congress held hearings as to whether MAP constituted a potential hazard to the public health. In step with the United Kingdom, Congress determined that there were sufficient grounds for concern to justify substantial funding to increase the “knowledge base”. Rather than awarding funding to the National Institutes of Health or the Centers for Disease Control and Prevention, Congress did something
surprising and gave USDA *stewardship of determining if MAP constitutes a public health hazard.*

With ultimately $90,000,000 at its disposal, USDA set about addressing MAP’s impact, primarily as it related to its ability to adversely affect production economics. In April of 2002, USDA-APHIS published and funded implementation of the Uniform Program Standards for the Volunteer Bovine Johne’s Disease Control Program and instituted a five year Johne’s Disease Prevention Dairy Herd Demonstration Program. Rather than addressing the elephant in the room, MAP as a public health hazard, USDA implemented a test-and-cull demonstration program. When it ultimately became apparent that identifying infected animals and removing them from the herd was neither economically feasible nor capable of eliminating MAP from infected herds, the massive demonstration project became primarily an expensive data gathering vehicle that lost its scientific identity.

USDA chose neither to address the challenges to the program’s governing premise nor to address Congress’s initial motivation for funding the program.
RECRUITMENT

How I became involved with the MAP began in 1969 on a cold January Saturday at Cross Creek, Florida. The organizers of the bass tournament drew for the pairing of partners. Once done, two individuals were left: J. Elliot Williams and me. Neither one of us had a boat, much less a bass boat; but, I had access to an electric trolling motor. Renting a boat and motor and having one person fish while the other held the trolling motor against the side of the boat, a friendship was born. Elliot won the tournament and I came in a respectable fifth.

Elliot had worked in various capacities as a laboratory technician and ultimately as a senior biological scientist at the University of Florida College of Veterinary Medicine. About the time I left the University of Florida College of Medicine to become a professor at Creighton University School of Medicine, and ultimately an assistant dean, Elliot begun working for a distinguished veterinary pathologist at the University of Florida College of Veterinary Medicine, Claus D. Buergelt. His research interests centered on *Mycobacterium avium* subspecies *paratuberculosis*. By virtue of his employment, Claus’s interests became Elliot’s. When not focused on fishing, the correspondence between Elliot and me often involved his work in Claus’ laboratory. In retrospect, he was slowly playing out the bait to me.

Even though I was then recognized in Who’s Who in Science and Technology as well as Medicine, co-founded both the U.S. and the International Infectious Disease Society for Obstetrics and Gynecology, and wrote the definitive text on the subject., as for knowledge about MAP, I was a little south of ignorant.

When you are not interested in a subject, you tend to be either a slow learner or what Italians term a “capta dura”. Exchanges of ideas about MAP did not graciously transcend the barriers of distance and time. When I finally got it, I got it. Veterinary medicine and that of humans were on a collision course from
which there would be but two losers. In a worse scene scenario, MAP had the potential to be an incredible two headed dragon: one, a threat to the nation’s economy and the second, a threat to the public health.

While I was still at Creighton University School of Medicine, Elliot arranged for me to meet Professor Claus Buergelt. Claus was then the longtime treasurer for the International Association for Paratuberculosis. For Claus, nirvana was to be in the necropsy room or behind a microscope. His fears of being wrong had been a source of frustration for Elliot.

While previously at the University of Florida College of Medicine, I had created in 1973 a virtual company, Infectious Diseases Incorporated (IDI) to capitalize on my knowledge about infectious diseases. IDI effectively worked as a research and educational resource for the pharmaceutical industry and the American College of Obstetricians and Gynecologists.

Once I became an assistant dean at Creighton, I had had to farm out scientific ideas to close colleagues at other institutions. I had been rusting out. Having published well over a hundred peer-reviewed papers and a similar number in non-peer reviewed publications, there were but a few mountains to climb. My work at the University of Florida had been the cornerstone of the CDC radical change in the therapy for women with acute salpingitis. The CDC’s final recommendations were written on my dining room table. I had co-founded both the US and international Infectious Disease Society for Obstetrics and gynecology. My text book on Infectious Diseases in Obstetrics and Gynecology was the prevailing text. When the opportunity presented itself for early retirement, I took it. MAP offered me the opportunity to return to engineering bench research. In 2001, I accepted a buyout and started “a daring adventure with cows” (Helen Keller - “Life is a daring adventure or nothing”).

Returning to Florida was a home-coming of sorts. Come football season, I would bleed orange and blue. My four children had
been born in Gainesville. Despite living in Omaha, Nebraska, I had kept my beach home in Cedar Key, some 60 miles due west of Gainesville.

Gaining acceptance at the University of Florida College of Veterinary Medicine was facilitated by my prior employment. While at the University of Florida College of Medicine, I had been one of two first time faculty members to be given tenure after three years. The current Vice President of Medical Affairs was an extraordinary leader named Gerald Schiebler. His strong endorsement of me carried uncontestable weight.

In 2001, Charles Courtney, Associate Dean for Research and Graduate Studies gave me a courtesy faculty appointment in the Department of Pathobiology as a Visiting Scientist. Later that year, a strategic partnership was signed between Infectious Diseases Incorporated and the College of Veterinary Medicine.

The initial passport into Dr. Buergelt’s laboratory was Elliot’s strong recommendation. Claus was true to his Germanic heritage. He was a strong believer in the law of gravity: translated, nothing was supposed to defy that law, including innovative ideas. Years before, Doctor Schiebler had taught me that “Fiscal control is total control”. The ultimate passport was money. The first seed money came from IDI. Subsequent funding was derived from grants that became the underpinnings of the laboratories expenses.

Despite our divergent French and German heritages, in time, Claus and I established a mutual relationship of respect. In the end, Claus would describe me to others as the scientist from Mars. At the University of Florida College of Veterinary Medicine, two very special individuals, Jerry Davis and Maureen Davidson, along with Elliot Williams, ultimately translated Martian into a living language for Claus.
A GARDEN OF WELL FERTILIZED WEEDS

“A little bit of fertilizer benefits the garden of science, but too much fertilizer stinks up the house of science.”

The garden of MAP was a mess. Creative investigative work into the immune response induced by MAP and genomic characterization of MAP and polymorphic variants had produced beautiful flowers. But, their presence tended to be overshadowed by a large number of “measurement papers” which, more often than not, lacked a governing hypothesis.

Measurement without a hypothesis to challenge is not science!

Worse was the frequent advancement of a theory as scientific law that had not been substantiated by experimentation designed to challenge its premise.

When you are extended an invitation to live in someone else’s conceptual house, you try to live by the house rules and so it was with paratuberculosis.

Explanation of the pathogenesis of MAP infection/Johne’s disease had been constructed by Claus and the godfather of veterinary pathology, Robert Whitlock. Based upon primarily measurement observations, they envisioned a three stage progression from infection to disease to disease. MAP infects the animal. The animal is asymptomatic. No detectable antibodies to MAP are present. Demonstration of the organism is limited to occasional MAP fecal recovery. In stage two, months or years later, antibodies to MAP are demonstrable; however, the animal is still without clinical manifestation of diarrhea and weight loss. Stage three is characterized by multiple soft stools that progress to watery diarrhea and, in time, the death of the animal.

To anyone with knowledge of infectious diseases, the proposed natural history of MAP and particularly the long period of latency were different from that known for other pathogenic mycobacteria. Only Mycobacteria leprae had any possible overlapping features.
My first instinct was to give my peers credence; but that was short lived. The natural history of Johne’s disease had been constructed using two tools: MAP identification in feces and demonstration of antibodies to MAP. The tools supported the proposed pathogenesis; however if you looked closely at the tools, problems became evident.

Fecal recovery of MAP was stated to be the “gold standard” by which MAP infection was documented. While being highly specific for MAP, culture identification was notoriously insensitive. You could have an animal with classical MAP clinical signs and symptoms, a high anti-MAP antibody titer and still not recover MAP from its stool. The obvious question was if you had a recovery system that failed to identify MAP in known cases of disease, how well did it function for animals with early or subclinical infection. The answer was poorly.

Cow feces became a cesspool for poorly thought out ideas. Feces from diseased animals contain large quantities of MAP. Such animals were designated as “super shedders” and, as such, constituted significant risk to their uninfected herd mates. When a fecal specimen grew out a certain number of MAP colonies, the significance of the observation and term was often transposed to the animal without a corresponding correlation to the animal’s health status. The designation implied that this was an animal with advanced subclinical or actual disease. Identification of being a super MAP shedder was a passport to a premature exit from the herd and transportation to a slaughter house.

Unlike *M. bovis*, MAP grows *in vivo* in clumps, As a consequence, its distribution could be uneven and its growth on artificial media could be influenced by the size of the clumps within a given sample. This fact should have alerted investigators to the potential that quantitative assessment of the growth of MAP could be biased by sample error or by the relative clump sizes within the fecal specimen.
To investigate the potential that sample error existed, we teamed up with USDA officials in Florida. They facilitated our access and use of USDA’s Florida Johne’s Disease Dairy Herd Demonstration Project. The hypothesis was that sample errors existed within MAP fecal specimens. The experimental design was simple enough: have three different samples from the same fecal specimen tested by three different tests done at different veterinary diagnostic laboratories. The participating laboratories were blinded as to the clinical status of the animals being sampled. In addition, serum from each animal was sent to the State of Florida Veterinary Diagnostic Laboratory for the determination of whether anti-MAP antibodies could be identified. Out of the 327 fecal samples analyzed, 22 animals were identified as heavy shedders. Ten fecal specimens lacked confirmation in either of the two parallel tests. All 10 animals also lacked identification of anti-MAP antibodies in their blood as determined by a USDA certified MAP ELISA test. Five of these animals had their blood retested from 8 to 14 months later. Again, no anti-MAP antibodies were identified.

This type of information had put into question the Buergelt-Whitlock postulate of the natural history of MAP. In defense of his postulate, Whitlock advanced the idea that the transient fecal identification of MAP in the absence of anti-MAP antibodies was due to “pass through”. What was meant by pass through was that the animal ingested MAP, but that microbes did not attach to the mycobacterium receptor sites that line the entire gastrointestinal tract. Such a phenomenon would have required an animal to ingest an incredible amount of MAP to saturate its mycobacterium receptor sites. That “pass through” had acceptance in the veterinary literature was a tribute to the esteem with which Robert Whitlock was held by the veterinary community.

The real gold standard was not fecal recovery but the demonstration of infection at necropsy. It was not used because it would be difficult to obtain a large number of observations in order to achieve statistical significance. Nonetheless, when it was in place and used, necropsy-based data demonstrated
that what was thought to be known about Johne’s disease was primarily a tale created with smoke and mirrors.

In the United States, the two principle blood tests to determine the presence of MAP antibodies were HerdChek® and ParaChek®. Both these tests were the tests certified by the USDA and set the standards against which every other test would be judged. When tested against the real gold standard, they identified at best 30% of infected animals. At worse, McKenna and coworkers showed that commercial MAP ELISA tests detected only 6.8-8.8% of tissue positive cattle. In one of our publications published in a peer-reviewed journal, the correlation between the presence in animal feces and a positive commercial MAP ELISA test varied between 7.3% - 13.5%.

