The Komaroff Lecture

This address was given on 18th November 1995 in London by Professor Anthony Komaroff, Professor of Medicine at Harvard Medical School, Boston, USA.

(Ed: This talk was also given as the Melvin Ramsay lecture at The First World Congress on CFS and Related Disorders in Brussels on 9th November. Here Professor Komaroff refers to CFS as M.E., for benefit of the UK audience. This is the first part of Dr Komaroff's address. The second part will be printed in a future edition of 'Emerge').

"I will try today to summarise some of the most important and provocative research that has been done on what in the States we call CFS and you call M.E., in a way that everyone here can understand. In the last two years there has been research reported from the UK, Europe and the United States showing new lines on this illness. They satisfy my bias as a clinician studying this illness for 15 years, because they point to the role of infectious agents, and also to the possibility of abnormalities in the brain.

Patients say their illness was often triggered by an infection, and many of the symptoms they've had would seem to involve the brain; and yet this illness is defined by a group of symptoms - symptoms are entirely subjective, anyone can claim them. But science regards it as proof only when there is objective measurable evidence of abnormalities. In my view one of the most important things that has happened in the past few years is that such objective evidence has increasingly materialised.

First - studies that have identified the frequency of this illness. This is a study conducted by our group (slide) on patients seeking care for any medical problem at all - not just for fatigue. We concluded that about one out of every hundred people, or 1,000 in 100,000, meet criteria for M.E. Another study we published several months ago, did a random survey of 4,000 people, regardless of whether they had sought medical care. The estimate was that 98 per 100,000 in the US meet criteria for this illness. Many more complain of debilitating chronic fatigue, but do not meet the criteria. For now, we can say with some certainty that 1 in 1,000 people in the States has this illness, which makes it as common as MS or Lupus.

Several things struck me when I was first seeing patients with M.E. many years ago. First, unlike people who seek medical care because of fatigue, in most of our patients their fatigue began suddenly with a flu-like onset,

they were saying 'it all started with that virus'. The second thing about the illness was the phenomenon we call 'post-exertional malaise'. After modest physical exertion, and typically not while the person is exercising, but the next day or two days later, there is a flare-up of fatigue, weakness, difficulty thinking, sore throat, fevers, in the majority of patients - as if physical exertion was provoking a response that affected the whole body. We think it may involve an unusual response of the immune system to exercise, and are currently studying this.

Thirdly, there's the possible involvement of the brain. Most patients complain of difficulty with concentration and memory, of other symptoms that suggest brain involvement, such as tingling and numbness, transient periods of weakness, photophobia or hypersensitivity to sound. Those symptoms are experienced, in our study, by the majority of patients. A small group had symptoms that clearly indicate a disorder of the brain - periods of total disorientation or confusion, seizures in patients who never had seizures before, ataxia - difficulty with balance, weakness of one side of the body, blindness, and one sided sensory deficit, meaning numbness or tingling sensations. This is a small group from a much larger group of patients, but they do suggest there's a process involving the brain.

Physical examination abnormalities are largely absent, with the exceptions - swollen lymph nodes in the back of the neck; and two tests of balance (part of neurological exam) are abnormal in a substantial fraction of patients. We did a study with physicians who did not know if they were examining a patient with M.E. or a healthy individual, and identified that these abnormalities were present more often in M.E. patients than the healthy population.

Recently we've completed a study to show how badly debilitated patients with this illness are. The most widely used measure to define functional capacity in various diseases is called the SF36. This test has subscales - physical function, general scores in thousands of healthy Americans - you can see the relatively high scores here (slide with graph). We also studied patients with heart failure, and major depression, and they are shown here in the middle. But patients with M.E. had scores that are lower on all except the mental health scales, where they have far better scores than the depressed patients. So by these measures, M.E. is a terribly debilitating illness, and M.E. patients are more functionally impaired than patients with congestive heart failure, major depression, and many other diseases.

