Four Problems with the Clinical Control of Interstitial Pneumonia, or Chronic Fatigue Syndrome, Using the Megadose Vitamin C Infusion System with Dehydroepiandrosterone-Cortisol Annex

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Abstract. Since 1996 in our clinic, the regular practice of megadose vitamin C infusion with dehydroepiandrosterone-cortisol annex and the continuous intake of erythromycin and chloramphenicol have been found useful for the clinical control of the autoimmune disease interstitial pneumonia, also known as chronic fatigue syndrome. The long-term use of these two systems for the treatment of the autoimmune disease has led to the emergence of four problems of theoretical or practical importance, as described below: i) Should maintenance of the above core treatments be continued for prophylactic purposes in the absence of acute signs of pneumonia? Evidence indicated that their use was essential to arrest the dynamic activity of an intrapulmonary bacterial colony in the immunodeficient host, and that the 5-year survival rate of interstitial pneumonia patients would have been worse without the prophylactic practice of the 2 treatments. ii) Evidence was presented to suggest that the activity of the intrapulmonary bacterial colony was becoming less responsive because of the emergence of a drug-resistant mutant bacterium. The introduction of new antibiotics (kanamycin) was found to improve the acute signs of pneumonia. iii) The bone marrow function of one male patient with interstitial pneumonia was found to decline during the observation period of 9 years. It was speculated that his bone marrow, like his lungs, was in the course of fibrosis. iv) One female patient was diagnosed with breast cancer in the course of interstitial pneumonia treatment – an example indicating that the persistence of an autoimmune disease in an elderly subject might be associated with the emergence of malignancy.

Dehydroepiandrosterone was shown to promote the recovery of hepatic function in the course of cancer chemotherapy with cyclophosphamide. The beneficial effect of the adrenal androgen was dose-dependent. The significance of this finding is discussed in the light of the steroid carcinogenesis concept. The reasoning behind the view that interstitial pneumonia and chronic fatigue syndrome are one disease is also discussed.

In 1989, Clemetson published 3 volumes of a monograph entitled "Vitamin C" (1), in which he suggested the possibility that megadose vitamin C may exert a beneficial effect in the case of immune disorders by way of an enhancement of endogenous glucocorticoid activity. Half a century ago, Giroud reported that endocrine organs were distinguished from non-endocrine tissues by their extraordinarily high content of vitamin C (2) – evidence to suggest that vitamin C may play an important role in the production and release of various hormones.

Clemetson also introduced a set of publications that reported beneficial responses to megadose vitamin C in patients with either diabetes mellitus or autoimmune diseases, such as rheumatoid arthritis (1). Vitamin C has generally been administered per os. In Japan, we were motivated to repeat the clinical investigation into the effect of vitamin C by using the drip infusion method in humans, and in an animal study on scurvy-prone ODS rats known to be incapable of vitamin C synthesis.

In 1996, we reported that intraperitoneal i.p. administration of vitamin C delayed the turnover of $^3$H-labelled cortisol in the plasma of an ODS rat, but not in a Wistar rat, the latter being capable of vitamin C synthesis. It was indicated that i.p. introduction of megadose vitamin C increased the concentration of plasma cortisol (3) via the pituitary-adrenal axis (4). In accordance with the above findings on the vitamin C-cortisol link, we showed that our megadose vitamin C infusion system was useful for the clinical control of both diabetes mellitus and autoimmune disease and allergy (5, 6).
In the spring of 1995 in Nagoya, Japan, an epidemic of chronic-type pneumonia occurred, the clinical manifestation of which was similar to that of chronic fatigue syndrome. The patients presented with specific changes in chest X-rays, the patterns of which were in good agreement with those of interstitial pneumonia – namely a linear or reticular pattern involving the lower lung fields bilaterally, more on the right (7). Though the epidemic had tapered off by the summer of 1995, two members of our clinic, M. and T. Kodama, were successively afflicted with the disease. Clinically, interstitial pneumonia has been classified as an autoimmune disorder. We found that the practice of megadose vitamin C infusion with dehydroepiandrosterone-cortisol annex, rather than the same infusion set with only the cortisol annex, gave favorable response in the clinical control of the interstitial pneumonia (8, 9). We continued accumulating clinical experience from patients, including the two members of our clinic, which was presented in 2004, after a time lapse of 8 years (10).

A total of four problems which interfere with disease control are presented.