Beyond the marginal predictability of determining whether an animal was infected was the observation that HerdChek® and ParaChek® occasionally would produce test results that contradicted the other test. The HerdChek(R) would identify a rare cow with Johne’s disease as having specific anti-MAP antibodies and the ParaChek® would not and vice versa. The “why” was dismissed as laboratory error, even when the sera came from the same diseased cow.

The WHY cried for an answer. That answer resided in the antigens used by the different utilized. In one case the antigenic array was not derived from a proto-typically strain of MAP, but from Mycobacterium 18, a mycobacterium that was more like Mycobacterium avium than MAP. The two tests had identified mycobacterial strains that were closely interrelated but yet distinct enough to cause a false-negative test.

Once we had developed our first-generation MAP ELISA test that USDA certified, comparative tests were done.

Test sera were drawn from specimens obtained from the University of Florida’s Demonstration Dairy Herd that Claus’s veterinary diagnostic laboratory had been monitoring. Eighteen sera with prior known varying titer of antibodies were identified
and rested using ParaChek®, HerdChek® and our early version of the FUIDI #1 MAP ELISA test. Neither ParaChek® or HerdChek® identified any of the sera that that tested out as being low positives; two and one respectively out of the six intermediate positive sera; and four and five out of the strongly positive sera.

To push what was becoming obvious a little further, we extracted from the archives of the College of Veterinary Medicine cases which by clinical and gross anatomical findings and histopathology were cases of Johne’s disease and which still had samples of both serum and feces available. The presence of a mycobacterium in the fecal specimen was confirmed using what are called primer pairs that identify specific coupling of genetic material. Instead of using primers specific to MAP, we used primers that could identify MAA-like mycobacteria as well as MAP. The ParaChek® tests were done at the State of Florida’s veterinary diagnostic center. Our test was used in Claus’s laboratory. Our test identified six of the nine sera as containing anti-MAP antibodies. The ParaChek® tested positive in two cases. The results were reported in The Paratuberculosis Newsletter.

What was important was that our serum MAP ELISA test had failed to identify MAP despite DNA evidence that the disease was due to a mycobacterium within the MAA-MAP genomic spectrum.

The inference was that these three cases of necropsy confirmed Johne’s disease were due to mycobacteria whose antigenic spectrum was not detected by our test. Hence the need to expand the test’s antigen profile.

USDA had made the internal decision that MAP was THE cause of Johne’s disease and that mycobacteria, like the Mycobacterium avium complex and Mycobacterium hominissuis, were but environment contaminants.

MAP is thought to have evolved from Mycobacterium avium (MAA); hence it was only logical for us to postulate that between
MAP and MAA, there existed pathogenic mycobacteria that differed sufficiently in their genetic makeup as to go undetected by MAP ELISA tests that identified but MAP. The challenge was to prove it.

One of the earliest tests for the detection of MAP was called the agar immunodiffusion (AGID) test. The test consisted of pouring a small amount of agar into a small dish and letting it harden like Jell-O that has been left in the icebox too long. One then punches a central hole and one or more outer holes. The MAP antigens go into the central hole and the serum, which may or may not contain anti-MAP antibodies, is placed in the outer hole. Both the antigens and antibodies move towards each other. If they unite, a precipitation band forms that can be seen.

The test has a 100% correlation with advanced systemic MAP disease. To Claus’s everlasting credit, he continued to use this test when every other diagnostic veterinary laboratory had abandoned it. Elliot and I researched the University of Florida College of Veterinary necropsy archives.

The experimental design was simple. The study population was composed of Johne’s diseased animals that at necropsy had had a positive AIGD precipitation band. Their serum was then tested with our highly sensitive new MAP ELISA test (certified by USDA for Claus’s laboratory use). Of the 71 cases of Johne’s disease with a positive AGID test, 12.7% of the animals lacked demonstrable anti-MAP antibodies.

Several cows demonstrated something not described in the literature, a second precipitation band. When queried about this observation, Claus said that it occasionally happened. The resultant question WHY went unanswered. Having made serial observations of the same “double-banded” animals, it became apparent that the second band appeared only when the MAP ELISA titer was very high and would disappear when the titer dropped.

The temptation was to presume that the first band was against MAP and the second band represented a less strong immune
response to another specific antigen. The fact that the first band could be demonstrated in Johne-diseased animals that lacked MAP antibodies reversed the sequence of interpretation.

Proof that the second band and not the first band was due to MAP specific antibodies was substantiated by an IDI animal. Dixie was a congenitally infected animal born to a Johne-diseased mother that we had decided to maintain on IDI’s so-called “immunotherapeutic nutrition” formulation Serial observations from birth through five months of age demonstrated that she eliminated her maternally acquired specific anti-MAP antibodies well before her AGID test became negative. That led to IDI’s quest for its “super antigen”; one apparently common to a number of different bovine pathogenic mycobacterium

The next step did not require an experimental design. We merely requested from USDA its mycobacterium isolation data derived from diseased cattle that had been forwarded primarily from slaughter houses. Among the isolates were M. hominissuis, M. avium complex isolates and a rare M. avium.

Why USDA tenaciously held to MAP being THE cause of Johne’s disease defied logic. In 2010, a friend handed me a copy of US patent number 6,277,581 B1 dated August 21, 2001: Species Specific genetic Identification of Mycobacterium Paratuberculosis. The patent’s inventors were Jay Ellington and Judith Stabel of USDA.

The next problem opened a second Pandora’s Box. When the diagnostic manufacturers and USDA who certified their tests were asked, not what a positive HerdChek® or ParaChek® signified, but what a negative test meant, the answer was silence. If a HerdChek® or ParaChek® did not demonstrate the presence of anti-MAP antibodies, the inference to the person requesting the test was that the animal had not been infected by MAP.

What we did was redesign the antigenic array of a MAP ELISA test so that it better covered the genetic spectrum of MAP and
Crohn’s Disease

Proceeded to use it in animal field studies. We collected blood from two separate dairy herds located across the road from each other. One brother’s herd had been enrolled in USDA Florida Dairy Demonstration Project for four years. When an animal tested positive in ParaChek’s MAP ELISA test, it was culled. His herd met USDA certification designation of being Johne’s disease/MAP free.

The other brother had had his animals tested, but if the cow looked good and was producing ample milk, she stayed within her milking group irrespective of test result. As to be anticipated, he had cows that developed clinical disease. In short, these two herds were a clear demonstration that USDA’s policy of test-and-cull could eliminate Johne’s disease from dairy herds in Florida. But that was not what Congress was seeking when it gave USDA stewardship of gathering more information as to whether MAP constituted a hazard to the public health of our nation.

The sera from both herds were coded and then mixed together so that the person doing the test would have no knowledge as to which herd the serum specimen came from. Again the ParaChek® tests were done by the State of Florida Veterinary Diagnostic Laboratory. Of the 27 sera obtained from the herd certifiable as MAP-free, all 27 tested negative by the ParaChek® MAP ELISA test; 10 sera were determined to be positive by Claus’s laboratory. In the results from the dairy known to have cows that had previously tested positive in the ParaChek® ELISA system, out of 23 sera analyzed, two were positive and 10 were identified as being suspicious. Our test identified 15 out of the 23 sera as testing positive for anti-MAP antibodies.

What distinguished the positive sera in the two dairy herds was the degree to which an individual cow’s immune system herd responded to MAP infection. Removal of seropositive cows that tested positive in the ParaChek® MAP ELISA test did result in overall lower titers of anti-MAP antibodies. Again this data was published in The Paratuberculosis Newsletter.
Our primary test (called the FUIDI #1 MAP ELISA test (FU = Florida University – IDI = Infectious Diseases Incorporated) was incorporated into US Patents No. 8,008,033B2, No. 8,143,012, and No. 8,3661,737 dealing with aspects of the FUIDI HERD MANAGEMENT SCHEMA. The foundation for a later patent had its genesis in a second MAP test.

E-mail September 6, 2012
Professor Eiichi Momotani
Director of Japanese Society for Paratuberculosis

Dear Gilles R. G. Monif, M.D.

“Thank you for your interest in my recent review paper on paratuberculosis. ……”

“I am very worried about severe situation of paratuberculosis in US and other countries, So that I really think your effort is very important.”

“As you know recent my study showed more quick strategies to control paratuberculosis is needed. You might read it http//www.paratuberculosis.info/webimages/proc11/379.pdf.”

Eiichi Momotani

The decision by USDA to have the MAP ELISA tests represent a statement of probability rather than a valid measurement of the amount of antibody permitted infectious cows to be transported across state lines and national borders with relative impunity. In so doing, USDA acted in a way contrary to the common good. The ramifications of altering recognition of MAP in animals within the human food chain were proven to be very significant. By USDA’s own published data, the spread of MAP among the US dairy herds was out of hand. In 2002, USDA had estimated that between 20-30% of US dairy herds contained one or
more MAP infected/diseased animals. By 2007, the number had increased to 70%. By 2014, any number between 90 and 100 would be close.

Traditionally, animal health quality of assurance is addressed by the animal’s health certificate. The language in many state health certificates tends to minimize any requirement that the animal be free of underlying infectious diseases. The certificates merely require that the certificate be signed by a veterinarian attesting to the apparent absence of any contagious or otherwise transmissible disease. The Code of Federal Regulations (CFR) specifically restricts the interstate movement of MAP-infected animals except to recognized slaughter establishments for processing. Documentation is contingent upon testing that, in most circumstances, is economically counter-productive for producers.

The Wisconsin Implied Warranty law is one of the few exceptions. It stipulates that cattle to be sold are guaranteed to be MAP-free unless sellers provide a written retraction of this guarantee at the time of the sale. Unfortunately few bother to ask.

The decision by USDA not to require a statement as to an animal’s MAP status has undermined its avowed intent to prevent dissemination of MAP into uninfected herds. By not requiring a statement as to whether an animal is infected by MAP infected on its health certificate, cows have been and are being shipped across state and even national borders.

The problem was further flawed by the fact that a USDA certified negative MAP ELISA test would not preclude the animal from being infected or infectious. The Japanese Health officials have documented that 54% of MAP infected/disease cows imported o Japan came from the United States.

Today, it would be shocking to find any large dairy herd that didn’t contain MAP infected animals.
THE PARATUBERCULOSIS NEWSLETTER

After publishing one or two scientific papers, Claus suggested that I join The International Association for Paratuberculosis; which I did.

The organization’s official publication was The Paratuberculosis Newsletter. Its editorial board had been composed of veterinarians primarily from the University of Minnesota and the University of Wisconsin.

When Congress’ concerns about MAP materialized into the funding of its mandate, the American contingent within IAP moved to create a parallel organization into which USDA directed a portion of its MAP-derived federal dollars. The leadership of Johne’s disease Interdisciplinary Program (JDIP) had convinced USDA to allow it to be one of the principal conduits through which it funded MAP research. The governors of JDIP then set out to unite all in the scientific community involved with MAP under their banner. The carrot held out was possible funding. Creating JDIP had the potential to be a brilliant move, had it been properly implemented. Unfortunately the Huey Long principle on how a fiscal pie is to be divided appeared to have prevailed.

The Paratuberculosis Newsletter moved the focus of their attention to JDIP and thereby left an informational void. Leadership of The Paratuberculosis Newsletter, fell to the Europeans.

