in vivo *22*: 263-268 (2008)

Short Review

Control of Interstitial Pneumonia by Drip Infusion of Megadose Vitamin C, Dehydroepiandrosterone and Cortisol. A Short Review of our Experience

MITSUO KODAMA[1], ATSUSHI OYAMA[2] and HIROSHI TAKAGI[3]

[1]*Kodama Research Institute of Preventive Medicine,* [2]*Hikarigaoka Clinic, and*
[3]*Second Department of Surgery, Nagoya University School of Medicine, Nagoya, Japan*

Abstract. *Interstitial pneumonia can be controlled by the combined use of a prophylactic antibiotic system and the drip infusion system including megadose vitamin C, dehydroepiandrosterone (D) and cortisol (F), a fortified substitute of 3 adrenocortical elements. The response of patients was satisfying with few side-effects of F. It was shown that an excess of vitamin C improved the therapeutic efficacy of D-F complex, and that D and F improved the immunodeficient state of the host. The benefit of D as an adrenal androgen in immunology found another example in the combined use of cyclosporine A (CS) and glucocorticoid (G) in the kidney transplantation clinic: CS and G helps improve graft take by creating a state of androgen excess, as testified in both humans and mice – an alleviation of immune conflict.*

Chronological Transition of Disease Concept in Interstitial Pneumonia

In 1957, Heilmeyer pointed out that a variety of infectious diseases might trigger the onset of his "chronische Pneumonien", a finding to suggest that the disease may not be aetiologically a specific entity. He also added that a group of researchers had noted the primary character of these phenomena (chronic pneumonias) (1). In the course of the lung infiltration, one sees microscopically the development of connective tissues and capillaries from the walls of bronchioles and the occupation of alveoli by granulatory tissue (1). The interstitial tissues are also involved in the site of granulation (1). All these descriptions are in good agreement with the pathological changes of interstitial pneumonia (2). In the treatment section, Heilmeyer warned of the possible emergence of antibiotic resistance in local bacteria (1). Eventually, cortisone and adrenocorticotropic hormone (ACTH) could be tried under the antibiotic protection (1). Above all, attention should be directed to the control of both the heart and the general circulation system (1). With the use of cortisone and ACTH, Heilmeyer might have been inspired by the opinion of a group of researchers that his chronic pneumonia might respond to a beneficial action of glucocorticoid, as is the case in arthritis and nephritis (1). In 1962, an article on interstitial pneumonia was presented in Harrison Principles of Internal medicine under the name of chronic bronchitis and emphysema(3). Knowles emphasized the significance of this disease with a remark as follows: "In England it is the commonest cause of death and morbidity among all respiratory diseases, including pneumonia, tuberculosis, asthma and lung cancer" (3).

As to the treatment, Robin also expressed rather a negatine opinion (4) thus: "a diagnostic and therapeutic trial with corticosteroids (C) may be indicated. Careful evaluation by serial test is necessary to determine the ultimate need for such therapy. Early and vigorous chemotherapy is important. Less well established is the use of prophylactic chemotherapy during infection-free periods. This problem is currently under study" (4). He expected the role of C to be that of a bronchial dilator alone (4). Knowles states that "roentgenography is of little help in diagnosis until the disease is advanced" (3).

The next Harrison Book, 11th edition published in 1987, makes a sharp contrast in many respects to the 4th edition: firstly the new book presented a beautiful X-ray image of interstitial pneumonia of an early stage, in which a linear or

Correspondence to: Dr. Mitsuo Kodama, Kodama Research Institute of Preventive Medicine, 3-108 Gardenhills, Fujimidai 4-1, Chikusa-ku, Nagoya 464-0015, Japan.