Materials and Methods

All subjects included were out-patients of the Kodama clinic, Japan. The progress of interstitial pneumonia was followed periodically by the use of both posterior-anterior and lateral X-rays. The clinical diagnosis of interstitial pneumonia was made on the basis of the description of Hirschmann and Murray, as given in Harrison’s Principles of Internal Medicine (7).

The analyses of clinical materials, including plasma tumor marker content, were conducted in the laboratory of Falco Biosystems, Nagoya and Kyoto, Japan. The sources of the drugs used in this study were given in our preceding papers (6, 8, 9).

Results

Medical parameters to assess the variable activity of interstitial pneumonia. The chronological changes depicted in Figure 1 are of the pulse rate (above) and leucocyte count (below) for Case 1 (M. Kodama), a 77-year-old member of the medical staff, from June 24 to July 13, 2004. It seems that both parameters fluctuated as 2 Fourier’s series in response to 8 vitamin C infusions at irregular intervals of 1 to 5 days. The 2 Fourier’s series in their phases are slightly different from each other, as shown in Figure 1. The first order correlation coefficient was calculated, using pulse rate as \( x \) and leucocyte count figure/10^4 as \( y \). The statistical significance was marginal \( (p=0.0734) \), as expected from the subtle phase difference in Figure 1.

The chronological changes of all pulse rates (dotted line in the middle) and systolic- (upper solid line) and diastolic (lower solid line) blood pressures of a 69-year-old woman with interstitial pneumonia (Case 2), who underwent 4 megadose/month vitamin C infusions with dehydroepiandrosterone-cortisol annex are presented in Figure 3. It is worth mentioning that the interval between the last year data (December 22, 2004) and the first year data (January 5, 2005) turned out to be the longest of a total of 16 vitamin C infusion sets, and was related to the New Year vacation in Japan. This 2-week-long lack of vitamin C infusion led to a gradual rise of systolic pressure (aggravation of interstitial pneumonia in January, 2005). On February 19, the systolic
blood pressure (close to 200 Hg mm) seemed to have reached its zenith, with a leucocyte count of 22,000 on February 12. By that time, the patient’s pneumonia had been counteracted by the two antibiotics (erythromycin and chloramphenicol, "E+C" in Figure 3). From February 19 to February 22, the oral intake of a new antibiotic, kanamycin (KM), was superimposed onto the old regimen. An immediate drop of systolic blood pressure was observed, as shown in Figure 3 – a finding which suggests the necessity of adding KM to the old regimen for the suppression of chloramphenicol-resistant bacteria.

Bone marrow function and clinical control of interstitial pneumonia. The chronological transition of both the systolic and diastolic blood pressures (upper), pulse rate (middle) and leucocyte count (below) of Case 3, a 68-year-old male with interstitial pneumonia, from March to May, 1996, are presented in Figure 4. The patient received a total of 26 megadose vitamin C infusions of which 11 infusion sets were associated with the dehydroepiandrosterone annex (50 mg/bag), as shown at the top of this figure. Both his pulse rate and leucocyte count declined distinctly and the pulse amplitude (difference between systolic- and diastolic-pressures) became larger over time – a finding which indicates that the pneumonia became less active over time. It is worth noting that the patient’s basal standard leucocyte count was between 3,000 and 4,000, and that the count did not reach 8,000 at the zenith of pneumonia activity, as shown in Figure 4. There was no bias in the relative weights among neutrophils, basophils, lymphocytes and monocytes, in spite of a low leucocyte count.

The chronological changes of leucocyte count (open circle), erythrocyte count (cross) and platelet count (closed triangle) for Case 3 from April 20, 1996, to January 5, 2005 are depicted in Figure 5. The above 3 parameters showed declining trend, and arrows 1 (July 2, 1999) and 2 (August 29, 2003) indicate the time-points where the erythrocyte and the platelet counts, respectively, were subnormal. The leucocyte count was already subnormal at the first blood test for Case 3 (April 20, 1996). To date, there has been no tendency towards spontaneous bleeding.

The pulse amplitudes before and after vitamin C infusion, and between December and January of the same fiscal year for Case 3 are compared in Table I. Generally speaking, megadose vitamin C infusion, with or without a dehydroepiandrosterone-cortisol annex, increased the pulse amplitude, as assessed for each comparison set by the Student’s t-test. The use of the dehydroepiandrosterone-cortisol annex was interrupted after April 11, 1997 because of insomnia, Case 3 receiving 25 mg cortisol acetate per injection i.m. together with the megadose vitamin C infusion, 8 g per bag, via the intravenous route instead.