In his resignation speech, the president of the International Association for Paratuberculosis, Michael Collins, stated “In spite of the fundamental importance of the zoonosis question, it is getting limited funding and therefore limited attention. Agriculture-related funding organizations do not consider the zoonosis question their funding responsibility; in fact they may feel it is not in their best
interest to discover that M. paratuberculosis is a zoonotic pathogen. Medical, food and water research funding organizations, generally do not fund research on animal diseases and seem to be waiting for someone else to decide that M. paratuberculosis is a zoonotic agent before investing in research on this pathogen. And so, year by year and colloquium after colloquium, we scientists produce data and exchange information on research questions, related to the veterinary concerns and not the zoonotic question.”

Soren Nielsen, a Danish veterinarian, took on the vacated the position of chief. Quarterly, the Paratuberculosis Newsletter publishes an extensive list of relevant publications dealing with MAP research. Research and its publication usually follow the money trail. Since most of the veterinary research was being done in the United States, the first choice for publication became U.S. journals whose principle reviewers were members of JDIP. The net result was that the informational content of The Paratuberculosis Newsletter became limited.

Nature abhors a vacuum. The resultant void created the opportunity for IDI to disseminate information without revealing information that could invalidate the patentability of its intellectual properties. IDI’s research objectives were to educationally advance the understanding of the MAP while advancing its patents. The negative by-product was a limitation on the information that it could freely disseminate or publish in peer reviewed journals.

The Paratuberculosis Newsletter became a vehicle in which IDI could share knowledge without divulging key information while patent applications were pending.

To expand the paratuberculosis dialogue, IDI began inserting into The Paratuberculosis Newsletter, a number of small bites of research based data; i.e.

A procedure to assist in the identification of slow growing mycobacterium from slants;
Duration of bovine maternally acquired antibodies to *Mycobacterium avium* subspecies paratuberculosis: A case study;

Use of blotted tissue impressions for the rapid PCR identification of *Mycobacterium avium* subspecies paratuberculosis;

Persistent bovine fecal MAP shedding in the first month of life; etc.

Once an academic footprint had been created, IDI’s focus turned to establishing an open forum on topics that were destined to adversely impact on milk producers and milk-based manufacturers.

The September 2008 issue contained a debate paper entitled *What if: A contrarian’s questioning of the natural history of bovine infection due to Mycobacterium avium* subspecies *paratuberculosis*. The article drew no response, but the idea had its public debut.

In December 2008, the discussion introduced centered on the lack of MAP certification of cattle being sold. Its conclusion statement stated: “Unless otherwise clearly stated, Certificates of Health for dairy cows need to have the words, buyer beware added”.

In order to stabilize the price of milk, in 2009, the National Milk Producer Federation Cooperative instituted a policy of reducing herd size by paying producers slaughter price for the cows removed from production. The comments in the September issue described the opportunity to improve herd quality through selective testing for MAP and animal slaughter selection based upon risk.

The December article, ‘An Ounce of Prevention is Worth More than a Pound of Cure’, again centered on animal certificates of health. Beef and dairy producers in Texas had a habit of reaching down into Mexico and buying cattle on the cheap. The problem was that many herds had not only paratuberculosis but also bovine tuberculosis. Mexico exports one million cattle annually to the United States. Based upon APHIS’s own statistics, 75% of bovine tuberculosis (*M. bovis*) detected through sometimes sporadic slaughter surveillance originated in Mexico. In 2009, chronic
draught conditions had forced relocation of cattle to a large number of dairy and beef states. Slaughter identification was detection after the fact and more importantly, after infected animals had been shipped out of the area. The problem that USDA was now having with *M. bovis* was a marker for the undetected dissemination of MAP throughout the U.S. dairy and beef herds.

The March 2010 contribution, *When is Mycobacterium Avium Subspecies Paratuberculosis Mycobacterium Avium Variant and When is Mycobacterium Avium Mycobacterium Avium subspecies Paratuberculosis?*, was an attempt to bring back into focus that Johne’s disease was not always caused by just MAP.

This editorial opinion was a partial restatement of a previously article published in the March 2009, “*The Difference between an A and The* (cause of Johne’s disease), and the March 2011 Paratuberculosis Newsletter, “*Are Mycobacterium Avium Subspecies Avium and Mycobacterium Avium Complex Pathogens*?”

Despite a steady diet of provocative editorials or opinion papers, no contrarian responses materialized in print, but in private, IDI’s voice had gained a critical audience.
MAP AND CROHNS DISEASE
FROM A MEDICAL PERSPECTIVE

While the non-PhD part of veterinary medicine was focused on feces and other biological fluids, the world involved with humans was penning a stronger circumstantial case for an etiological connection between MAP and Crohn’s disease.

Ghadiali et al. documented that the human MAP isolates exhibited similar polymorphic locus patterns to animal MAP isolates, making it, more probable than not, that MAP isolates cultured from human beings could produce disease in susceptible animals. Other investigators have documented that MAP isolates cross species lines with relative ease. A goat or sheep MAP isolate can infect cattle and vice versa. Rabbits that share pasture with cows have the potential to be a reservoir of disease.

Naser et al. cultured MAP from the blood of 50% of patients with Crohn’s disease, 22% of patients with ulcerative colitis and 0% of individuals without inflammatory bowel disease. His finding was of immense scientific significance; yet Naser was basically shunned by the world of veterinary medicine. In time the federal funding of his research vaporized.

Sechi et al. identified MAP DNA in 83.3% of the biopsies from patients with Crohn’s Disease and 10.3% of control patients. Other investigators including Autschback et al. and Bull et al. confirmed the positive correlation between MAP and diseased gastrointestinal tissue from individuals afflicted with Crohn’s disease. The positive correlation between the demonstration of MAP and diseased gastrointestinal tissue from Crohn’s disease-affected individuals was but inferential.

A “scientific truth” must account for the exceptions. The presence of MAP in tissue from individuals without Crohn’s disease required explanation.
The explanation advanced was that Crohn’s disease was but the pinnacle of MAP progression. Scana et al. presented evidence incriminating MAP as an etiological component of “irritable bowel syndrome” in humans. What was emerging was the inference that human MAP infection had a spectrum of possible outcomes ranging from asymptomatic subclinical infection, a slight increase in the number of bowel movements a day, irritable bowel disease, to Crohn’s disease. But the explanation posed the very real possibility, if not probability, that human MAP infection is so prevalent that it could be represent in study control groups.

By 2008, sufficient evidence existed that the American Academy of Microbiologists published its report on *Mycobacterium avium paratuberculosis*: Infrequent Human Pathogen or Public Health Threat. The executive summary states, “the association of MAP and CD (Crohn’s disease) is no longer in question. The critical issue today is not whether MAP is associated with CD, but whether MAP causes CD or is only incidentally present.”

In 2009, three independent diagnostic laboratories (Michael T. Collins of the University of Wisconsin, Saleh A. Naser of the University of Central Florida, and Jack Crawford of the Centers for Disease Control and Prevention) tested blood from 58 individuals. Viable MAP was detected in 22 out of 40 with Inflammatory bowel disease (20 with Crohn’s disease and 20 with Ulcerative Colitis) and 4 of 18 subjects without inflammatory bowel disease. Two of the diagnostic centers detected MAP in 41% of the blood from individuals with inflammatory bowel disease and 0% in the “control “blood samples. In four cases, MAP was isolated from the blood of individuals without Crohn’s disease. Their findings were subsequently confirmed by Juste and co-workers.

Again, MAP could be isolated on occasion from the blood of individuals not afflicted by Crohn’s disease. WHY?
SIGNIFICANCE OF MAP INFECTED HUMANS WITHIN THE CONTROL GROUPS

The mere presence of an organism does not necessarily imply causality. The predominance of recovery of MAP in the feces and tissues from individuals with Crohn’s disease had been off-set by the demonstration of MAP in gastrointestinal tissue and feces of health control subjects.

Rather than undermining the presumption of causality, the findings of infected healthy human beings signals that MAP has achieved a significant penetration into the population from which the control subjects were drawn from.

All humans have MAP receptors within their gastrointestinal tract. With at very least 2% of the milk that human consume containing viable MAP organisms and MAP potentially being in powdered milk and milk based foods like soft cheeses, it is only a question of time and diet as to whether or not one becomes infected. According to the National Animal Health Monitoring System, 31.2% of bulk tank (pooled collections of milk) collected from 515 dairy farms in 2007 contained MAP DNA. What this figure is in 2015 is open to speculation.

The isolation of a microbe from blood conclusively documents that an individual is infected by that organism. That healthy human beings in the control groups may have MAP in their white blood cells is consistent with the premise that MAP infection is widespread in the general population. Whether one is infected or not appears to be a function of diet.

The current number of MAP infected controls appears to have increased ten-fold since the human MAP studies from the 1990s. WHY?
SPREAD OF MAP IN U.S. DAIRY HERDS.

In 2008 USD unveiled its National Johne’s Disease Control Program Strategic Plan that identified but three specific goals:

- Reduce the prevalence of Map/Johne’s disease in the national herd
- Reduce the impact of Johne’s disease on individual herds
- Reduce the risk of introducing Johne’s Disease to uninfected herds

USDA’s strategic plan would be re-named “Closing the Barn Door after the Cows Had Left”. If in 2008, 70% of large dairy herds had MAP infected cows using USDA’s insensitive testing tools, any number over 95 would probably be a reasonable guess.

USDA’s prior decision that allowed MAP ELISA tests to basically be a statement of probability rather than a valid measurement of the amount of antibody undermined two of its three mission objectives.

Infected cows are transported across state lines and national borders with relative impunity. The net result was not only the introduction of infected animals into uninfected herds, but an increased prevalence of MAP infection in the national herds. From 2001 thru 2014, what USDA had effectively done was to take a manageable problem and make it into one of colossal proportions. Today, it is more probable than not, that no large dairy operation in the United States is free of cows infected by MAP.
The 10\textsuperscript{th} INTERNATIONAL COLLOQUIUM ON PARATUBERCULOSIS

Minneapolis MN October 28\textsuperscript{th}, 2010

The 10\textsuperscript{th} ICP was chosen to present our contrarian versions of errors-up-to-date/scientific truths. In collaboration with our colleagues from the University of Florida College of Veterinary Medicine and Purdue University School of Veterinary Medicine, IDI submitted with eight presentations that spanned everything from diagnostic immunology to herd epidemiology.

Being a Johne’s disease Interdisciplinary Program, we had little illusion that our papers would crack a largely pre-selected program agenda. That actually worked in our favor. With poster presentations, an author would stand in front of large five foot by six foot posters and discuss the embedded data with interested parties. Elliot and I worked the Poster Sessions. It is thus that we established contact with Robert Greenstein, Ivo Pavlik and Eiichi Momotani among others. A number of individuals voiced that our data had corroborated some of their long held doubts and/or unpublished data.

The best part of the 10\textsuperscript{th} ICP was a one sided debate between Thomas Bull from Hermon-Taylors group and a senior veterinary pathologist. The topic involved MAP ‘being linked to Crohn’s disease. The counter arguments to Dr. Bull’s position were both conceptually flawed and data weak...

Before he left, Tom gave me a video copy of his presentation which found a home on IDI’s web site.

