Article Index

A note from the Editors: The following is a write-up of Dr. Anthony Komaroff's April 24, 2010 lecture to the Massachusetts CFIDS/ME & FM Association. *View the full video* *of his lecture.*

We think a written review of the lecture may be of benefit to patients, their family and friends, as well as health care providers. We would very much appreciate your thoughts on the usefulness of this write-up, as your feedback can indicate to us the need for write-ups of future lectures. Please Contact Us to tell us what you think.

Special Note: In the text, we will refer to some of the slides by title. You may view the slides Dr. Komaroff used in his lecture;
this opens a separate window so you can click between the text and the slides with the corresponding titles to see the data.

Use of initials/acronyms: Dr. Komaroff in his lecture used the initials "CFS", which still designates the name most used in the medical research community, i.e. Chronic Fatigue Syndrome. Elsewhere on this website we refer to the illness as CFS/CFIDS/ME, for the Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome/Myalgic Encephalopathy.

For an explanation of p-values, which Dr. Komaroff frequently refers to in his slides, refer to the Association's page on research notes .

A turning point in understanding CFS as a real, physical illness

By Ken Casanova and Liz Knights

Introduction: A message of real hope

The Massachusetts CFIDS/ME & FM Association was delighted to welcome back Dr. Anthony Komaroff of the Harvard Medical School, one of the preeminent pioneers in the research and treatment of CFS, as our guest speaker for the first of our 2010 lecture series. Dr. Komaroff tailored his lecture specifically to review research developments in CFS over the past decade. Though looking back over a period of ten years might seem dated, a major portion of the information presented was strikingly new to many in the audience.

In fact, Dr. Komaroff delineated the existence of a watershed juncture in the state of CFS research and scientific knowledge, since a number of major doubts as to the validity of CFS as a biological illness have finally been overcome.

"Are there objective biological markers in people with CFS? Until this question was answered, skepticism was appropriate – because in a biologically-based illness it would be expected to be able to measure what is wrong biologically. *My answer to this question is, now, absolutely yes! The controversy is over!"*

Dr. Komaroff's lecture's major theme is that there is now a turning of the tide. Not only did he look back to the more recent accumulation of evidence that CFS is a biologically-based illness, he also looked ahead with optimism toward more rapid advances in the research and treatment of CFS.

His lecture was largely a presentation of research findings as to how CFS affects the different physiological systems in the body. He also outlined his own hypothesis as to the probable causation of the illness. Finally, in his concluding thoughts, he presented his inside-view that much progress has been made in the acceptance of CFS by the medical and research community ("though not as much progress as I would like.")

Dr. Komaroff, through reviewing various studies, definitively demonstrated that various viruses and some bacteria can "trigger and perpetuate the illness." It was not so long ago that the U.S. Centers for Disease Control and Prevention (CDC) denied the role of viruses in the essential physiology of the illness.

Back to top

The early years—patients struggle to validate their illness

As most patients are too painfully aware, throughout the history of CFS, the illness has been branded by many physicians and federal research agencies as a type of psychiatric illness. "Atypical depression", the "yuppie flu", "neurasthenia", and "a cognitive/behavioral inability to handle stress due to poor coping skills" were some of the common descriptions.

Again, Dr. Komaroff returned to late 1980s by remembering a meeting of the American Psychiatric Association in which deep skepticism about the illness was expressed. This skepticism was reflected far more broadly, not only by psychiatrists, but also by medical doctors. But now, Dr. Komaroff asserted: *"The day for that skepticism has long since passed."*

He acknowledged that when not much was known about the illness in the late 1980s, there was very little evidence "to either support or reject the skepticism". But in the last 20 years there has been an enormous amount of research that has clarified and defined major aspects of the illness. He stressed that, usually, in medical science the understanding of the cause of an illness and its effective treatment takes many years of careful medical research that builds upon itself.