Key Words: Interstitial pneumonia, drip infusion, megadose vitamin C, dehydroepiandrosterone, cortisol, fortified adrenocortical elements, short review.

reticular pattern involves the lower lung fields bilaterally, more on the right (2). Secondly, the book shows that the condition is an autoimmune disease of which the emergence is often associated with concomittant eruption of other autoimmune disorders (2). In contrast to the 4th edition, chest X rays test show abnormalities in the lung parenchyma in 90% of cases in the posteroanterior and lateral image (2). Thirdly, "specific therapy for most of the interstitial lung disorder (ILD) is directed toward suppressing the inflammatory process in the lower respiratory tract. Typically, oral corticoscosteroids are used starting with a high dose (usually 1 mg/kg of prednisone daily) for 4 to 6 weeks and then gradually tapering to a low maintenance dose (0.25 mg/kg of prednisone). If the disease is suppressed, no therapy" (2). The opinion of King in the 15th edition published in 2001, again sounds rather negative. He says that, in the case of idiopathic pulmonary fibrosis, "the clinical course is variable with a 5-year survival rate of 30 to 50% after diagnosis" and that "there is no firm evidence that any of these treatment approaches improves survival or the quality of life" (5). The presented X-ray image of interstitial pneumonia does not serve as a guide to the readers who want to diagnose the disease at an early stage, since the image in this book belongs to an advanced stage of the disease.

The Significance of Vitamin C and Adrenal Steroids as immunomodifiers in Immunological Disease

In 1989, Clemetson reported a case in which he took 5 blood samples from a 19 year old Irish woman who was critically ill with a reccurence of rheumatic fever, having excessive vaginal bleeding (6). Clemetson investigated the plasma contents of total ascorbic acid (TAA), reduced form ascorbic acid (AA), and dehydroascorbic acid (DHAA) with 5 blood samples before, during and after prednisone treatment. The ratios of AA to DHAA were as follows: i) 0.9:1 (before); ii) 0.8:1 (before); iii) 3.2:1 (5th day on prednisone); iv) 1.8:1 (after prednisone); v) 2.3:1 (convalescent). For reference, the mean ratio for 5 healthy nurses was 7.2:1 (6). It was indicated that her rheumatic fever required the supply of both vitamin C and corticosteroid for its cure (6). At the time of convalescence, her vitamin C content (TAA) was 7.2, a value which was much lower than the normal figure of 12.3 (6). Clemetson cited another example of vitamin C supplementation in the elderly population in Russia. A total of 144 elderly men and women (aged 60 to 90 years) were subjected to a vitamin C study at the Leningrad Medical Institute of Sanitation and Hygiene for healthy old people. It was reported that ascorbic acid loading (500 mg daily for 12 to 14 days) improved the functional state of the adrenal cortex; 70% of the people showed increased blood levels of 17-hydroxycorticoids (17-OHCS) after this vitamin supplementation. The ascorbic acid loading also raised their urinary output of 17-ketosteroids (17-KS) and intensified their response to ACTH, as judged by the eosinopenic effect and by the effect on their production of steroid hormones (7). It is now asked whether or not a deficiency state of vitamin C and adrenal steroids is the *sine qua non* condition of autoimmune disease and/or aging. As regards the adrenal steroids, one should keep in mind that the adrenal cortex, when stimulated by ACTH, increases secretion of both glucocorticoids and D, the latter being an adrenal androgen which comes from the zona reticularis and zona fasticulata of the adrenal cortex (8). Similar responses of 2 steroids to ACTH strongly suggest the possibility that F and D may be functionally interrelated with each other. Furthermore, the administration of ACTH causes glucocorticoid secretion and a rapid and profound but temporary depression in the vitamin C content in the adrenals of rats, guinea pigs, and other animals (7). Evidence is available to indicate that ACTH causes both an accelerated uptake and release of vitamin C by the adrenals (9). All these observations in experimental animals are in good agreement with the vitamin C loading study in Russia (7). It will be pertinent to recall the well-known fact of immunology that D can significantly prolong the lifespan of (NZBxW) F1 females with the murine model of systemic lupus erythematosus (SLE) (10).

Drip Infusion System of Megadose Vitamin C and Adrenal Steroids in the Treatment of Autoimmune Disease

Our study with the drip infusion of vitamin C for diabetes mellitus (DM) was started in 1992 using 7 g of vitamin C and 25 g of glucose dissolved in 500 ml water solvent as the drip infusion set (11). Results obtained are as follows: i) the plasma concentration of insulin revealed two surges, each 7 minutes and 2 hours after the start of drip infusion, a finding indicating that two distinct mechanisms are in action with the promotion of plasma insulin by vitamin C infusion. ii) Distinct clinical improvements were observed with the long-term use of vitamin C infusion in 3 DM patients (11).