At the lunch recess between sessions, I asked Robert Whitlock to join me and discuss “pass through”. As we walked out of the building, I saw a veterinarian from Thailand bow his head as a sign of respect as Professor Whitlock walked by.

Robert Whitlock had been Claus’ teacher and as such, he was personified as being holy ground to him and a vast number
of veterinary pathologists. Such adulation had permitted his words to be unchallenged gospel; but at a price that had been costly in terms of advancing scientific knowledge. So the two of us sat on a bench on the grounds of the University of Minnesota and had our own private debate about “pass through”.

At the end of the 10th ICP, Robert Whitlock and Claus Buergelt were honored for their lifelong service to International Association for Paratuberculosis.

The “educational event” occurred in a USDA semi-closed session in which Prionic of ParaChek® fame, petitioned USDA to have their test and laboratory become the reference against which all certification MAP ELISA test would be judged. It was fascinating hearing a fox asking to be the keeper of the hen house. Michael Collins and the representative of IDDEX (manufacturer and distributor of HerdChek® and its successor) turned the tide of transfer of responsibility back to USDA.
REVAMPING MAP’S NATURAL HISTORY

The Buergelt-Whitlock theory of the pathogenesis of MAP infection/disease was embedded in the prevailing herd management schema. Its evidentiary foundations were flawed.

Rather than embrace it as a “scientific truth’, we thought that it was, more probable than not, that the real natural history of MAP infection paralleled that described for other pathogenic mycobacterium. The European experience with MAP vaccines had demonstrated that though vaccination reduced Johne’s disease in dairy herds, it did little to prevent lateral dissemination within herd mates.

In the evolving paradigm for MAP, the critical issue was not disease, but rather the shedding of pathogenic mycobacteria into milk and milk products embedded in the human food supply. Our own data as well as that of others had documented that subclinical MAP infection did not preclude the presence of MAP in milk. Of even greater concern was the presence of pathogenic mycobacteria identified by IS 1311 primers in the milk that possessed no detectable antibodies by the FUIDI #1 MAP ELISA test.

What we presumed was that MAP acted very much like another mycobacterium, *M. tuberculosis* (the dominant cause of tuberculosis in humans). Infection had the potential to be broad based among exposed individuals. But relatively few of those infected had their infection progress to actual disease. After World War II, better than 30% of medical students in European University had positive skin tests for tuberculosis. We postulated that the majority of MAP challenged cows would develop a transient active infection, from which the majority of these cows would recover. The key to testing this hypothesis would be designing a way that would distinguish infected cows who had recovered from animals with still recent or active infection.

To challenge that hypothesis, we engineered a new MAP ELISA test (FUIDI # 2 MAP ELISA test) that identified the probability that infection was either active or of recent origin.
IDI tested 1,113 cows within USDA’s Florida Johne’s Disease Dairy Herd Demonstration Project. One hundred and ten cows had any anti-MAP antibodies as identified by the FUIDI #2 test. Nine of these cows had levels consistent with advanced disease. Another six cows had titers consistent with either evolving or receding significant MAP infection.

Fourteen months later 551 of the original 1,113 cows were available for re-analysis. Of the original 91 infected cows, 54 were available for retesting, 35 cows no long tested positive for active infection. Eight cows had serological evidence of continuing infection and two had progressed to very active infection/disease status. What was most impressive was that of the 540 previously test negative cows, fourteen months later 18.9% of these cows now had evidence of acute infection.

IDI has patented the FUIDI Herd Management Schema whose foundations centered on the demonstrated fact that host immunity in most case of bovine MAP infection can abort MAP’s continued replication and distinguish past infection from recent or active MAP infection.

The FUIDI Herd Management Schema was designed to be more than a tool by which producers could reduce losses sustained from decreased milk production, lower cow fertility, reduction in slaughter weight and increase herd immunity to environmental mycobacterium challenges. Dairy cows live as long as they can pay for room and board with milk.

The FUIDI Herd Management Schema is designed to decrease the amount of MAP in milk, cheeses, baby formula and other milk-based foods while creating economic benefit for producers. MAP can be detected in 4.2%- 31.7% of cheeses tested. More disturbing is the finding of specific DNA from 48 to 32,500 MAP organisms per gram in 35% of 51 samples of powdered infant milk.
In 2012, OIE threw in the towel. MAP had become so prevalent among milk producing animals that it proposed removing paratuberculosis as a disease entity from the Terrestrial Animal Health Code “because MAP infection is so widespread, continued recognition of MAP as an animal pathogen would only cause economic losses through the restrictions in international animal trade.

MAP’s penetration into the nation’s food supply is thought to be the engine that is driving the ongoing Crohn’s disease epidemic.
THE HOLY TRILOGY

Science approaches an infectious disease through 1) its identification, 2) its cure, and 3) its prevention. This is the Holy Trilogy of infectious diseases. Virtually everything already addressed pertains to DIAGNOSIS.

CURE?

The veterinary literature is uniform in its statement that there is no cure for Johne’s disease. That “scientific truth” could have been embraced were it not for cow number 6142.

Number 6142 was a six year old Holstein cow with far advanced Johne’s disease. Polymerase chain reaction (PCR) testing of milk and blood samples was repeatedly positive. When she had to go, she had to go. I watched a stream of liquid feces splatter against a wall some six feet away. What endeared her was the high titer of anti-MAP antibodies in her serum. The cow was purchased from the University of Florida Demonstration Dairy Herd and relocated to a controlled research facility. The goal was to obtain a large amount of serum for diagnostic use before her anticipated demise.

Normally, an animal in her condition will die within two to three weeks. In an attempt to delay her necropsy, the cow was placed on supplemental nutrition selected to enhance cell-mediated immunity. Cow 6142 decided that dying of diarrhea induced malnutrition was not an option that she liked.

Within ten days on the supplemented diet and near complete stress reduction, her watery diarrhea converted to soft stools. Four months later, her AGID tests had become negative. Her MAP ELISA titer dropped significantly and she gained almost 200 kg. At necropsy, there was no gross evidence of Johne’s disease.

Microscopic examination of 34 microscopic slides of her gastrointestinal tract failed to identify any demonstrable MAP.
The area below the lining of the bowel showed the prominent presence of eosinophils. With the exception of rare granuloma in the corresponding, lymph nodes, no evidence of MAP and its induced destructive change could be identified.

Claus, unaware of what was being done to her, published cow number 6142 as a case of spontaneous remission of Johne’s disease.

In our subsequent studies with diseased animals, the supplemented nutrition, now termed immunonutritional therapy, would terminate the watery diarrhea in seven to ten days and sustained the animal’s life; but it did not impact of the totality of disease without concomitant near total stress reduction.

If Crohn’s disease is causally related to MAP, cow number 6142 told the world that Crohn’s disease can be beneficially impacted on, if not cured, by aggressive, monitored nutritional intervention and stress reduction.

To further explore this possibility, IDI contacted a group of veterinary nutritionists headed by Chet Crum to adapt the veterinary formula for potential human use. The formula’s end product received the patented trademark name of ImmunoBit. However, when funding was sought from industry, it was stated that the reachable target population was too small and that the recommendation that individuals work with a certified dietician was a deal buster. The need for comprehensive product insurance, and the cost of human clinical trials made the project economically unfeasible.

That such an approach works in humans has been inferred by biographical books written by individuals afflicted with Crohn’s disease. A number of individuals have achieved permanent clinical remission through selective nutrition supplementation and stress reduction.

Scientifically, cow number 6142 made an even more important contribution. When I reviewed her necropsy findings,
I was shocked. If I had not known 6142’s background history, her diagnosis would have been idiopathic eosinophilic enteritis. The area under the intact lining mucosa is called the lamina propria. On all her slides taken of her gastrointestinal tract, the lamina propria was crammed full of white blood cells called eosinophils. Eosinophils are important in disease due to certain parasites as well as allergic reactions.

What cow number 1642 has demonstrated is that the release of eosinophil-derived neurotoxins, enzymes and cationic proteins are instrumental in the end stage destruction of pathogenic mycobacteria.

This hypothetical inference demanded proof. We pulled from the necropsy files of the University of Florida College of Veterinary Medicine sequential cases of bovine Johne’s disease that Claus had done. Slides of ileum were reviewed in order to identify the presence or absence of increase eosinophilia. The two study subgroups thus established. In each case, the slides of ileum and a corresponding lymph node were analyzed to determine the amount of mycobacteria identifiable by special stains.

Significant increase in the amount of eosinophils inversely correlated with the amount of detectable MAP, in both small bowel and the draining lymph node.

In the veterinary pathology literature, two different types of Johne’s disease are described: multibacillary Johne’s disease in which many acid-fast bacilli are demonstrable and paucibacillary Johne’s disease in which the number of acid-fast bacilli are markedly reduced. The explanation that had been advanced was that multibacillary and paucibacillary presentations reflected divergent host responses to MAP. What cow 6142 told us was that these two observations were not horizontal cuts through two divergent responses to infection, but rather a horizontal cut through various phases of the same infection.

Cow number 6142 should be enshrined in the Johne’s disease bovine Hall of Fame.
PREVENTION

Live and killed MAP vaccines have been effective in reducing the progression of MAP infection to disease form. What they have failed to do is interrupt the spread within the herd. What became apparent was that the proposed newer vaccines were designed more to circumvent problems like cross reactivity with *M. bovis* or the granulomatous lesion at the site of infection rather than break new ground. The vaccines that are being developed are basically more of the same in a different wrapper.

Because MAP can be disseminated to other organs, a key question has been why the gastrointestinal tract is the sole manifestation of disease. A presumed answer resides in MAP being acquired through oral ingestion. In Johne’s disease, the portal of infection and the target organ were one and the same. Unlike tuberculosis due to *Mycobacterium tuberculosis*, secondary redistribution of the organism to the target organ is not necessary. The effector immune cells reside within the submucosa. For a vaccine to be effective, the vaccine candidate has to 1) be orally administered, 2) be effectively attenuated and 3) after inactivation, effectively bind to complimentary mycobacterium receptor sites.

The US Patent Office awarded IDI US patent 7,476,539 B1 which describes methodology that 1) attenuates oral MAP vaccine candidates, 2) effects inactivation of the MAP oral vaccine candidates, 3) documents the integrity of receptor cites after inactivation.
DONALD BARRON

While at the University of Florida College of Medicine, I had the privilege to have as a co-faculty member a scientist by the name of Donald Barron; better known to others as, the father of perinatal research. He became my mentor.

For him, science was the burning desire for answers. He taught me that the creativity of a true scientist is not in the answer, but in the question asked: the quality that separates the poet from the writer.

One of his quotes resides at the top of IDI’s stationary: “Knowledge is the only gift that enriched the giver and the receiver”.

Time with him built a foundation for a subsequent relationship.
SILENCE WHEN MEN SHOULD CRY OUT

In the United States, the veterinary response to MAP as a public hazard, much less the cause of irritable bowel syndrome (IBS), had but a muted voice. When investigators were privately or publicly pushed on the issue, the lack of absolute proof would be offered in response. The proposed relationship between MAP and Crohn’s disease would occasionally get lip service in the introduction of a paper. The topic was rarely revisited in the discussion of the significance of authors’ findings. Lack of conclusive scientific proof would, more often than not, be cited as the rational for not pursuing in depth discussion of the issue.