The rescue effect of the dehydroepiandrosterone annex in the clinical control of a female patient with both interstitial pneumonia and local breast cancer recurrence. Case 4 refers to one of the 2 medical personnel in our clinic. A 65-year-old doctor was found to have interstitial pneumonia in the lower lobes of both lungs in the late summer of 1995 (10), though no pneumonia-like signs were noted at that time. On January 2, 1996, she felt sick, and her chest X-ray of that day revealed that her pneumonia was taking on an active form.
of interstitial pneumonia. A regular regimen, twice-weekly megadose of vitamin C infusion, 8 g/infusion, without dehydroepiandrosterone annex, with a daily intake of antibiotics (E+C), was immediately started. In spite of the above prophylactic cautions, she again felt pneumonia-like signs on December 21, 1996, and the chest X-ray taken on that day revealed the presence of the active form of interstitial pneumonia. In both cases, the pulmonary lesions became inactive after treatment. After an interval of 4 years, the patient was found to have breast cancer at the r-chest wall. On June 26, 2000, she underwent radical mastectomy. There was circumstantial evidence to imply that the emergence of the above breast cancer could have been triggered by the preceding 2 eruptions of active pneumonia, without, however, any substantial proof. Two years post-operation, a local tumor recurrence was identified, and the necessity for anti-pneumonia therapy became all the more urgent, since the antitumor agent cyclophosphamide (endoxan) is known to accelerate the progression of interstitial pneumonia.

A series of 7 tumor control regimens, given in the following chronological order, are illustrated in Figure 6: stage 1, January 28, 2002 to February 20, 2002 (Tamoxifen + Co90 irradiation); stage 2, February 21, 2002 to February 20, 2003 (Tamoxifen only); stage 3, February 21, 2003 to May 28, 2003 (Aromasin only); stage 4, May 29, 2003 to September 24, 2003 (Endoxan + 5-FU); stage 5, September 25, 2003 to August 26, 2004 (Endoxan + dehydroepiandrosterone 4 mg i.v.); stage 6, August 27, 2004 to December 5, 2004 (Endoxan + dehydroepiandrosterone 50 mg i.v.); stage 7, after December 6, 2004 (Endoxan + dehydroepiandrosterone 100 mg i.v.). It can be seen that Co90 irradiation (stage 1) and Tamoxifen intake (stage 2) might have delayed tumor growth, though far from completely arresting it. Aromasin (stage 3) did not affect the rate of tumor growth. Endoxan and 5-FU (stage 4) certainly reduced the tumor size (tumor marker assessment), but at the sacrifice of hepatic function (GTP parameter). The combination of Endoxan per os and dehydroepiandrosterone i.v. markedly improved the liver function, in a dose-dependent manner. The combination of Endoxan and dehydroepiandrosterone slowed down, but did not arrest, tumor growth. Replacement of Endoxan with another anticancer agent is now under consideration.

### Table I. Chronological changes of pulse amplitude in Case 3, as presented for the pre-infusion stage ($\Delta 1$) and the post-infusion stage ($\Delta 2$), as well as for each December (Dec) and January (Jan) of one fiscal year.