And the research in CFS has been productively building upon itself: in the last 20 years over 5,000 scientific articles have been published—over 300 of which were in the some of the world's most prestigious journals. There have been more than eight international conferences, which contained over 160 scientific presentations from scientists and doctors from all over the world. One of these conferences was in Boston and co-sponsored by the International Association for CFS/ME and the Massachusetts CFIDS/ME & FM Association.

Back to top

The actual severity of CFS

Most patients will describe the severity of their fatigue in CFS as being quite disabling. However, it is possible to measure and even score the severity of fatigue in this illness and others by using an instrument, called the SF-36. It is a method that can assess patients, by applying a multidimensional health survey and specific health parameters, and then come up with scores/ demonstrable level of impairment within patient groups.

Dr. Komaroff reviewed a major study which demonstrated this technique (Komaroff A, *et al, Amer J Med*
101 (1996): 281)—see slide,
SF36 Health Status Subscale Scores: CFS vs. Comparison Groups
) by comparing the severity of illness among healthy individuals, patients with heart failure,

depression, and CFS according to a number of illness variables. It should be noted that the study included a large number of patient subjects and healthy controls, and that the measurement instrument, SF-36, is considered one of the best for determining illness status.

A quick description of the results shows that the *physical status* of CFS and heart failure patients were nearly equal, much below that of healthy individuals and depressed patients. The *bodily pain* in CFS patients was the highest in all the groups. The *health perception* of the patients and their actual *vitality* and *social function* was the lowest of all the groups. And yet the *mental health* of CFS patients was substantially better than that of the depressed patient group.

How CFS hurts the economy

Dr. Komaroff discussed a U.S. Centers for Disease Control and Prevention (CDC) study that found, on average, a 37% decline among patients in ability to function in the household, and a 57% decline in function in the workforce. The estimated loss to the U.S. economy each year from the resulting productivity loss is $9.1 billion (and this does not count the cost of medical care for the illness.) This loss to the economy is greater than the bottom line of Wal-Mart, the biggest corporation in the world.

Is Chronic Fatigue Syndrome real?

Since CFS is still diagnosed primarily by its symptom complex—after elimination of other illnesses—a major question in the history of the illness has always been: is there objective evidence of pathological processes in the body that do not occur in healthy people, depressed people, or people with other illnesses? After 20 years of research, Dr. Komaroff answers unequivocally: "Yes." He then asked the next question: "Do we understand how the symptoms are caused?" And he answered, "No, we don't understand that yet." Yet getting answers to the first question gets us nearer to answering the second question.

Back to top

How is the body affected by CFS?

Most of the rest of the lecture is a specific review of the pathological (abnormal/harmful) changes in the different physiological systems in patients with CFS. These include:

a. The autonomic nervous system, which controls vital functions in the body, including temperature, blood-pressure, certain hormonal functions, heart-beat, etc.;

b. The immune system, which is responsible for fighting-off and controlling viruses, bacteria and other pathological microorganisms;

c. Energy metabolism and the mitochondria (which are organelles in every cell that control energy metabolism.)

d. Genetic studies, which illustrate differences in the genetic background of many CFS patients, and more recently in the active process of "gene expression" in the illness;

e. Links that have been shown between the illness and infectious agents.

Back to top

The brain

In discussing how the body is affected by CFS, Dr. Komaroff first focused on the brain. He cited six different areas of evidence that the brain is highly involved in the disease process of CFS, including both clinical manifestations and physiological abnormalities which have been demonstrated by brain imaging technologies: neuroendocrinological abnormalities, cognitive

dysfunction, autonomic impairment, and abnormalities apparent in MRI, SPECT and EEG testing.

Neuroendocrine dysfunction: The neuroendocrine system in the brain controls and coordinates the glands elsewhere in the body that produce hormones. Neuroendocrine dysfunction in CFS is evident in the limbic-hypothalamic-pituitary axes—a complex system of interactions in the brain involving the limbic system, the hypothalamus and the pituitary gland. These together, in addition to fulfilling important functions such as regulation of the immune system and digestion, also control production of the hormones cortisol, prolactin, and growth hormone by glands elsewhere in the body. The serotonin (5-HT) system is also affected.