Unlike mathematics or physics, medicine is not a pure science. Medicine is a pseudoscience in which its scientific truths are but converging multiple probability based upon the best evidence at hand. Stated another way, medical “scientific truths” but are error up to date.

A cigarette being the cause of lung cancer is a medical “scientific truth” That “truth” is not based upon absolute proof, but allegedly became accepted by government agencies when the insurance lobby demonstrated that the costs embedded in cancer exceeded the revenue stream, directly or indirectly, derived from tobacco. Whether that story is mere confabulation or not, the fact remains that the causation link between tobacco and cancer rests on something other than absolute proof.

When you want something done, you seek out the person in charge. In the military, that individual is called the MIFIC. In today’s world, that person is called the CEO (Chief Executive Officer).

The topic proposed was preserving the economical integrity of the dairy industry. The letter’s last line stated: “For anything to work, it must obviously come from industry.”
That a public health hazard had been inferred by credible scientific evidence should have been sufficient to penetrate industry’s imposed shield of silence. Despite a number of follow up telephone calls no response was forth coming.

Persisting further, more likely than not, would invite retribution. What the Cattlemen’s Association did to Oprah Winfrey had served as notice to the world of the virtue of sinning by silence.

My first attempt to publish in a U.S. veterinary journal a paper that challenged the prevailing dogma turned out to be an interesting exercise. I learned quickly why Naser, Hermon-Taylor etc. had used non-U.S. journals to published their findings. I had a reviewer who did not believe anything that was not already proven.

The reviewer’s comment that the data was inconsistent with other publications was not well received. When research data permitted sharing, subsequent submissions went across the pond or international. The problem was that, as a rule, much of the critical audience did not subscribe to non-U.S. veterinary journals and apparently never read medical journals.

Since one robin doesn’t herald spring, a decision was made to test whether I was dealing with “bright men who were faking it or idiots who meant it.” The instrument chosen was a Letter to the Editor. The integrity of any journal resides with its Editor. The topic chosen was based on observations whose scientific validity was beyond scientific challenge.

Crafting the prevailing data into a coherent statement of facts in 300 words or less was analogous to fitting a size six document into a size two dress.
Letter to the Editor  
Failed Goals within the  
National Johne’s Disease Control Program  

The 2008 National Johne’s Disease Control Program Strategic Plan has failed in meeting two of the three of its stated objectives: reducing the prevalence of Map/Johne’s disease in the national herd and reducing the risk of introducing Johne’s disease to uninfected herds (1)

The current commercial MAP ELISA tests measure anti-MAP antibodies, but the interpretation of a positive test is predicated on the identification of a level of antibody that predicts a high probability of a progression of MAP infection to overt enteritis or confirmation of disease. A negative commercial MAP ELISA test does not address the issue of whether or not a given animal is or ever has been infected by MAP. The decision by USDA to have the MAP ELISA tests represent a statement of probability rather than an accurate statement of the amount of antibody present has permitted infectious cows to be transported across state lines and national borders with relative impunity. The net result is not only the introduction of infected animals into uninfected herds, but an overall increased prevalence of MAP infection in the national herds. In 2007, an estimated 70% of U.S. dairy herds contained one or more infected animals (2).

The Japanese approach to containing MAP is embodied in its Act on Domestic Animal Infectious Disease Control. After 1998, every Japanese dairy farm is examined for MAP every five years. Imported cattle are subjected to quarantine in which they are screened using a MAP ELISA test, fecal bacterial culture, PCR analysis for fecal MAP DNA, and Johnin skin test. Fifty-four percent of diseased animals detected by the Japanese Animal Quarantine Service came from the United States (3). The number of infectious cows shipped from the United States that escaped serological detection is open to speculation.

Gilles R.G. Monif, M.D.  
Infectious Diseases Incorporated
The rejection came directly from the Editor. What was unique was his comment that the editorial was “a thinly veiled advertisement of IDI” Nothing was directed to the message contained within the Letter,

A reviewer can lack knowledge. An editor of an influential journal has the right disavow his duty to disseminate knowledge. Making an unprofessional remark became his invitation to a pointed discussion.

Dear ______;

“I was disappointed by your rejection of my letter to the editor. To present a case in 300 words or less, effectively limits citing the documentation in the literature. As an editor of a scientific journal, you would have had merely to read the manufacturer’s product material to confirm an absence of any explanation as to the significance of a negative MAP ELISA test. The literature is overburdened with articles documenting the inability of the

References*

- (Publication of references at the discretion of editor – 300 word limit)
various certified MAP ELISA tests to achieve a reasonable correspondence between serological test results and culture data and/or slaughter observations. More simply put, the current negative MAP ELISA test results do not address the issue of whether an animal has had prior antigenic processing of MAP antigen (infection) and more importantly whether or not the animal is infectious. This is a subject very worthy of public scientific debate, i.e. an editorial debate. I would be more than willing to offer one side of the debate. I would be impressed if you would be able to find someone in USDA willing to debate in open forum the validity of a negative MAP ELISA test.”

“I went to great length not to bring into focus any of IDI’s work, expressively to avoid accusation of bias or as you chose to phrase it “thinely veiled advertisement of IDI”. If my association with IDI is a concern for you, that could have handled simply by you deleting my affiliation with IDI. The content of that editorial letter has nothing to do with IDI and everything to do with USDA and the consequences of their actions. Had I not clearly identified my association with IDI that would have been contrary to the policy of disclosure. The letter was an observation confirmable any one with reasonable knowledge of the literature.”

“As far as advertisement of myself, I have no need. I am a nationally and international recognized researcher and leader in the area of infectious diseases as they adversely affect women and their unborn babies. More precisely I have published well over a hundred articles in peer reviewed medical journals, co-founded both the Infectious Disease Society for Infectious Diseases in Obstetrics and Gynecology and its internal counterpart, was the special interest consultant for the American College of Obstetricians and Gynecologist for over a decade, wrote the definitive text book on OB/GYN infection (currently in its sixth addition), was instrumental in developing CDC’s change of position on two key infectious disease issues affecting women, etc., etc.”
“IDI is a medical education/research entity founded in 1973. Why is a medical research entity involving itself into veterinary business? The answer is simply MAP is a zoonotic pathogen that, like *M. bovis* in milk, appears to constitute a public health hazard. The bottom line is “a risk is a risk and must be addressed”; however, given the political power of the lobbyist of organizations like the _____________ and the _____________ open debate is being held hostage until means are attained that will assure the welfare of the dairy and milk related industries. In the meantime everyone is asked “to sin by silence when men should cry out makes cowards of men (A. Lincoln)”. “Shortly, IDI expects to be announcing its schema that may allow the majority of infected cows to remain in production while decreasing the amount of MAP entering the human food supply. But IDI can do nothing about the spread of MAP into uninfected herds or decreasing the prevalence of MAP within a given herd. What was a containable problem in the late 1990s is now out of control.”

“To quote T. Roosevelt: “When a decision is required, the best decision is to do the right thing. The next best decision is to do the wrong thing. The worse decision is to do nothing.” Doing nothing has prevailed.”

“If your ego is a little bruised, the easy thing will be to put this e-mail in a circular file. Perhaps a better course of action would be to forgive me for my aggressive response and have us to work together for a better future outcome for the dairy industry.”

Sincerely,
Gilles R. G. Monif, M.D.
President, IDI
Dear Dr. Gilles R. G. Monif:

Thank you for your e-mail. You are welcome to submit your research to Journal of _______ for consideration as a published research article. If you are so inclined, submit it through normal channels (____). In glancing at your attachment, I note that you will need to conform to the guidelines for authors. Also, in the submission process, you will have the opportunity to suggest reviewers. In terms of guidelines, the short communication guidelines may be most consistent with your intent.

………………

Sincerely,

________________, Ph.D.
KAREL HRUSKA

What prompted me to contact Professor Karel Hruska was that something that Donald Barron had ingrained in me.

When the issue of a possible relationship between MAP and Crohn’s disease achieved center focus, the paper either bore the imprint of having originated somewhere within the United Kingdom or the Veterinary Research Institute (VRI) of the Czech Republic.

The Veterinary Research Institute at Brno in the Czech Republic was an intellectual powerhouse for the veterinary science. Monthly, it compiled and made available to all comprehensive lists with short abstracts on various veterinary infectious disease topics through its Centaur Global Network Information, The amount of work and dedication involved was very impressive.

E-mail August 12, 2012

Dear Dr. Monif:

“Your suggestion to open a dialogue about collaborative research in MAP dilemma is greatly appreciated. I am not authorized to speak on the behalf of Prof. Pavlik, but I’ll inform him and I believe in his positive approach. We are both sure that mycobacteria in the environment and water play an important part in pathogenesis of many chronic inflammatory diseases.”

“…….. So much data available should beat the buck-passing empty phrase, “Crohn’s disease and MAP links still unproven”.

Karel Hruska
With the voices demanding an answer becoming more distant and time’s cruel dead-lines pressing on, I contacted Professor Karel Hruska and proposed that we become ‘soldiers with a pen’. In today’s world, the pen may be the individual’s last weapon, provided that he or she pens “error-up-to-date” (better termed a scientific truth).

E-mail September 7, 2012

Dear Gilles:

“Thank you for your notes as well for your last e-mail and correspondence with Professor Momotami. I agree with your idea to decrease the amount of MAP contamination of food and the environment…”

“Apart from a reduction of the number of MAP shedding, I consider the following issues important:

• To induce an interest of the dairy industry to produce a few brands of baby food including formula and some part of cheese and retail UHT milk products from “MAP free” raw milk (alternatively a limited MAP contaminated can be legally introduced

• The meat and food industry could introduce the production of beef and beef products from MAP free or MAP limited slaughtered cattle and sheep

• The finding of paratuberculosis during a meat inspection in slaughter houses should be obligatory.”

Karel
E-mail September 9, 2012

Dear Karel:

“The MAP Dilemma is like trying to eat an elephant. The only way one can “is one bite at a time.”

“The comments in the September 2012 Paratuberculosis Newsletter were directed at embarrassing USDA.”

“I have great difficulty with the Stabel et al. paper (Appl. Environ. Microbiol. 1997; 63:4975-77)...

When the American Academy of Microbiologist indirectly acknowledged the zoonotic character of MAP, FDA convened a panel of PhDs that attempted to defuse the situation. A democratic government is supposed to function in the public trust. Much of the world believes some aspect of that statement. When USDA or FDA speaks, their voices are heard afar. I apologize for unloading the soot of my displeasure. I love my country, but fear that it is being transformed into something else.”

“Going back to eating an elephant, voluntary programs will not work until there are consequences that bias economic consideration strongly in the favor of doing something. The literature has documented the benefit to producers of putting in place a herd management schema, but to do so still requires some financial outlay and exposes the producer to some liability. Currently individual producers are hard pressed to make money.”

“... The paper on powdered milk is powerful. I strongly concur that milk-related products need to carry some declaration as to the risk assessment of the key ingredients. As you stated milk sold to babies and small children should be designated MAP free...”

“The potential movers are the manufacturers that use milk ...”