Next, the drip infusion of similar megadose vitamin C was tested as regards its effect on plasma cortisol (F). Results obtained are as follows: i) the plasma F concentration increased 2 hours after vitamin C infusion. The same treatment also enhanced diuresis and excretion of urinary 17-OHCS, as tested in a healthy male volunteer. ii) Distinct clinical improvements were observed in 4 patients with autoimmune diseases (two cases of rheumatoid arthritis, one case of nephritis-linked hypertension and one case of hepatic dysfunction) (12).

We then investigated the relation between ACTH, F and vitamin C in plasma in the course of vitamin C infusion treatment with and without the use of methylprednisolone, a suppressor of the homeostatic mechanism of the pituitary ACTH. A healthy male volunteer was used as the study subject. Results obtained are as follows: i) the practice of the steroid-free vitamin C infusion treatment induced a small surge of plasma F at the middle stage and a skyrocket-like rises of both ACTH and F of plasma at the terminal stage (about 3 hours after the start of infusion treatment) (13). ii) The use of methylpredonisolone annex in the vitamin C infusion set completely suppressed the emergence of the plasma ACTH / F surges at the terminal stage, but not the small surge of plasma F at the middles stage (13). It has been indicated that vitamin C infusion increases plasma F concentration *via* the pituitary ACTH route (13).

In late August of 1995, Mitsuo Kodama was afflicted with bronchopneumonia, of which the lesion was located at the lower part of the right lung. The clinical course of the disease as well as the X-ray examination showed a close resemblance to those of interstitial pneumonia (autoimmune disease). Furthermore, he noted skin eruption as well as muscle pain in both arms (complication of dermatomyositis). He tried to confront the situation by use of a combination of chemotherapy (erythromycin and chloramphenicol) and the vitamin C infusion therapy. His wife, another medical staff member, also got pneumonia in October. In 1995, a total of 313 outpatients with a bronchopneumonia-type ailment came to our clinic. We tentatively marked the disease with the name of chronic fatigue syndrome (CFS). Our experience with those patients including 2 medical staff members were published (14, 15). The first paper described the medical course of the disease of Mitsuo Kodama, chief medical staff member and author of this article. The second paper was concerned with the medical and epidemiological aspects of other pneumonia patients.

The results given in the first paper are as follows: i) the combination of the annex-free (old) vitamin C infusion therapy and the chemotherapy, as practised till the end of 1995, only induced unstable recession but not long-lasting control of CFS (14). ii) To improve the response we created a new vitamin C infusion set by adding a dehydro-epiandrosterone - cortisol annex (D-F). The combined use of the old and new infusion sets, as practiced from February to May 1996, guaranteed a long-lasting control, as tested by leucocyte count and pulse rate (14). iii) The combined use of the old and new vitamin C infusion sets also significantly increased the urinary excretions of 17-KS and 17-OHCS (14). iv) The immunological survey found no change in the lymphocyte population (14).

Results given in the 2nd paper are as follows (15): i) our patients with chronic pneumonia (CFS) included 106 males and 207 females (mostly within the adult age range) (15). ii) The time distribution of the above 313 patients covered the range from January to December of 1995, leaving a few spill-overs in 1994 (15). One would say that 1995 was the year of a pneumonia epidemic. iii) The inspection of individual clinical cases indicated that the responses of the disease to the combined use of chemotherapy and vitamin C infusion therapy with and without D-F annex was promising, as in the case of Mitsuo Kodama (14, 15).

Thus, the year 1996 marked the beginning of our fight against CFS (14, 15). In due course, accumulation of clinical experience at the Kodama Clinic led us to the conclusion that the nature of disease of our CFS patients, including 2 medical staff members should be classified as interstitial pneumonia, since every patient from our CFS population showed pneumonia signs on chest X-rays. We have recently learnt that X-ray examination is valid only when a physician has enough skill for early detection of the disease. If not, "roentgenography is of little help in diagnosis until the disease is advanced", as pointed out by Knowles (3). We believe that a CFS patient represents the "escape" example of early stage interstitial pneumonia whose X-ray image has "escaped" the notice of the attending doctor. One should note that CFS and interstitial pneumonia very often share a common onset of pneumonia stroke in their long-lasting histories. Further examination of the chest X-ray should be warranted in CFS.