Cognitive (thinking) difficulty is apparent in neuropsychological studies of CFS patients. These tests demonstrate deficits in memory and attention as well as speed of information processing—*deficits that cannot be accounted for by concomitant psychiatric disorders.*

Autonomic dysfunction is found in 30% to 80% of those with CFS. This means that for those patients there is some level of impairment of the sympathetic and parasympathetic nervous systems.

MRI scans of CFS patients show punctate areas of high signal intensity in the white matter of the brain.

SPECT scans, which measure cerebral blood flow, indicate areas of decreased blood flow in CFS patients.

EEG tests, which measure electrical activity in the brain of CFS patients, show abnormal spikes and sharp waves and a spectral coherence pattern unique to CFS that Dr. Komaroff elaborated on a bit later.

At this point, Dr. Komaroff paused to emphasize that none of the brain studies just mentioned show chronic or progressive brain damage, but rather brain "abnormalities that come and go" and mirror the ebb and flow of symptom severity experienced by many of those with CFS.

Importantly, these brain abnormalities also clearly distinguish people with CFS from healthy people, people with depression, and people with other fatiguing illnesses.

Back to top

Spinal fluid abnormalities in CFS

The human brain is bathed in the cerebrospinal fluid, a sample of which can be obtained by spinal tap. A sample of the fluid will reflect what is happening in the brain. The best method for measuring proteins in the spinal fluid is mass spectroscopy. Dr. Komaroff cited one study (Baraniuk J, *et al*.—refer to slide, *Proteomic Markers in Spinal Fluid*) which found specific "proteomic markers" (proteins) in one-third to one-half of CFS patients and none in healthy controls—a highly significant difference. These proteins are indicative of a low-grade inflammation in the brain, "that there is something that the immune system ...wants to get rid of, and this process is reflected by these proteins in the spinal cord."

A 2008 study demonstrated that many CFS patients also have elevated levels of lactic acid in their cerebral spinal fluid relative to healthy controls and patients with Generalized Anxiety Disorder (Mathew S, *et al.*— refer to slide, *Lactate in Spinal Fluid in CFS: In vivo Proton MR Spectroscopy*). The researchers involved with this study postulated that the cause of increased lactate could be oxidative stress, a condition that sets off a chain reaction in which isoprotanes (by-products of oxidative stress) decrease blood flow by constricting cerebral arterioles, which in turn, increase brain lactate levels. They also hypothesized that the lactic acid could be building up due to a secondary mitochondrial dysfunction, which itself can cause increases in anaerobic glycolysis and lactate.

Back to top

EEG: spectral coherence studies

At this point in the lecture, Dr. Komaroff returned to the use of EEG to study spectral coherence in CFS. (EEG stands for an electroencephalogram or "brain wave" test.) Spectral coherence measures a disorder in the brain between two neurons firing (i.e., when one neuron fires, others should fire simultaneously and when those other neurons fail to fire, an incoherence is created). Different illnesses can present with different patterns of spectral coherence. In fact, a study that

will shortly be submitted for publication, demonstrates that un-medicated CFS patients can be diagnosed using spectral coherence with nearly 90% accuracy (Duffy F, *et al.*—refer to slide, *EEG: Spectral Coherence Studies*
.) The study also included CFS patients who were on medication. However, these patients could only be diagnosed with about 73% accuracy, a result which could potentially be due to the remedial effects of the medicine—effects which could result in some increased spectral coherence. The same study accurately classified both healthy and depressed controls. Dr. Komaroff expressed the hope that with validation of these results through further studies, spectral coherence could be accepted as a reliable method of diagnosis of CFS.