Gilles
In September 23, 2012, the Centaur Global Information Network call for mini-reviews on mycobacteria was published. Its summation states”

“A risk, even hypothetical, has to be treated as a risk. MAP and mycobacteria in general are harmful organisms or elements of bacterial origin. It does not matter if they are not culturable, really dead, or still revitalisable (sp). Dozens of citations refer to this fact indirectly, but fully convincingly. Even if accepted as a hypothetical risk, this fact should be managed as a risk... Why is the present understanding of inflammatory pathways based on immunology and molecular biology superseded by the formal classification of non-pathogenic mycobacteria, originating in the time of absolute validity of the Koch postulates? I do not know the answer, but I am sure that it is time for a change.”

Professor Karel Hruska

E-mail August 12, 2012

Dear Drs. Hruska and Pavlik:

“IDI and CGNI or OIE are in agreement. We differ only in our approach: i.e. Koch vs. Pasteur.”

“I have attached the 2012 IDI White Paper (please treat as confidential) and a copy of an open letter that hopefully will be one day published. Neither of these documents has CGNI precise care to details, but rather paints with broad strokes what is held as “error up to date.”

“IDI’s conception of the natural history of MAP herbivore infection is different from that advanced in the veterinary literature. Simply, MAP in its spectrum of infection and disease, parallels that documented for *Mycobacterium tuberculosis*: infection is common; disease is significantly rarer. Which occurs is determined by a simple formula:”
Inoculum Size times (its) Virulence divided by Host Immunity.

“Like tuberculosis, significant compromise of the host’s immune system can select for reactivation.”

“IDI has a first generation solution that, more likely than not, if implemented, will reduce the amount of MAP entering the human food chain through milk. This is a starting point, but a scientific one. Addressing the new paradigm is a major IDI mission.”

E-mail August 13, 2012

Dear Karel;

“Upon re-reading my late night e-mail, I realized I did not address the central issue: how CGNI and IDI can potentially interact.”

“The discipline of infectious diseases grew immensely through the work of two groups; immunologists and immunochemists: immunologists identified the phenomenon; immunochemists took it to the micro-molecular level and beyond.”

“IDI is more immunologist than immunochemist. It also possesses one other thing, a public voice... Being free of governmental regulations, IDI can speak with a stronger voice than most.”

Gilles
E-mail August 13, 2012

Dear Gilles:

“Thank you for both e-mails, attached documents and the last suggestion. I prepare a short list of premises to complement yours. ….. .”

“I understand the last paragraph and agree with it. In my opinion it is necessary to address also a problem of public health risk posed by MAP and MAC. …. it does not need more experiments. A summarization and interpretation of existing data can support the key idea.”

E-mail August 17, 2012

Dear Karel and Ivo

“Attached are IDI’s premises for your review. Right now IDI’s first generation solution is to reduce the amount of MAP entering the human food chain through milk. The proposed next generation schema to further reduce the amount even further is vaccination using a novel approach to vaccine development. The problem is that it is too novel to satisfy those who demand near certainty before committing money to action.”

Gilles

E-mail August 17, 2012

Dear Gilles:

“Thank you very much for sharing IDI’s premises. I am sure we are in general agreement. I wish most of our colleagues to share the same idea. We have posted our document at CGN web page and opened it for discussion. How do you intend to continue with IDI’s mission? .......... . I am looking for your opinion.”

Karel
E-mail August 18, 2012

Dear Karel:

“The basic answer is yes, but some modifications are needed: i.e. deleting #12 under MAP & Johne’s disease. Will send you an updated list.”

“I am a bit skeptical that the dissemination of knowledge alone can achieve the desired results.”

Gilles

E-mail August 18, 2012

Dear Gilles:

Thank you. Please send the list when it is updated.

“I understand your skepticism (sp). ..... . However, a distribution of short and provocative premises probably could influence some discussion to eliminate a hackneyed phrase “links of MAP to Crohn’s disease is possible but not confirmed’ from 90% of publications, describing for already decades the participation of (MAP) in inflammatory diseases.”

“....... , it is impossible to design an experiment of feeding several thousands of newborn babies with hopefully devitalized 1000 MAP cells per gram baby food or serve weekly three hamburgers from animals with bacteremia to NO2 defected consumers and to evaluate results after 20 years. Perhaps a dissemination of parts of the puzzle can wake up at least a few people who can read and summarize the relevant pieces of knowledge.”

Karel
E-mail August 18, 2012

Dear Karel:

“There will be retributions to IDI and myself in publishing IDI’s premises, but we have to live with a concept of a god-within and have the courage to not “sin by silence”.

“Attached are IDI’s premises with a short introduction putting them into perspective.”

Gilles

Infectious Diseases Incorporated Premises were published in the CGIN Bulletin’ section on Paratuberculosis and Crohn’s Disease: Premises and Open Questions.

In the December 2012 issue of The Paratuberculosis Newsletter, Soren Nielsen also reprinted IDI’s premises as an academic challenge for open debate.

E-mail August 22, 2012

“Gilles: For information. The first comment arrived just 7 minutes after releasing Gin (Ginny) from a bottle. During the next two hours, Joe Falkingham sent me two excellent papers...”

Karel

E-mail August 23, 2012

Gilles
I agree that the answers lie in nature, not only because it is for scientists to find them, but also because natural experiments are infinitely more creative than anything we can dream up in the lab.”

Karel
E-mail December 20, 2012

Dear Karel:

Battles are ultimately won by the persistent and, if there is a higher power, the righteous. Slowly is good; persistent is best. The key will be to induce the proponents of silence into open discussion. Their weapon has been silence, not science.

What may ultimately bring the zoonotic potential of MAP into open debate is either one of two issues. If anyone had a large human serum bank with corresponding demographic data, it would be demonstrated that a very significant portion of the human population in wealthy industrialized countries have been infected by variants of MAP. (I will either give our MAP technology to an investigator or do the testing per se as a co-investigator.) The second issue is the labeling of food for human consumption. Anything made with milk needs to have on its packaging a statement indicating that the product may contain a zoonotic pathogen, particular baby food made with powdered milk.

When individuals understand that their government has allowed them to be exposed to an organism which is a documented pathogen, the public outrage that has been lacking to date may manifest.

Right now, my science is being compromised by its need to be heard. Until the milk and milk-related industries are assured of their respective survival, they will use every weapon available to them to subvert the truth.

I too am concerned for the number of individuals who will dare to speak out. It is as if we are in a card game in which a 45 automatic gun triumphs four aces. What has just been achieved is an energizing of individuals who previously lacked confidence in their beliefs. I like your suggestion to invite individuals to address some limited issue close to their area of expertise that does not put them in harm’s way. More focused discussion
or data, unless published in open journals, will never see print in veterinary journals for political reasons.

Gilles

E-mail January 2, 2013

Dear Gilles and Ivo,

Few comments received from Prof. George Poppensiek, USA, Prof. Kouba, Former Chief, Animal Health Service, FAO, Joe Falkinham, A. Maraz, Hungary.

Seven new subscribers for CGNI 08 Mycobacterial diseases from USA, Egypt, Pakistan, Malaysia.

Karel
A VOICE WITHIN THE DOME OF SILENCE

Exerts from ACVIM Consensus Statement


“……. Some authors argue that there is “no conclusive evidence” that MAP is a cause of Crohn’s disease. Direct scientific evidence that MAP is a human pathogen by experimental challenge of young children to fulfill Koch’s postulates is unethical. There will never be conclusive evidence. Instead, the scientific community must base any decision on the zoonotic potential of MAP on multiple indirect lines of evidence as discussed below.”

“……. Molecular finger-printing demonstrates extensive MAP strain sharing among species. Evidence that MAP can infect taxonomically diverse species is strong.”

“……. interestingly, many of the genes associated with a higher frequency of Crohn’s disease are also those affecting susceptibility to mycobacterial infections (New Engl. J. Med. 2009; 361:2666-2668).”

“…….Experts suspect that finds humans an abnormal host and adopts a different form, e.g. a spheroclast (cell-deficient) ….”

“…….Hill’s 10 criteria for causality. For seven of the criteria the authors gauged the evidence as strong or moderate and for two conflicted (Crit. Rev. Microbiol. 2012; 38:52-93).”
TOO BIG TO TOUCH

E-mail December 18, 2012

Ray Sweeney, Secretary-Treasurer IAP

To membership

Dear IAP members:

It has recently come to my attention from several national official sources that the World Organization for Animal Health (OIE) is working on a new simplified Terrestrial Animal Health Code from which paratuberculosis will be taken out. The main reason appears to be that there is no satisfactory diagnostic method for detection of infection in individuals. This coupled with the widespread presence of the infection in most of the member countries represent a hurdle to international trade that would not be justified by the economic losses it causes or the real chances to apply effective restrictions in international animal trade. Although some countries that declare themselves free of the infection are opposing this decision, it seems that the majority support it. This seems to be part of broader strategy affecting several other diseases, currently including Enzootic Bovine Leucosis, but that could be extended in the future. Anyway, I have no first-hand information on this issue, and therefore, I would like to encourage asking your national animal health authorities about the issue and sharing the information with the rest of the IAP members.

Ramon A. Juste, DVM, PhD, ECSRHM
E-mail December 18, 2012

Dear Karel:

A problem that may be an opportunity to have different voices heard

Gilles

E-mail December 18, 2012

Dear Ray:

Thank you for the heads up,

On the medical side of the issue, MAP is a zoonotic pathogen. To deny that paratuberculosis is a medical as well as veterinary issue that requires an answer/solution and then facilitate dissemination of infection and disease on a global level is grossly irresponsible. JHEP needs to flex its intellectual muscle in this issue.

Gilles

E-mail December 20, 2012

To Ramon A. Juste, DVM, PhD, Dip. ECSRHM

Dear Ramon

Because my letter to you is going to be circulated, I needed to make some minor grammatical and content changes. Please insert this as my response to your e-mail.

Re.: The World Association for Animal Health (OIE)'s proposal to remove paratuberculosis from the Terrestrial Animal Health Code
Any decision by the World Organization for Animal Health OIE to remove paratuberculosis as a disease entity from the Terrestrial Animal Health Code lacks scientific merit. If enacted, the consequences will only exacerbate significant agricultural and societal public health issues that, if not addressed, will in time destroy the dairy industry.

To state that there is no satisfactory way to detect animals infected with MAP is a distorted interpretation of the relevant scientific literature. The FUIDI #1 MAP ELISA test specifically addresses the issue of whether detectable MAP is present or not. What has adversely colored the diagnostic literature concerning Mycobacterium avium subspecies paratuberculosis (Map) is the fact that the current commercial MAP ELISA tests certified by the United States Department of Agriculture (USDA) measure anti-MAP antibodies, but the interpretation of a positive test is predicated on the identification of a level of antibody that predicts a high probability of a progression of MAP infection to clinically overt enteritis (Johne’s disease) or confirms its presence. A negative commercial MAP ELISA test does not address the issue of whether or not a given animal has ever been infected by MAP.