In 2005 and 2006, we presented two reports on the use of a megadose vitamin C infusion system with dehydro-epiandrosterone–cortisol (D-F) annex (16, 17). Over the course of 9 years, our strategy for the control of interstitial pneumonia underwent some changes in response to the complex aspects of the disease. The results obtained in the first paper (2005) are as follows: i) the combined use of the prophylactic chemotherapy and megadose vitamin C infusion therapy with D-F annex in our clinic covered a time range of 9 years. ii) The long-term maintenance of the above treatment system was essential for preventing the recurrence of an active form of pneumonia. iii) The merit of our treatment system was to create a new hormonal milieu so as to improve the state of immunodeficiency by use of a non-steroidal substance, vitamin C, which encounters little resistance from the feedback mechanism of steroid metabolism in the in vivo system (16). iv) Evidence suggested that insufficiency or lack of our infusion therapy might increase the risk for malignancy in elderly patients (16). v) Excess use of F might also increase the risk for depression (18).

The second paper (17) presented some unexpected outcomes of our control system of interstitial pneumonia which are given as follows: i) the pneumonia control of some patients, including Mitsuo Kodama, became poor because of resistance of local bacteria to chloramphenicol. The disease control was achieved with kanamycin (a new

antibiotic agent) (17). ii) Bone marrow fibrosis was detected in one patient with interstitial pneumonia (17). iii) Toshiko Kodama, (medical staff of the clinic) died in late August of 2005 at 75 years of age with lung metastasis of breast cancer 5 years after radical operation. As mentioned above, she was afflicted with interstitial pneumonia in October 1995. There was a time lag of 5 years between the onset of pneumonia and the discovery of breast cancer. Retrospectively, she was rather reluctant to receive both the prophylactic use of antibiotics and the inclusion of D annex, the latter having the inclination to induce vomit in a poorly controlled patient. After the discovery of breast cancer, she never declined the inclusion of D annex. She left a precious lesson to us all: a state of glucocorticoid excess is associated with increased risk for breast cancer (19).

The clinical course of Mitsuo Kodama, 80 years old, is also described briefly as follows: i) he was afflicted with both interstitial pneumonia and dermatomyositis (DM) in late August 1995. Five years later, he was found to have type-2 diabetes mellitus. At present, the above three autoimmune disorders are all in quasi-controlled states (16, 17). The oral intakes of 1.2 g/day erythromycin and 1.5 g/day kanamycin constitute the chemotherapy of his pneumonia regardless of the disease activity (16). He undergoes drip infusion treatment twice weekly of 500 ml 5% glucose, 8 g Ascorbic acid, 100 mg D and 100 mg F together with some cardiac stimulators. The emergence of pneumonia activation is detectable in terms of an increase of both pulse rate and leucocyte count (16). The inspection of posteroianterior and lateral X-ray images provides definite information regarding disease progress.

The Significance of Cyclosporin A as an Immunomodulator in the Kidney Transplantation Clinic

King, the author of the article "Interstitial lung disease (ILD)", made the following remark: "Many cases of ILD are chronic and irreversible despite the therapy discussed above, and lung transplantation may then be considered" (5).

Incidentally, Mitsuo Kodama and Hiroshi Takagi published two papers in 1992 indicating that "Cyclosporin A is a hormonal immunomodulator" (20, 21). The use of cyclosporin A (CS) helped improve the success rate of kidney transplantation no matter whether the source of the transplant was cadaverous or non-cadaverous (20). In the cadaver transplant group, CS user- and CS non-user- groups comprised 100% and 35.7% of successful transplants respectively , whereas in the non-cadaver groups, CS users and CS non-users comprised 85% and 69% respectively (20).