<table>
<thead>
<tr>
<th>Time</th>
<th>$\Delta 1$ (n)$^1$</th>
<th>$\Delta 2$ (n)$^1$</th>
<th>$t^2$</th>
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<tr>
<td>Dec 1996</td>
<td>59.00±8.78 (8)</td>
<td>60.25±4.33 (8)</td>
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<td>Jan 1997</td>
<td>66.25±8.15 (8)</td>
<td>68.13±6.45 (8)</td>
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<td>Dec 1997</td>
<td>81.33±16.56 (8)</td>
<td>94.22±13.65 (8)</td>
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<td>Jan 1998</td>
<td>71.75±13.46 (8)</td>
<td>87.75±5.20 (8)</td>
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<td>Dec 1998</td>
<td>61.25±7.67 (8)</td>
<td>75.38±4.27 (8)</td>
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<tr>
<td>Jan 1999</td>
<td>58.63±7.74 (8)</td>
<td>83.25±4.36 (8)</td>
<td>7.795</td>
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<td>Dec 1999</td>
<td>64.50±11.54 (8)</td>
<td>75.88±13.12 (8)</td>
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</tr>
<tr>
<td>Jan 2000</td>
<td>68.25±7.11 (8)</td>
<td>77.88±10.71 (8)</td>
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<td>Dec 2000</td>
<td>62.25±5.97 (8)</td>
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<td>62.43±10.86 (8)</td>
<td>63.14±9.74 (8)</td>
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<td>44.88±8.04 (8)</td>
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<tr>
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<td>68.25±8.80 (8)</td>
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<td>79.75±3.28 (8)</td>
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<td>Dec 2004</td>
<td>59.63±5.90 (8)</td>
<td>79.63±12.43 (8)</td>
<td>4.111</td>
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<tr>
<td>Jan 2005</td>
<td>64.38±10.36 (8)</td>
<td>79.00±6.97 (8)</td>
<td>3.112</td>
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$^1$ The letter n denotes the number of infusion days for each month.

A positive $t$-value ($^*$italics) means that $\Delta 2$ is significantly larger than $\Delta 1$ ($p<0.05$).
Discussion

Whether or not prophylactic practice should be maintained in the absence of acute signs (fever, tachycardia, cough, general malaise, etc.) of interstitial pneumonia is a question we attempted to address. A textbook of internal medicine gave a simple answer: "if the disease is suppressed, no therapy" (11). However, how does one know that the disease is completely suppressed? Our out-patients with interstitial pneumonia (including the 2 medical personnel) knew that the clinical signs of acute-form pneumonia would come back 2 or 3 weeks after the interruption of both the oral intake of the antibiotics (erythromycin and chloramphenicol) and the regular practice of megadose vitamin C infusion with dehydroepiandrosterone-cortisol annex. Another author stated that the clinical course was variable with a 5-year survival rate of 30 to 50% after diagnosis (12). To our knowledge, the 5-year survival rate at the Kodama clinic is not this low, possibly due to prophylactic disease control (maintenance of drug intake and regular practice of megadose vitamin C infusion, irrespective of disease stability). There is another interpretation for the marked difference in mortality between the USA and Japan. The above US data came from the description of idiopathic pulmonary fibrosis, a common interstitial lung disease of unknown etiology (12). The 15th edition of Harrison’s Book presents a posteroanterior chest radiograph of a patient with interstitial lung disease due to idiopathic pulmonary fibrosis. On the other hand, the 11th edition of the same book presented another posteroanterior chest radiograph of interstitial pneumonia in which "a linear or reticular pattern involves the lower lung fields bilaterally, more on the right" (7). Roentgenologically, the former is a far more advanced disease than the latter, in spite of the same classification of interstitial pneumonia. It is quite possible that Hirschmann and Murray (7) share the same opinion as the authors of this article, that the roentgenological diagnosis of interstitial pneumonia is useful and should be made at an early stage. Our experience is that most physicians in Japan (as well as in the USA) will not accept the diagnosis of interstitial pneumonia until devastation of the lung tissue reaches the stage of complete lung fibrosis. In 1996, an elderly couple visited our clinic, and were found to have 2 diseases in common: interstitial pneumonia and light grade diabetes mellitus. They received 2 courses of treatments: oral intake of 2 antibiotics and megadose vitamin C infusions with dual steroid annex. The male patient soon left our clinic looking for an alternative therapy. A nearby hospital accepted him as having silicosis that did not require special treatment. The female patient currently continues on our regimen. Pulmonary devastation occurred in the male patient and, 2 years later, he died of a heart attack. It is well known in Japan that Hibari Misora, queen of the popular song world, died in her mid 50s from interstitial pneumonia. While she was active, she suffered from hypofunction of the lung (short breath), but not from cough or fever. The physicians in charge of her health care reached the diagnosis only 5 months before her death. It is almost certain that roentgenological diagnosis of early stage interstitial pneumonia in not an option for most physicians in Japan, and is the reason why chronic fatigue syndrome has been treated as a new disease that was found to share a set of key clinical symptoms, including sore throat, with interstitial pneumonia. If the investigators of chronic fatigue syndrome had the roentgenological skill of a specialist in early stage interstitial pneumonia, they would have no hesitation in reaching the conclusion that chronic fatigue syndrome and interstitial pneumonia should be treated as a single disease.