Back to top

Measuring the effects of post-exertional malaise in CFS patients

As patients, we know what often happens after "we do too much." We "crash", we have to go to bed for one or more days, we're sick, in pain, and have no energy whatsoever. Would it ever be possible to compare effects in the body after exertion between healthy people who don't suffer any substantial effects and CFS patients who do? Could one measure substantial physiological changes in CFS patients that confirm a pathological biological response to the exertion?

Dr. Komaroff reported, in fact, that a major study has found just such physiological changes in CFS patients that do not occur in healthy individuals. The importance of this study and its further confirmation cannot be overestimated. The study was conducted by Alan Light, *et al.* and published in the journal
Pain
in 2009. The human body contains molecules that can sense fatigue and pain. These molecules occur as ion channel receptors, adrenalin receptors, and immune system molecules. The study, by means of a blood assay, measured these groups of molecules in both CFS patients and healthy controls before and after exercise—beginning 25 minutes after exercise, and then 8 hours, 24 hours, and 48 hours afterward. The exercise consisted of 25 minutes on a combined arm-leg cycle ergometer.

The difference between patients and healthy controls post-exercise was absolutely striking, if not amazing—see slide, *Fatigue & Pain Sensing Molecules: Normals vs. CFS, Post-Exercise.*

Before exercise—"at baseline"—there was actually not much difference between the molecular

profile of patients and "normals". Following exercise, the study measured "fold increases" in the molecular profiles of both patients and controls at each interval period. In controls, the highest changes occurred at about 8 hours, but were less than 2 ½ times base line, and these were mostly in adrenergic and immune groups of molecules.

But in CFS patients, changes in specific sensory, adrenergic, and immune measures substantially exceeded the control group. At 30 minutes, two pain measures and one adrenergic measure had increased over four-fold. At 8 hours, an adrenergic measure had increased six-fold, and at 24 hours, almost nine-fold. Sensory measures at 24 hours and 48 hours remained extremely high—as well as the adrenergic measures. Most immune measures exceeded those of healthy controls from 80-100% throughout the post-exercise period.

Dr. Komaroff pointed out that while this study brings to light further objective biomarkers of CFS, it does not prove that these biomarkers, these molecules, are the cause of post-exertional malaise. The association is one of correlation, not necessarily causation.

Back to top

Immunological abnormalities in CFS

Dr. Komaroff then shifted his focus to the immune system and its role in CFS. He mentioned four different CFS immunological abnormalities in particular:

1. Increased number of CD8+ "cytotoxic" T cells bearing activation markers (CD38 +, HLA-DR). This type of white blood cell normally attacks viruses.

2. Poorly functioning natural killer (NK) cells—this immune cell attacks viral infections.

3. Upregulation of the 2,5-A system—this anti-viral system in cells turns on when an RNA virus is present and this occurs more often in CFS than in healthy controls, but not in all CFS patients.

4. Increased production of pro-inflammatory cytokines—these immunological molecules are found to be significantly elevated in CFS patients at certain times, for example, during a bout with an infectious agent. Cytokines are small proteins involved in the intercellular signaling that ultimately generates an immune response. Interestingly, it is this process that actually makes people feel so sick and not the infectious agent itself.

Back to top

Energy metabolism

In addition to various organs and organ systems being affected by CFS, there may be a malfunctioning at a more basic level: the energy metabolism that occurs in each individual cell. Researchers have posited that the lack of energy seen in CFS could be directly related to the poor energy output of individual cells. When this idea was first presented to Dr. Komaroff about 10 years ago at an international scientific symposium, he was very skeptical. He now feels, however, that there is "abundant evidence, from many studies from all over the world, in my view, that energy metabolism inside cells are adversely affected in CFS … no one yet knows what is adversely affecting energy metabolism in the cells. But one very well known cause is viral infection."

Back to top

Genetic component to CFS

Dr. Komaroff asked if there is a genetic component to CFS, and then stated that the answer is almost surely yes. There are certain molecules that are genetically-linked, called histocompatibility antigens which are found with increasing frequency and are more prevalent in this illness. (Significantly increased are DR-4, DR-3, DQ-3, and DQ-1.) Twin studies show about 51% hereditability in CFS—identical twins are much more likely to have the illness than fraternal twins.