In my mind there are two basic controversies about this illness. Is it all imaginary? Is there anything there that says 'this person is sick'? The other question is - is M.E. a psychological illness? Many people ask 'why isn't M.E. or CFS just depression or some other psychological illness?' That way of asking the question says the asker doesn't take psychiatric illness seriously - it is diminished and trivialised that way. Depression is a serious illness, just as M.E. is, but I don't think they are the same thing. These are the reasons why:

First, there are a group of symptoms in M.E. - sudden onset, lymph gland swelling, this post-exertional malaise, and night sweats. None of these symptoms reflect psychiatric illness. Secondly, there is a whole series of good studies that find abnormalities of the brain in the hypothalamic-pituitary axis, different to what one sees in major depression or other psychiatric illness. Third, there is the failure of this illness to resolve fully with psychiatric therapy. In my experience, many M.E. patients do develop psychiatric illness, and the depression responds to appropriate therapy. However, ***not once,*** has anyone's illness gone away with psychiatric therapy. There was an important paper presented at the Brussels conference, that used a treatment for depression called Prozac; in a randomised trial they found absolutely no benefit to M.E. from Prozac. And then there is the failure to find evidence of psychiatric disease, either before or after the onset of M.E., in a large fraction of our patients.

To summarise an important study of this hypothalamic-pituitary-adrenal axis that I mentioned - the hypothalamus makes hormones that affect the pituitary, and the pituitary makes hormones that affect the adrenal gland. In healthy people a normal amount is made by each of these glands. In major depression, you see a very hight amount of these chemicals made by each organ; but in ME/CFS what you see is the opposite from major depression - an underproduction by the pituitary of ACTH, which leads to an underproduction of cortisol by the adrenal glands. This objective measure in M.E. is different from healthy people and even more different from major depression.

Another test of the hypothalamus is a study from Behan's group at Glasgow. They looked at a hormone called Prolactin, after giving a compound that affects the brain chemistry called Buspirone. In healthy individuals, and patients with depression, you see a slight increase in the level of Prolactin when you give Buspirone. And in CFS or M.E. you see a very striking higher rise in the prolactin level following giving this compound.

So the simple answer to the question 'why isn't it all just depression or some other psychiatric illness, is because it's not! When we looked with our psychiatric colleagues we could not find evidence of psychiatric illness in the majority of M.E. patients.

Now let's turn to other objective laboratory studies. This is a paper published three months ago, in which we basically summarised 10 years of laboratory studies, conducted on over ***700 patients*** with M.E. from two different geographic areas in the States, who over ***10 years*** have had 18,000 lab tests. These patients were compared with healthy people of the same age and sex. All blood samples were tested by technicians who did not know if a sample came from a healthy or an M.E. person.

We found very striking increased frequencies of abnormalities: Immune complexes were found nearly 27 times more often in M.E. patients than

in healthy controls. Elevated levels of immunolglobin G were found nearly nine times more often in the M.E. patients. Unusually shaped white blood cells were found 11 times more often. Several other abnormalities were also found. So these tests are saying there is, in the M.E. patient, an activation of the immune system. The unusual white cells are typically taken to mean evidence of a virus infection. There is more evidence in the literature that the immune system in M.E. is chronically turned on. I think the body of evidence overwhelmingly says there is a chronic state of immune activation in these patients - as if they're fighting against something - what are they fighting?

Now what is the evidence of abnormalities in the brain? This (slide) is the top part of the brain of a 55 year old man who became suddenly ill in 1985 and has never returned to full health. Here are black areas of what we call 'white matter', and here you see circular white spots that shouldn't be there. Another patient (slide), and here in the deeper part of the white matter, you see larger white spots. And that patient had no clinical evidence of multiple sclerosis. This (slide) third patient had terrible problems with balance and gait early in her illness. This part of the brain, the cerebellum, is important for balance, and there in the cerebellum are those white spots. In a large study of 150 patients we found nearly 80% had these spots, compared to only 20% of healthy age- and sex-matched people. Many of us have some inflammatory illness of our brain at some time that leaves a little spot. So these spots don't always indicate a current abnormality. What's striking was the much higher frequency of these abnormalities in the patients. Three other research groups have reported similar results.