Additional evidence is provided in reference 10, where we reported that our patients with interstitial pneumonia were shown to have a high incidence of depression. Straus stated that: "mild to moderate depression is present in half to two-thirds of patients" with chronic fatigue syndrome (13). More interestingly, "disturbances in endocrine function, consistent with reduced production of corticotropin-releasing hormone in the hypothalamus, have been reported in controlled studies of CFS (chronic fatigue syndrome). Mean serum cortisol concentrations were lower in patients than in controls; levels of adrenocorticotropic hormone were correspondingly high. Hypothetically, these neuroendocrine abnormalities could contribute to the impaired energy and depressed mood of patients" (13).

The second problem in this investigation concerned the acquisition of drug resistance by the bacterial colony in the lung. In Case 2, the 3-day intake of KM resulted in a
remarkable drop in the systolic blood pressure, and this parameter gradually increased after terminating the new antibiotic intake – a finding that suggests that the emergence of a chloramphenicol-resistant mutant bacteria rendered the control of interstitial pneumonia difficult in Case 2, and that the introduction of KM led to the eradication of the chloramphenicol-resistant bacteria. Chloramphenicol and KM are known to suppress gram-negative bacteria, while erythromycin is effective against gram-positive bacteria. The question of whether or not the intrapulmonary bacterial colony became chloramphenicol-resistant is still under investigation. If so, the drug control of Case 2 is going to be much more expensive in the future.

The third problem is concerned with the gradual decline of bone marrow function in Case 3. The general leucopenia of Case 3, similar to other interstitial pneumonia patients, was already present before the use of antibiotics – a fact that excludes the possible participation of chloramphenicol in the observed reduction in leucocyte count. In Case 3, the relative weights of neutrophils, eosinophils, basophils, monocytes and lymphocytes were well-balanced. His leucopenia is to be differentiated from agranulocytosis. Interstitial pneumonia, a collagen diseases, is often associated with other collagen disease such as dermatomyositis. Case 1 experienced dermatomyositis at an early stage of interstitial pneumonia (8). Case 4 is currently suffering from myositis of the right leg 9 years after the onset of interstitial pneumonia (unpublished data). Approximately 8% of all cases of myositis are associated with malignancy (14), including cancers of the lung, the breast, the gastrointestinal tract and myeloproliferative disorders (14). Taken together, one has to consider the possibility that the general depression of the bone marrow of Case 3 may lead to myelogenous leukemia.

As mentioned above, the emergence of breast cancer may etiologically be related to the persistence of interstitial pneumonia in Case 4. As seen in Figure 6, dehydroepiandrosterone had a rescue effect on the hepatic dysfunction (elevation of GTP), and that the steroid action was dose-dependent. This raises the question of whether a suppressive effect on the growth of residual breast cancer can be expected.

The fourth problem is concerned with the effectiveness of dehydroepiandrosterone in the control of mammary tumor recurrence. In 1998, Couillard and others reported that dehydroepiandrosterone at doses of 0.3, 1.0 or 3.0 mg suppressed the growth of the estrone-stimulated ZR-1 xenograft tumor in nude mice (15). The above steroid effect was dose-dependent. For reference, low serum dehydroepiandrosterone levels have been associated with breast cancer in women (16). Experimentally, treatment with dehydroepiandrosterone markedly delayed the appearance of breast tumors in C3H mice that were genetically bred to develop breast cancer (17). Luo and his associates investigated the effects of dehydroepiandrosterone and anti-estrogen EM-800 alone or in combination on DMBA-induced mammary cancerogenesis. Treatment with the adrenal androgen or anti-estrogen alone partially prevented the development of DMBA-induced rat mammary cancer, the incidence being reduced to 57% (p<0.01) and 38% (p<0.01), respectively (18). The combination of the 2 compounds led to a significantly greater inhibitory effect than that achieved by each compound administered alone (p<0.01 vs. adrenal androgen or anti-estrogen alone).

Finally, women with breast cancer were found to have low urinary levels of androsterone and etiocholanolone (2 metabolites of dehydroepiandrosterone) relative to urinary tetrahydrocortisol (urinary metabolite of cortisol) (19). The question of whether or not dehydroepiandrosterone, when combined with appropriate anti-estrogen or anticancer agents, may pave the way to the eradication of recurrent breast cancer will be answered in the future.

References