Neuroendocrine gene variants: Are there genes that are simply built differently from birth that people with CFS inherit, that are different from most peoples' version of that gene? There do appear to be a few such genes, as shown in studies done by the CDC.

Gene expression studies in CFS

Perhaps a more useful mode of investigation comes from studies that consider gene expression— i.e., the genes which are actually turned-on during specific cell activity. What a cell does in a particular physical process depends upon which genes are turned-on and which genes are not. During the past ten years with new technology to measure gene expression, it is now possible to look at the white blood cells of CFS patients and determine which genes are turned on or off in contrast to those same genes in healthy individuals, individuals with depression, and individuals with other illnesses.

In fact, patients with CFS do have different patterns of gene expression, such as in genes that are involved in immune system activation, in energy metabolism, in producing neuro-hormones that are involved in the stress response. "Many studies from different laboratories show that the genes are activated more often in patients with CFS. Here is another objective abnormality in this illness that distinguishes CFS patients from healthy people," said Dr. Komaroff.

Back to top

Infections in CFS

Temporary vs. permanent

Most infections that we have, like the flu, are those that come and go. A pathogen enters the body, the immune system responds, we're sick for a while, and then after the immune system wins the battle, as it usually does, the pathogen is totally eradicated. This is the typical kind of *te mporary*
infection.

However, we also have, as human beings, within us a whole group of *permanent infections:* for instance, we have bacteria that live in our gut (there are more bacteria living in our gut than there are cells in our body. There is evidence that these bacteria in our gut may play an important role in many different diseases.) However, some pathogenic infections come and

stay—for example, infections triggered by the herpes virus. Cold sores on the mouth are caused by the herpes virus—the sore itself comes and goes, but the virus which causes it remains permanently in the body. Once a person becomes infected, the virus stays in the body for the rest of the person's life. There is no way the immune system can eradicate the herpes virus.

In most people, the herpes virus is kept suppressed by the immune system—it is not active in the body and does not cause symptoms. The same is true of other kinds of viruses, like retroviruses—once people are infected with these, the immune system cannot get rid of them. The best that can be done is to keep them suppressed. This is an important concept since Dr. Komaroff believes it applies to CFS.

Infections and syndromes, more than one microbe

Another important concept is that many syndromes can be caused by multiple different pathogens. Colds are caused by hundreds of different viruses. Hepatitis can be caused by a group of different viruses. Many syndromes, and Dr. Komaroff believes it will be true of CFS, can be triggered by multiple different microbes.

Dr. Komaroff noted that some diseases may not occur when only one infectious agent enters the body—instead they may require several infectious agents in the body that then collaborate with one another to make the person sick.

Back to top

Telescoping CFS time—1989 to 2010

The first time Dr. Komaroff spoke to the Massachusetts CFIDS/ME & FM Association in the late 1980s, based on his developing knowledge of a then little-known illness, he offered the following view:

- Infectious agents can probably trigger and perpetuate CFS—not in all cases, but in many.

- The agents cannot be fully eradicated by the immune system. Instead, these agents that can cause CFS can be very different from each other in many respects, but they will share the property of being resistant to full eradication by the immune system in a CFS patient.

- There is evidence that CFS can follow a new infection.

- It is also possible that in CFS different agents interact to cause CFS.

Back to top

Infectious agents linked to CFS

Dr. Komaroff listed a number of infectious agents and illnesses that have been linked to CFS:

Epstein Barr virus: A minority of CFS patients develop CFS after an initial infection with Epstein Barr virus (This can include people who come down with mononucleosis, who instead of getting well after 3-6 months, become chronically ill with CFS.)

Q-fever: People can develop CFS after coming down with Q-fever. This illness normally occurs in farming communities where the Q-fever bacterium most often lives.