Another way of taking a picture of the brain is called SPECT scan. A chemical is injected and travels through various parts of the body including the brain. That chemical emits a signal of radioactivity that is picked up by a special camera. It creates a picture (slide) - this is a healthy scan and here you see the outer part of the brain, called the cortex. In a healthy individual there would be no holes in the evenness of this picture.

Look at the outer part of the brain in this M.E. patient (slide). You can see holes where it should all be smooth. We started SPECT scanning in 1982 on a patient I'd been following for five years. He said "I've got to see you, this has been the worst week since I got sick. All week I've been bedridden, but I also have trouble thinking and particularly expressing myself - my family says I'm not making sense, I'm saying words that are not really words. And the entire right side of my body feels numb, with tingling."

Now that combination of symptoms suggests there's something wrong with the left side of the brain, which is critical in speech and for sensation on the right side of the body. I saw him and did a very careful examination. I wasn't sure I could find any objective evidence, so we got a SPECT scan. And there (slide) was the left side of the brain - there

should be a yellow margin around it, and there's none. Three months later much of that abnormality had gone away. Now it was the left side of the brain that doesn't look so good, and that week, although he felt much better, the one problem he was having - he's a computer graphic artist - was getting the objects straightened out on his computer screen. The part of the brain that looks at space and understands spatial geometry is there on the left (slide).

So is there an objective abnormality in M.E. patients with symptoms that suggest the brain is involved? We subsequently did SPECT scans of a large number of M.E. patients, patients with AIDS encephalopathy, major depression, and healthy individuals. The computer counted how much signal was coming from the brain. Here (slide) is the signal in healthy people, and in major depression which is essentially the same. But here was the signal in patients with AIDS involving the brain, and here in M.E. involving the brain. Both statistically significantly lower. So there's something impairing the blood flow to the brain in these two groups (AIDS encephalopathy and CFS) compared with these two groups (depression and healthy controls). Is there objective difference?

In studies we have underway now, not yet submitted for publication, we have measured brain waves (EEG) - activity generated by the brain. We also did this with the computer which is scoring a brainwave as normal or abnormal. Two kinds of abnormal brainwaves, called sharp waves or spikewaves, are seen more often in patients with M.E. than in patients with major depression or healthy people. Yet another objective measure that says 'there's something wrong in the brain.'

Recently a group from Johns Hopkins medical school looked at the autonomic nervous system, part of the brain that controls blood pressure, heart rate, breathing, and other basic processes. And they used tests of the autonomic nervous system including 'tilt-table testing', and found this test was abnormal by very stringent criteria, in 70% of M.E. patients and none of the healthy control people. We have also been doing similar studies for the past four years. We published a paper a few months ago on balance, or disequilibrium, in patients with M.E. On objective tests of the balance centres of the brain and the inner ear, we found very abnormal results in a substantial fraction of the patients.

So the answer comes back 'there is something wrong with the brain'. I don't believe, fortunately, that M.E. produces permanent damage. What is plain, from the research that's been done is that there are cyclical or periodic dysfunctions of various kinds in the brain."

The following is the second part of an address given on 18th November 1995 in London by Professor Anthony Komaroff, Professor of Medicine at Harvard Medical School, Boston, USA.

Q. (Dr Charles Shepherd) A lot of us do not like the term Chronic Fatigue Syndrome, which seems to have become a dustbin diagnosis for everyone

who is tired and unwell. I think research is moving towards this disease being some form of encephalopathy. Do you have views on what we might call it in a few years' time?