The laboratory of the Aichi Cancer Center Research Institute investigated the excretions of 14 urinary steroids for each of 52 kidney transplant-recipients to find a specific changes between CS users and CS non-users. The logarithmic ratio of androsterone (A) to terahydrocortisol (THF) in urine was proposed as the common discriminator. Thus, the log A/THF was calculated for each patient, and the intergroup difference was tested by Student's *t*-test. Briefly, CS use significantly increased log A/THF in both males ($t=+2.104$) and females ($t=+4.172$), a finding indicating that CS increases androgen activity regardless of the Host's gender (20). When plotted on log A/THF scales, all 4 rejection cases (2 males and 2 females) were located on the negative side (log A/THF <0), and all CS users of both sexes were located on the positive side (log A/THF >0). Male non-users were distributed in between the 2 rejection cases and the users, and female non-users were located in between the 2 rejection cases (20). CS prevented the transplant rejection by making a shift towards the increase of log A/THF (a rise of androgen activity) (20).

The second paper (21) tested the validity of human study in Swiss mice of both sexes as follows: i) Plasma cortisol (F) in males and plasma estradiol (E2) in females were consistently resistant to the depressant effects of F and CS, the 2 immunosuppressants. ii) Under the CS-aided immunosuppressive treatment, a male mouse reached a stage of androgen excess by combining an increase of plasma testosterone (T) and decrease of plasma estradiol (E2) , whereas a female mouse reached another state of androgen excess by way of T predominance over F in plasma (21). Estrogenic and androgenic impacts of CS on the forestomachs of male and female mice agreed with the reported side-effects of gynecomastia in a male subject and hirsutism in a female subject (20, 21). The possible relation between the hormonal and immunological impacts of CS was discussed in the light of differential steroid sensitivities of helper T and suppressor T (10).

Epilogue

As anticipated by Clemetson (6, 7) the sole use of vitamin C per os may well help in improving autoimmune disorders. As far as the treatment of interstitial pneumonia is concerned, fortification of three elements (vitamin C, D and F) as well as the use of the drip infusion system are essential. Certainly, the sole use of vitamin C infusion leads to the release of vitamin C, D and F, but it is not strong enough for disease control. It is possible that relative deficiency of both D and prophylactic chemotherapy might have triggered the onset of breast cancer in the case of Toshiko Kodama (17), a warning against excess use of corticoids in the treatment of interstitial pneumonia. Retrospectively, a shocking warning was found: in the case of polymyositis, "the most common malignancies are lung, ovary, breast, gastrointestinal tract, and myeloproliferative disorders" (22). We also experienced multiple malignancies in our drop-out population (17).

Toshiko Kodama has surely been afflicted with myositis having strong muscle contraction of right leg for the last 5 months. She was a high risk patient with a history of mammary fibroadenoma. The combined use of CS and F may well emerge as a substitute for our infusion therapy in the future. Further effort is warranted before we can learn more about how to create a state of immunotolerance in a patient with an autoimmune disorder.

References

1 Heilmeyer L: Chronische Pneumonien. *In*: Lehrbuch der Inneren Medizin . Springer-Verlag, Berlin, pp. 642-643, 1957.

2 Crystal RG: Interstitial lung disorders. *In*: Principles of Internal Medicine. 11th edition. Braunwald E, Isselbacher KJ, Petersdorf RG. Wilson JD, Martin JB and Fauci AS (eds.). McGraw-Hill Book Company, New York, pp. 1095-1102, 1987.

3 Knowles JH: Chronic bronchitis and emphysema (Chronic nonspecific lung disease). *In*: Principles of Internal Medicine, 4th edition. Harrison TR, Adam RD, Bennet IL Jr, Resnik WH, Thorn GW and Wintrobe MM (eds.). McGraw-Hill Book Company, New York pp. 1514-1521, 1962.

4 Robin E: Therapy of respiratory insufficiency. Ibid pp. 1573-1577, 1962.

5 King TE: Interstitial lung disease (ILD). *In*: Principles of Internal Medicine 15th edition. Braunwald E and Fauci AS, Kasper DL, Hauser SL, Longo DL and Jameson IL (eds.). McGraw-Hill Book Company Medical Publishing Division, New York, pp. 1499-1505, 2001.