The decision by USDA to have the MAP ELISA tests represent a statement of probability rather than a valid measurement of the amount of antibody present has permitted infected cows to be transported across state lines and national borders. The net result was not only the introduction of infected animals into uninfected herds, but a dramatic increased prevalence of MAP infection in the national herds. In 2002, 30-40% of U.S. dairy herds had animals with MAP. In 2007, USDA acknowledged that an estimated 70% of U.S. dairy herds contained one or more infected animals (USDA-APHIS Johne’s Disease in U.S. Dairies 1991-2007. http://nahms.aphis.usda.gov/dairy/dairyo7/Dairy 2007-Johnes.pdf.2007). If a test is now used that truly measures the presence or absence of MAP antibodies, the number of infected animals in a large, confined dairy operation may exceed the 2007 seventy percent figure that identified merely one or more MAP infected animals.
Central to the herd monitoring schema proposed by the 2008 National Johne’s Disease Control Program for Johne’s disease was identification and removal of infected animals from the herd. Reducing the introduction of MAP infection and potentially Johne’s disease into uninfected herds is largely contingent upon the buyer having the proper information to go along with eyeball analysis of the animal’s body condition score. Quality of merchandise is theoretically addressed through the animal’s health certificate. In the United States, revision to parts 71 and 80 of the Code of Federal Regulations (CFR) is supposed to restrict the interstate movement of MAP-infected animals except to recognized slaughter establishments (United States Department of Agriculture Animal Plant Health Inspection Service. 9, Parts 71 and 80.2000. Johne’s disease in domestic animals: interstate movement. Federal register 65:18875-188879). With an artificially constituted threshold for a positive test, the pertinent CFR regulations do not truly address the quality of merchandise issue. By not stipulating on the animal’s certificate of health its MAP status in a manner comparable to Mycobacterium bovis, animals with subclinical disease are and have been transported across state and national boundaries. The decision by USDA not to require a statement as to an animal’s MAP status has been a prime factor that undermined its avowed intent to prevent dissemination of MAP into uninfected herds. USDA’s decisions have effectively masked the presence of infection in dairy cows, and by so doing exported disease across state and national boundaries.

The Japanese perception that MAP constitutes a potential public health hazard has engendered a different schema (Eiichi M.2012. Epidemiological situation and control strategies for paratuberculosis in Japan. Japanese J. Vet. Res. 60:19s-29s). In accordance with the Act on Domestic Animal Infectious Disease Control, after 1998, every Japanese dairy farm is examined for MAP every five years. Imported cattle are subjected to quarantine in which they are screened using MAP ELISA, fecal bacterial culture, analysis of feces for MAP DNA and Johnin skin test. If a new cow is to be introduced into a herd, the recom-
mended procedure is that the cow should be negative in more than two ELISA tests within three-month intervals during the last six months, negative at least once in culture for Map, and kept in quarantine until proven non-infectious. Fifty-four percent of diseased animals detected by the Japanese Animal Quarantine Service came from the United States. Owing to the high antibody threshold for a positive test of the current MAP ELISA tests, the real number of exported infected cows from the United States escaping detection is open to speculation.

The cost of USDA’s current policies has been the widespread dissemination of MAP within the nation’s dairy and beef herds in the name of protecting agriculture. In trying to placate a threat to the dairy and related industries, USDA has dramatically magnified the threat. Once introduced into the production area, eradication of MAP from that environment is nearly impossible. MAP dissemination within a herd has been documented to be progressive with time.

In its attempt to insulate dairy producers from incurring added production costs embedded in implementing an effective herd management plan, USDA has cost producers money. Multiple studies have demonstrated a reduction in milk volume and fat content as well as impaired reproductive outcomes occur long before clinical signs become manifested. Instead of having occult losses from a few cows, the producer now had occult losses in milk production, unsuccessful reproductive outcomes, and decreased slaughter weight occurring in the majority of his cows. Once unidentified MAP infection becomes prevalent within a large herd, by itself, small occult milk production losses can become very substantial over time owing to the number of animals now infected.

The more immediate threat to the dairy industry is not whether MAP is the direct (cytokine/tumor necrosis factor) or indirect (induction of an autoimmune response) cause of irritable bowel syndrome and Crohn’s disease; it is that milk and milk products may contain an element (the MAP organism) that
may be harmful to the public health. A statement to this effect is not on the labels of milk, of baby food made from milk, of products made from milk or powdered milk, etc. Knowledge that 1) MAP is recognized as a zoonotic pathogen; 2) the organism has been identified significantly more frequently in disease tissue, milk, and blood from individuals with Crohn’s disease than from individuals without gastrointestinal diseases; 3) the majority of individuals who consume milk regularly are projected to be infected; and 4) even killed MAP release muramyldipeptides that are potent immunomodulators that trigger inflammation. To falsify a product label by deleting the inclusion or potential inclusion of a potentially harmful ingredient is inviting civil, if not criminal proceedings.

Recognizing USDA’s administrative blunders, the World Organization for Animal Health (OIE) now seeks to whitewash the damage done on a global level using the rationale that because MAP infection is so widespread, continued recognition of MAP as an animal pathogen would only cause economic losses through the restrictions in international animal trade. Ethically, as well as scientifically, OIE has chosen to disregard the preponderance of scientific evidence incriminating MAP in the pathogenesis of human diseases: in particular Crohn’s disease and childhood autism.

To do nothing is to do something. The cost of USDA doing nothing has been the widespread dissemination of MAP within the nation’s dairy and beef herds in the name of protecting agriculture. OIE is to be congratulated for doing the next best thing to nothing, the wrong thing. Let the International Association for Paratuberculosis (IAP) do the best thing and speak out against a proposal that puts us and our children’s children all at a greater risk.

Gilles R. G. Monif, M.D.
E-mail December 21, 2012

Dear Gilles:

(The president of IAP asked that the content of his response not be published.)

Ramon

E-mail December 19, 2012

Dear Gilles

Thank you for e-mails on OIE decision. I have been informed few days ago by Ivo (Pavlik) about the video meeting of the IAP officers, who are obviously unable to address Dr. Vallat or to publish arguments against this professional approach of OIE. I really appreciate your precise description. The open discussion on Biomedical Technology, Epidemiology and Food Safety Global Network is ready to publish your opinion with a footnote that the statement of IAP President has been requested and will be published by the same way as soon as it would be available.

The event encourages me in the trust that we should continue in publication of mini-reviews...

Unfortunately, we are nearly totally paralysed by actions against the five most efficient VRI representatives, suspended by the new management from their positions of deputy director or head of the department without any known reason. Details are not needed, nobody would believe them. It’s a cruel life story like an absurd theatre

Please, see the attached draft and let me know if it can be posted and distributed by CGNI.

Karel
E-mail December 19, 2012

Dear Karel:

I cannot tell you how saddened I am by what is happening. (A sudden change of leadership at Brno’s Veterinary Research Institute). I have held your institute and your country in highest regards for its role in disseminating scientific information.

My mentor taught me that the sharing of knowledge is the greatest of all gifts: it enriches both the giver and the receiver. His name was Donald Barron (considered by many to have been the father of perinatal research).

That IAP officers chose not to put themselves in harms way is not surprising; yet they can manufacture a response through the 2014 IAP meeting in Parma, Italy. … Between now and then, if Ramon Juste would initiate the dialogue with a strong letter stating his concerns about the pending OIE action, a resultant dialogue could expose the fallacy of OIE’s proposal and delineate the projected dire societal consequences.

With respect to using my response to Ramon’s e-mail, the answer is yes, but please allow me to rewrite a small portion as I wrote it the night I received his e-mail.

The issue of MAP as a public health hazard is too threatening to those in power. Only when they are assured that their wallets will not be lightened will any progress be made in lessening the consequences of their greed.

Greenstein, Naser, etc. all know the consequences of speaking out. Protect yourself from evil. The American Indians recognized the negative force that emanates from gold and shun it. Gold (money/power) is a destroyer of those who embrace it solely for self.

Gilles
DISCARDING IMPEDIMENTS

If MAP is causally linked to Crohn’s disease and irritable bowel syndrome (IBS), two glaring objections had to be effectively accounted for by the hypothesis seeking to be a scientific truth.

1). That MAP can be isolated from the tissues and blood of individuals not afflicted by Crohn’s disease violates the argument for causality.

The observation that MAP can be isolated from apparently healthy individuals has to be interpreted by the inability to accurately characterize the control populations. The criteria for sampling were that they had no signs or symptoms of gastrointestinal disease and, in the cases of DNA tissue analysis, that there was a medical reason for the biopsy.

USDA and FDA have yet to certify a serum test for humans that identifies the presence of MAP antibodies, much less active infection. Infection with mycobacteria involves a phase in which the organism is in the person’s blood stream.

The best studied pathogenesis of a mycobacterium is that of *M. tuberculosis*. The inhaled organisms come to be deposited primarily in the middle or longer divisions of the lungs. Disease occurs in the upper segments of the lungs as a result of the organisms invading the blood and being transported to a more favorable site for their continued propagation.

Humans have receptor sites for pathogenic mycobacteria through their gastrointestinal tract. If you drink milk or eat soft cheeses containing MAP, based upon parallel scientific data, you will become infected. The disconnect between the number of individuals who theoretically have ingested viable MAP and the number of individuals experiencing MAP’s theorized consequences (Crohn’s disease) has implied that, unless host cell-mediated immunity becomes compromised, MAP infection is of little consequence for the vast majority of individuals.
Given the theorized, unintended infection of a large segment of the nation’s population has occurred, that a small percent of individuals without clinical disease should have MAP or its DNA in their tissues and/or blood is not surprising. The inability to exclude MAP infected individuals from the control groups significantly undermines the counter argument against MAP being involved with Crohn’s disease.

2). Accepting the postulates that, predicated upon diet, a significant segment of a nation’s population is infected and that MAP is causally related to Crohn’s disease, how does one explain that, given the tens-of-millions of individuals theorized to have been infected, there are only 800,000 cases of Crohn’s disease currently acknowledged.

A partial answer resides in the equation that determines whether a pathogenic mycobacterium causes just infection or disease. The amount of the pathogen times that strain’s virulence battles against the person’s immune system.

Under appropriate conditions, most *Escherichia coli* bacterial isolates can produce disease, but only a very specific strain of *E. coli* produces toxins responsible for the majority of *E. coli* food poisonings. By selecting a toxigenic strain of *E. coli*, strain virulence is a constant. If 100 individuals eat hamburger meat contaminated with toxigenic *E. coli*, only a small number of the challenged individuals will develop signs and symptoms of disease. WHY? Either the number of organisms in their hamburgers was insufficient to overcome the ability of host immune system to effectively handle the bacterial challenge or the individual’s immune system was genetically programed to be less proficient.

The overall governing factor that defines whether human sub-clinical infection or disease ensues as a result of microbial challenge is the role played by the individual’s immune system.

\[
\text{Inoculum Size \times (its) Virulence \divided by Host Immunity.}
\]
Prior to MAP’s incrimination as the cause of Crohn’s disease, MAP produced disease primarily in individuals with retrovirus compromise of their cell-mediated immune system (AIDS) or with immunodeficiency syndrome. As has been theoretically inferred, adult immunity appears to handle most MAP challenges well. If the amount of MAP ingested is large, in some cases individuals may be at apparent risk to develop irritable bowel syndrome (IBS).

So in theory how did MAP cause the current global Crohn’s disease epidemic? In protecting the dairy and milk-based industries, USDA allowed the presence of MAP infected cows to become widespread within the nation’s dairy herds. By USDA’s own admission in 2007, 31.7% of bulk tank milk sampled contained MAP DNA. That is 2007 data; not 2014 data.