A. (Prof Komaroff) I share your views on CFS, which has not only become a waste-basket, but because fatigue is a universal experience, and it trivialises the illness. I think CFS is a terrible name, and I'm partly responsible for it. I would have said five years ago M.E. was a bad name because there was no evidence at that time of any inflammatory process of the brain or spinal cord. I actually think M.E. is getting to be a better name, but I'm reluctant to keep changing the name of this darn illness, before we understand it better. Even though M.E. may be a name no-one understands, and CFS trivialises it, now that most of the public knows what these are, we would confuse people. I think that bad as the names are, we should stick with them until we are in a position to find a much better name.

A. Well the question was about ataxia, which is a kind of balance disorder when a person's gait is very broad. In my experience, that kind of broad gait is not permanent - it can be transient for days or weeks. Dysequilibrium, being a little bit unbalanced or bumping into walls, that's much more common.

Q. What do the little white spots on the MRI images mean?

A. Without a brain biopsy of those little spots, and then looking at them under the microscope, there's no way of answering that question. But based on studies in animals, they could mean a small patch of inflammation, that could now be an old scar, or could be currently active. And that inflammation could be caused by a virus infection, or just by a non-infectious immune system attack on parts of the brain.

Multiple Sclerosis for many years has been believed to result from an immune system attack on the cells that make what's called 'myelin', that wraps itself around the brain cells. That doesn't imply there's an infection going on, it could be what's called an auto-immune disease. It is also possible that the spots indicate an impairment of blood flow in very small blood vessels that led to a period when those vessels blocked off and scarred the part of the brain they would normally feed.

A. Infection can change the body chemistry in ways that could be pertinent to M.E. At the Brussels meeting there were some studies where changes in the energy chemistry, in the mitochondria, were examined in patients with M.E., and there were indications that there were abnormalities there.

Q. How close are we to a good diagnostic test for M.E.?

A. I don't see a single test or even a small battery of tests that would be good enough to qualify as a diagnostic test. But that could change tomorrow. There were some papers at the Brussels meeting that looked pretty promising, but I've been down this road many times before. It's common in science that some initially encouraging reports on diagnostic tests later prove not so useful.

Q. A question about the age of M.E. patients .

A. This illness typically affects young adults, but can affect children down to the age of five, and can affect people for the first time in their lives in their 50s and 60s. So it's not an illness restricted to young adults. A couple of other stereotypes are demonstrably wrong - it is not restricted to upper or middle class, and it is not restricted to people who are Caucasian (white), it appears to affect people from all walks of life, in the developed nations of the world where it has been studied.

Q. Were there any new treatments discussed at the Brussels conference?

A. There were papers on the metabolism of carnitine, but there was no paper on treatment results with carnitine, as there was not enough information to present a statement. There was only one paper on treatment, that was from a Dutch group that showed Prozac was of no benefit.

Q. What do we mean by fatigue? Is fatigue distinguishable from fatiguability?

A. Fatigue means different things to different people. For a muscle physiologist it means that when a muscle is challenged repeatedly, it loses strength more rapidly than it should. For some people with CFS, fatigue means a listlessness, an inability to get up the energy to do anything, physical or mental. I don't think I would make the distinction between fatigue and fatiguability, as much as this post physical exertion malaise, that is a very important part of the syndrome; it's very commonly present, and my guess is it is surely telling us something about what the immune system abnormalities in this illness broadly are.

Q. Can HHV-6 virus be responsible for glandular fever (infectious mono) in some patients, and when M.E. has started as glandular fever, could HHV-6 be the culprit?

A. The answer is Yes. There are studies both from Germany and from the US showing that HHV-6 can be a cause of glandular fever - not as commonly as Epstein-Barr virus, but often enough.

Q. What makes people recover?

A. Patients have recovered from M.E. and we have gone through our groups to see if there is something in the data we've collected that predicts that they will recover, and therefore gives a clue as to what made them sick in the first place. And we've been unable to come up with anything that's useful, to my disappointment. I have studied about 500 patients with the illness, and I was sure we could find recoverers who would teach us something about the illness, but try as we might, we have not found what predicts who will recover.