6 Clemetson CAB: The effect of cortisone on ascorbic acid metabolisism in rheumatic fever. *In*: Vitamin C vol III, CRC Press, Boca Raton, Fl, p. 127, 1989.

7 Clemetson CAB: Adrenal corticoid metabolism II. Human study. *In*: Vitamin C, Vol III. CRC Press, Boca Raton, Fl, pp. 101-111, 1989.

8 Bell JBC, Bhatt K, Hyat PJ, Tait JF and Tait SAS: Properties of adrenal zona reticularis cells. *In*: Adrenal Androgens, Genazzani AA, Thijssen JH and Siiteri PK (eds.). Raven Press, New York, pp. 1-6 1980.

9 Clementson CAB: Hormone administration II. Adrenocorticotropic hormone (ACTH). *In*: Vitamin C, Vol I, CRC Press, Boca Raton, FI, pp. 141-142, 1989.

10 Roitt I: The control mechanism. *In*: Essential Immunogy, 8th edition. Blackwell Scientific Publications, London pp. 210-214, 1994.

11 Kodama M, Kodama T, Murakami M and Kodama M: Diabetes Mellitus is controlled by vitamin C Treatment. In Vivo *7*: 535-542, 1993.

12 Kodama M, Kodama T, Murakami M and Kodama M: Autoimmune disease and allergy are controlled by vitamin C treatment. In Vivo *8*: 251-258, 1994.

13 Kodama M, Kodama T, Murakami M and Kodama M: Vitamin C infusion treatment enhances cortisol production of the adrenal *via* the pituitary ACTH route. In Vivo *8*: 1079-1086, 1994.

14 Kodama M, Kodama T and Murakami M: The value of the dehydroepiandrosterone- annexed vitamin C infusion treatment in the clinical control of chronic fatigue syndrome (CFS). I. A pilot study of the new vitamin C infusion treatment with a volunteer CFS patient. In Vivo *10*: 575-584, 1996.

15 Kodama M, Kodama T and Murakami M: The value of the dehydroepiandrosterone- annexed vitamin C infusion treatment in the clinical control of chronic fatigue syndrome (CFS). II. Characterization of CFS patients with special reference to their response to a new vitamin C infusion treatment. In Vivo *10*: 585-596, 1996.

16 Kodama M and Kodama T: The clinical course of interstitial pneumonia alias chronic fatigue syndrome under the control of megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex. Int J Mol Med *15*: 109-116, 2005.

17 Kodama M and Kodama T: Four problems with the clinical control of interstitial pneumonia, or chronic fatigue syndrome, using the megadose vitamin C infusion system with dehydroepiandrosterone-cortisol annex. In Vivo *20*: 285-292, 2006.

18 Thomas JA and Mawhinney MG: Pharmacology of the adrenocortical steroids. *In*: Synopsis of Endocrine Pharmacology. University Park Press, Baltimore p. 178, 1973.

19 Kodama M and Kodama T: Further development of steroid carcinogenesis hypothesis in the time range of 1970s to 2003. *In*: Historical Transition of the Steroid Carcinogenesis Concept. Current Topics in Steroid Research 4, Fotherby Gronemeyer H, Huhtaniemi I, Kloosterboer HJ, Labrie F, Liao S, Mahesh VB, Murphy LJ, Parker MG, Sutherland R, Tuohimaa P, Verhoeven G (eds). Research Trend TC 17/250 (3), Chandiyara Road, Poojapura, Trivandrum 695012, India, pp. 38-44, 2004.

20 Kodama M, Kodama T, Murakami M, Akita T, Takagi H and Kodama M: Cyclosporin A is a hormonal immunomodulator. I. Human study. In Vivo *6*: 167-174, 1992.

21 Kodama M, Kodama T and Kodama M: Cyclosporin A is a hormonal immunomodulator. II. Mouse study. In Vivo *6*: 175-182, 1992.

22 Bradley WG: Dermatomyositis and polymyositis. *In*: Harrison's Principles of Internal Medicine 11th edition, Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Fauci AS (eds). McGraw-Hill Book Company Medical Publishing Division, New York, p. 2070, 1987.

Received July 2, 2007
Revised December 12, 2007
Accepted December 31, 2007