MAP’s penetration into the potentially global food supply has resulted in viable MAP being present in powdered milk and MAP DNA in baby formula. WHY is this observation theoretically of such great significance; the period of maximum compromise of the human immune system occurs in utero and in the first month or two of life.

The incompleteness of fetal and neonatal cell-mediated immunity is best illustrated by a large number of experiments in nature.

Congenital and neonatal infections with the Herpes simplex viruses, the cytomegaloviruses, and the Coxsackie group A & B viruses, among others, result in widespread systemic disease often culminating in the infant’s death or residual lifelong disabilities. The same infections after the third month of life usually result in minimal, if any, clinical manifestations.

Given that viruses and mycobacterium achieve termination of active replication by the same immune mechanisms, it is logical to assume that the principles identified with congenital and neonatal viral infections are applicable to mycobacteria. MAP in infant formula and milk containing MAP fed
to newborns constitute the zoonotic bridge across which an animal pathogen produces disease in humans.

Very young animals, including the human species, do not handle intracellular pathogens, and specifically viruses and mycobacteria, effectively. For a neonate to terminate mycobacterium replication, its immature cellular immune response is taxed a probable maximum. Unlike extracellular pathogens, (bacteria intracellular viruses and mycobacteria) undergo a process termed immune capture in which the overt presence of the organism is no longer demonstrable, but evidence of continued stimulation of a species specific antibody production continues.

In the early 1940s, a rubella virus epidemic occurred on a remote island off the coast of Alaska. Thirty years later, a second epidemic occurred. Those individuals who had been born following the initial epidemic were the individuals who contracted infection or disease. Serological testing demonstrated that the majority of those who had lived at the time of the initial epidemic had pre-existing anti-rubella antibodies.

DNA viruses such as the varicella-zoster virus (chickenpox/shingles), the cytomegaloviruses, and the Herpes simplex viruses, and mycobacteria have the very real potential for reactivation in which the organisms escape immune containment and can again induce disease.

The fundamental points are that 1) once infected with MAP, an individual will continued to harbor the organism for a prolonged period of time and 2) his or her immune system will continue to receive low level stimulation from MAP’s antigenic array.

Johne’s disease in cattle and Crohn’s disease are unique in that the portal of infection and the target organ of disease are one and the same. By design, the lining and submucosa of the gastrointestinal tract constitute a formidable barrier to organismal systemic penetration. Immune and cytotoxic defenses of the body are maximized at this site. What has been clearly documented is that storage of MAP DNA resides within the submucosa of
the gastrointestinal tract. What distinguishes the response of an individual who acquired infection in the period of maximum immaturity of his or her cellular immune system and that of an individual who become infected later in life is the magnitude of the cytotoxic cytokine response delivered by lymphocytes. Therapies that have had success in ameliorating Crohn’s disease symptomology or in inducing temporary remissions have involved the destruction of effector lymphocytes or neutralization of cytotoxic tumor necrosis alpha.

As the prevalence of MAP in a nation’s food supply parallels that of MAP’s presence in milk-producing animals, gastrointestinal tracts previously primed for hyper-production of cytotoxic cytokines are now more frequently presented with MAP. For those whose immune response to MAP is preset for overproduction, eventually the cytotoxic excess results in loss of mucosa integrity in the areas of maximum stasis. The induced destruction of the gastrointestinal tract’s lining initiates the second element in the production of Crohn’s disease. Bacterial and other intestinal microbes that invade the submucosa literally engage in a pitch battle with the site specific host defenses. Diseased tissue is the net result of two separate mechanisms concomitantly working. Bowel perforation and fistulous tracts occur when the bacterial flora of the gastrointestinal tract wins.

What determines if an infant infected or in the neonatal period will develop Crohn’s disease later in life is again the formula, inoculum time virulence offset by host immunity.

Karel Hruska has long postulated that MAP infection occurring very early in life causes an impairment of one or more of the immune system’s negative feedback systems. The net effect of continued or re exposure to MAP antigens results in the release of inflammatory cytokines.

When a disease occurs in humans, it is in essence an experiment in nature. Experimentation on humans crosses a line that should not be crossed. Fortunately, experimentation to prove the
hypothesis that Crohn’s disease is the consequence of quantitative MAP infection at a time of cellular immunity vulnerability needs never be done. The definitive experiments are already in place.

**Iceland:** MAP infection and ruminant paratuberculosis was basically unknown in Iceland. In 1933 sheep, among which were animals with subclinical MAP infection, were imported into Iceland. With time, MAP disease became epidemic in sheep and, eventually, in its cattle. The mean incidence of Crohn’s disease from 1950-1959 was 0.4 cases per 100,000 individuals per year; from 1960-1969 0.9; from 1970-1979 3.1; from 1980-1989 3.11 and from 1990-1995 5.6.

Iceland’s physical isolation made it an ideal epidemiological laboratory. This “experiment in nature” demonstrated that widespread dissemination of MAP among the milk producing animals was the prerequisite for the initiation of Iceland’s Crohn’s disease epidemic.

**The Czech Republic:** The same sequence is repeated in the Czech Republic. Prior to 1990, World War II and then the Iron Curtain had isolated the Czech Republic from the world. MAP infection and paratuberculosis in its domestic herds were virtually unknown. Economic hardships required that most mothers breast feed their infants.

Following the crumbling of the Iron Curtain, some 30,000 heifers were imported from countries whose herds contained animals with paratuberculosis. As the local economy improved, women began abandoning breast feeding in favor of milk or infant formula. Initially infant formula was produced from local herds; however, the single local producer was bought by an international company and local production was stopped. The domestic product was replaced by imported formula. In 2005, 49% of 51 brands of baby formula manufactured by 10 different producers in seven different countries were demonstrated to contain the DNA of MAP.
Between 1995 and 2004, the incidence of Crohn’s disease increased 4.5 fold among 0-19 year olds and 6.5 fold in 65+ year old individuals.

These two experiments in nature demonstrated that widespread dissemination of MAP among milk-producing animals was the prerequisite before epidemic increases in the number of citizens afflicted with Crohn’s disease occurred.

The Czech Republic data provided the next step in unraveling the pathogenesis of Crohn’s disease. Embedded within the Czech Republic, there was and is a subpopulation composed of Roma (gypsies). Breast feeding is culturally based among Roma women. Unlike their Czech counterparts, Roma women were much slower to adopt change. The rate of Crohn’s disease among Roma was half the incidence of the rest of the population.

Investigators, analyzing risk factors for Crohn’s disease, have clearly indentified that breast feeding confirms a protective effect.

The Hruska hypothesis as to the zoonotic bridge being MAP’s contamination of milk and milk products is embodied in http://vri.cz/docs/vetmed/59-12583.pdf. A global market has made baby food and dairy products from MAP infected herds accessible to the countries previously MAP free.

WHY the United States is experiencing an epidemic of what was once an infrequent disease is implied by the Iceland and Czech Republic MAP experience. MAP must become first widespread among milk producing animals before the incidence of Crohn’s disease increases. The Czech Republic MAP experiment tells those who act in the public trust how to abort what is a life destroying affliction.

The WHY of the why United States is experiencing an epidemic of what was once an infrequent disease has an answer that has the real potential of being a “medical truth.”
Absolute or conclusive proof that a zoonotic mycobacterium causes Crohn’s disease can never be achieved. That fact has permitted FDA to remain silent as to whether or not MAP’s presence in our the Nation’s food supply constitutes a public health hazard.

FDA continues to demand “conclusiveness” before labelling products contaminated with MAP as being a potential public health hazard because it lacks the vision to see a way out of the problem. The well-worn phrase that the cause of Crohn’s disease can never be proven with absolute certainty and will continue to be advanced despite the knowledge that medicine is, at best, a pseudo-science whose “scientific truths” are the product of multiple sustaining probabilities.

Public health is a civilization issue. The demand for absolute certainty has been used to preclude the need of telling Americans of the hypothetical risk to their health.

In a democracy, the ethical obligation of government is to identify and address defined risks to the public welfare. That obligation is clearly stated in the Rio Declaration on Food Safety “In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full knowledge shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation”. Regulatory measures are allowed “where relevant scientific evidence is insufficient to demonstrate the safety of a product or commodity”.

To act, a government doesn’t have to believe that MAP is the cause of Crohn’s disease. It only has to accept that a hypothetical risk to the public health is present.

Unless the Rio Declaration is but an exercise in penmanship, the U.S. government has pledged itself to treat a hypothetical risk as a risk.
As of now, that entails telling pregnant women to breast feed their babies for the first two months of life and making certain that the milk used in baby formula is MAP free.
HOMAGE TO THOSE WHO CONTROL

The French have an old adage that states; “To criticize is easy, to create is difficult”.

Milk and milk–derived products are backed by powerful economic interests that are too big to …. (The 20th century’s catch phrase for “to be protected at the public’s expense”). Without their consent, a resolution to the Crohn’s epidemic, more probably than not, can’t be achieved.

Annually, Crohn’s disease costs the United States government billions of dollars. Individuals are being prematurely forced out of the work force in their prime earning year. Others have to seek lesser employment to accommodate their disease. The cost of achieving a sustainable level of remission using TNF “knock out” drugs is now a big ticket item for individuals, insurance companies, and government.

The increasing number of citizens becoming afflicted with Crohn’s will eventually force governments to choose among their funding priorities.

If “error up to date” is correct, stopping the Crohn’s disease epidemic is simple. Milk and infant formula given to newborns in the first six weeks of life must be absolutely MAP free.

This can be done relatively easily. Only bulk tank milk certified as being MAP free should be certified for inclusion in infant formula. Milk sold in stores specifically marked for early infant feeding must similarly be MAP free. The technology to achieve it is already in the public realm.

The penalties of falsifying the MAP status of bulk tank milk need to be intimidating!
With the possible exception of inflammatory bowel disease and the absence of infection with the AIDS virus, the majority of us can enjoy milk-based products with relatively little fear of consequences.

Implementing change will require governments to underwrite the cost of testing and to compensate producers for loss of revenue incurred in complying. The liability for the spread of MAP and, theoretically, that of Crohn’s disease resides with USDA, thus making government the ultimate payee.

In the longer run, reducing the amount of MAP entering the human food supply needs to be implemented, if only to reduce the potential size of the MAP inoculum within the equation that determines whether infection or disease occurs.

“To do nothing is to do something.”

The cost of government doing nothing has been the widespread dissemination of MAP within the nation’s dairy and beef herds in the name of protecting agriculture. The real cost of doing nothing, more likely than not, has been the placing of hundreds thousands of Americans, without their knowledge or consent, in potentially harm’s way.

But the greatest cost of doing nothing is the loss of belief in a country for the people and by the people.

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In the 1990s, circumstantial evidence had been advanced that a mycobacterium, *Mycobacterium avium* subspecies paratuberculosis (MAP), was the possible cause of Crohn’s disease. When it was documented that this organism survived pasteurization and was present in milk, infant formula, powdered milk and cheese, a global panic button was pushed.

*The Story of Crohn’s Disease* describes MAP journey across the zoonotic bridge and the unique circumstances with which it allegedly produces disease in human.

**Author:** Gilles Monif, MD, an internationally recognized leader in infectious diseases, describes his decade long involvement in addressing a human disease whose answer had resided in the world of veterinary medicine.