Q. Where do you think the next research should go in this illness?

A. There are so many areas that appear to be fruitful, studies of brain chemistry, studies of various infectious agents. We need to do studies of the immune system to explain the post-exertional malaise and possibly other symptoms. Then studies of what some might regard as the softer sort - what's the effect of this illness on the patient's family, for example. I think it's terribly important to understand the burden this illness places on the family and friends who are sharing the work of dealing with it.

I believe that you throw the door wide open, and then you read a lot of people's ideas and decide which seem the most promising. You may get hundreds of ideas for research, you may think 10 of them are good, and some of those are things you would never have though of in a million years.

Q. A question about young people, and I take it you mean children as well as teenagers.

A. Whether the incidence in young people and the general population is rising, is a very hard question to answer. There's such great public awareness now, and greater awareness among doctors, that what appears to be a rising frequency may be nothing more than a rising understanding of the illness. There is no good scientific evidence to say that the frequency is rising over the last decade. The literature suggests its been with us for a long time. As for whether children recover more rapidly, we only have anecdotal evidence at present.

Q. Are there parallels between neurasthenia, which was a diagnosis made in the 19th Century, and M.E.?

A. From reading the literature of a hundred years ago I would say that neurasthenia sounds a lot like M.E. There's no evidence that neurasthenia as an illness died out, it died out as a diagnosis, because without the capacity to understand what was causing it, and with no treatments for it,

doctors lost interest in using that diagnosis, that's how I read history. None of the tests we are doing now in M.E. cold have been done in the late 19th Century with neurasthenia patients.

Q. What causes the muscle pain that is part of the illness, and how do you treat it?

A. There's reason to believe that poor quality sleep - inadequate amounts of time in delta-wave stage 4 restorative sleep, may be an important part in what causes myalgia; I'm a believer in the use of low doses of tricyclic drugs which improve the quality of sleep, and analgesics, but they are not fully helpful in many patients. I wish I really knew what causes it - there is growing evidence that there is something wrong with muscle, and with mitochondrial function particularly. That's preliminary evidence, but if it becomes firmer, it may explain some of the underlying pathology in myalgia.

As for disbelievers among physicians, when I think of what it was like a decade ago, then none of my colleagues knew or cared to know anything about this illness. The situation now is the difference between night and day. As one example of the interest in the medical profession, since the new case definition for CFS was published last December (1994) in the Annals of Internal Medicine, there has been the greatest outpouring of requests for that publication to my knowledge of any scientific article - over 100,000 requests for reprints. So I think there's a growing interest and understanding of the illness.

Q. A question about balancing activity and rest, for recovery.

A. I believe, without any scientific basis for it, that regular limbering exercises and light aerobics are useful, and at the same time, that if people push too hard they can cause a relapse of the illness. I believe in rigid hours of work, rest, and sleep, of trying to avoid sleeping during the day, and in getting a long and good night's sleep at night, I think this is good for all of us.

Q. A question about chest pain and sudden episodes of rapid heartbeat.

A. Most patients experience episodes of palpitations, for no apparent reason, not related to physical exertion or other stressors; and a much smaller number, in my experience, getting chest pain. I think the chest pain is mostly not of the heart, but of the wall of the chest, and involves muscles holding the ribs together, that get strained and hurt in the same way as muscles in the rest of the body. The rapid heartbeat is most likely a reflection of this autonomic nervous system abnormality - not an effect of the heart itself, but of the way the nerves regulate the heat rate and

rhythm.

At the moment I would say there's no evidence, and we've looked, with a number of tests for abnormalities of the heart and muscle per se, and have not found any such abnormalities. I am aware, however, of very early research in the UK that shows there may be involvement of the heart muscle. But this work is much too early to say what will come of it.

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