Ross River virus—Ross River virus is an RNA-virus endemic to Australia and South Pacific Islands that causes the mosquito-borne illness Ross Valley fever.

Lyme Disease: Lyme Disease is a bacterial infection (B burgdorferi). Dr. Komaroff stated that Lyme Disease "can lead to CFS."

Parvovirus can lead to CFS. Dr. Komaroff stated, "We published a paper a month ago, mainly work by Jonathon Kerr, which shows this pretty nicely."

Enteroviruses are another group of viruses, which he believes have been linked to CFS.

CFS may be linked to *Borna disease virus,* but this linkage is not at all solid.

Human Herpes Virus-6 (HHV-6): Dr. Komaroff and his associates have spent decades studying this virus and its association with CFS. More on the role of this virus with CFS will be discussed below.

Xenotropic Murine leukemia-related retrovirus (XMRV): In October 2009, the journal Science published an important paper about the possible association of this retrovirus with CFS. More on this possible association will also be discussed below.

Back to top

The 2006 Australia study (Hickie I., et al.)

This study organized by the U.S. Centers for Disease Control and Prevention (CDC) was conducted in a very small, remote farming community in Australia in which there was only a small group of doctors, one hospital, and one medical laboratory.

"People lived in that community, got their medical care there, you could follow what happened to every single person in that community who got a particular type of infection—and you knew you could follow every single person in the study for several years. There are not many places you could do such a careful study."

[Editor Note: Many CFS studies are not able to study patients from the time they first became

ill, and therefore can only utilize medical and lab records, as well as patients' and doctors' memories as to the natural history and pathophysiology of the illness as it developed. This type of study is called a retrospective study. The Australian study was a prospective study, meaning that the patients' illnesses could be watched and measured from the very beginning; moreover, the patients were known before they became ill, so that further objective conclusions could be drawn.]

This study consisted of 256 patients who had come down with 3 different infectious illnesses. The patients were followed from the date they became ill for one year (in the first report).

The 256 patients had acute laboratory-identified EBV, Q-fever, or Ross River virus infections. 11% of the entire group developed CFS. In fact, 11% of patients in each virus group came down with CFS—the same percentage with each of the very different infectious agents.

CFS was more likely to occur in the people "whose illness was most severe initially, and who were producing these cytokines." Cytokines are the immune system chemicals which assist the immune system in fighting the infectious agent. Dr. Komaroff stated that these cytokines, in his judgment, are very likely the cause of CFS symptoms.

Depressed patients no more likely to develop CFS than non-depressed patients in the Australian study

A major benefit of the Australian study was that the psychology of the patients could be studied, both before they got sick, and after they became ill with CFS. *The study could not find any psychiatric factors or demographic factors that made people more likely to develop CFS.*

Some people who had a history of depression before they became sick did go on to develop CFS. But patients, without prior history of depression, who developed one of these infections, also sometimes went on to develop CFS. In fact, people without a prior depression developed CFS just as often as patients who had a prior depression. *"So no psychiatric link could be found."* The lead researcher, Dr. Ian Hickie, was himself a psychiatrist.

The study was very effective by showing that CFS could follow an infection with a virus, and that those who developed CFS were initially more ill than the other patients. And, that there was no psychiatric link between CFS and pre-existing psychiatric illness.

Back to top

Enterovirus infection and CFS.

Dr. John Chia in Los Angeles has done much of the research on the role of enteroviruses in CFS. Dr. Chia has biopsied the lining of the stomach in patients with CFS—typically patients with a lot of stomach symptoms. He has found enteroviruses in the lining of the stomach *much more often in people with CFS than in healthy controls.*

Study results—(refer to slide, *Enteroviral Infection in CFS: Gastric Antrum Biopsy Positive*) demonstrated that 135 of 165 (82%) of CFS patients had enteroviral infection in the lining of the stomach as opposed to 7 of 34 (20%) healthy controls (p