

## Are There Any Objections against Our Hypothesis That Buerger Disease Is an Infectious Disease?

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**In 1878, Winiwarter used a microscope and reported a case of 57 year-old man demonstrating Buerger disease. After that, 134 years passed. Leo Buerger and Edgar V. Allen strongly suggested that Buerger disease is an infectious disease without any doubt. Also, an etiologic point is the luminal infectious thrombus, which is thought to be the core of the disease. Many etiological factors were proposed and then discarded after academic scrutiny, but two big discoveries were made in 2005 and 2008. Namely, periodontal bacteria DNA was found in the occluded arteries of 93% of patients with Buerger disease, and periodontal bacteria (typical weak bacteria) were found to dwell in the platelets. Using these evidences, supported by genetic and epidemiological facts, we could almost explain the pathogenesis or clinical course of Buerger disease, which had been already studied.**

**Keywords:** oral bacteria dna, the oral bacteria dwelling in the platelet, platelet aggregation, periodontal disease, phlebitis migrans

### INTRODUCTION

Flex von Winiwarter made a precise report of Buerger disease in 1878<sup>1)</sup> 134 years ago. In the beginning of the 20th century, Dr Leo Buerger and Professor Edgar V.N. Allen of Mayo Clinic, suggested that the core of Buerger disease is luminal infectious thrombus.<sup>2,3)</sup> We have reconfirmed this theory in our further investigations. For over five years, we studied images of pathology, all of Professor Allen's and Dr. Buerger's papers, many Japanese pioneers' papers and recent papers from all over the world.

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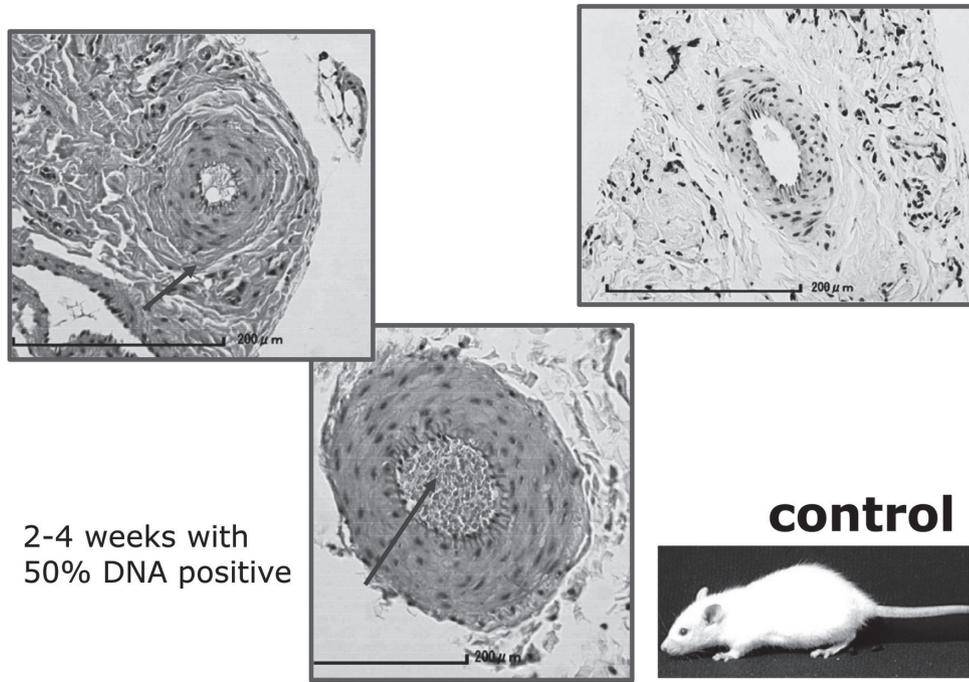
Our hypothesis was based on one suggestion and three of our discoveries. Namely, in 1928, Allen and Brown suggested that oral infection may be a cause of Buerger disease. One of our discoveries was of a causative agent reported in 2005. Oral bacteria DNA from periodontal source were observed in arterial matter of 93%<sup>4)</sup> of Buerger disease patients. In addition, we found the possible transportation system of the oral bacteria dwelling in the platelet,<sup>5)</sup> and we also knew that the oral bacteria aggregates platelets very strongly.<sup>5)</sup> A genetic study,<sup>6)</sup> epidemiologic factors,<sup>7)</sup> and an antibody titer study<sup>8)</sup> supported our hypothesis.

### ANIMAL EXPERIENCE

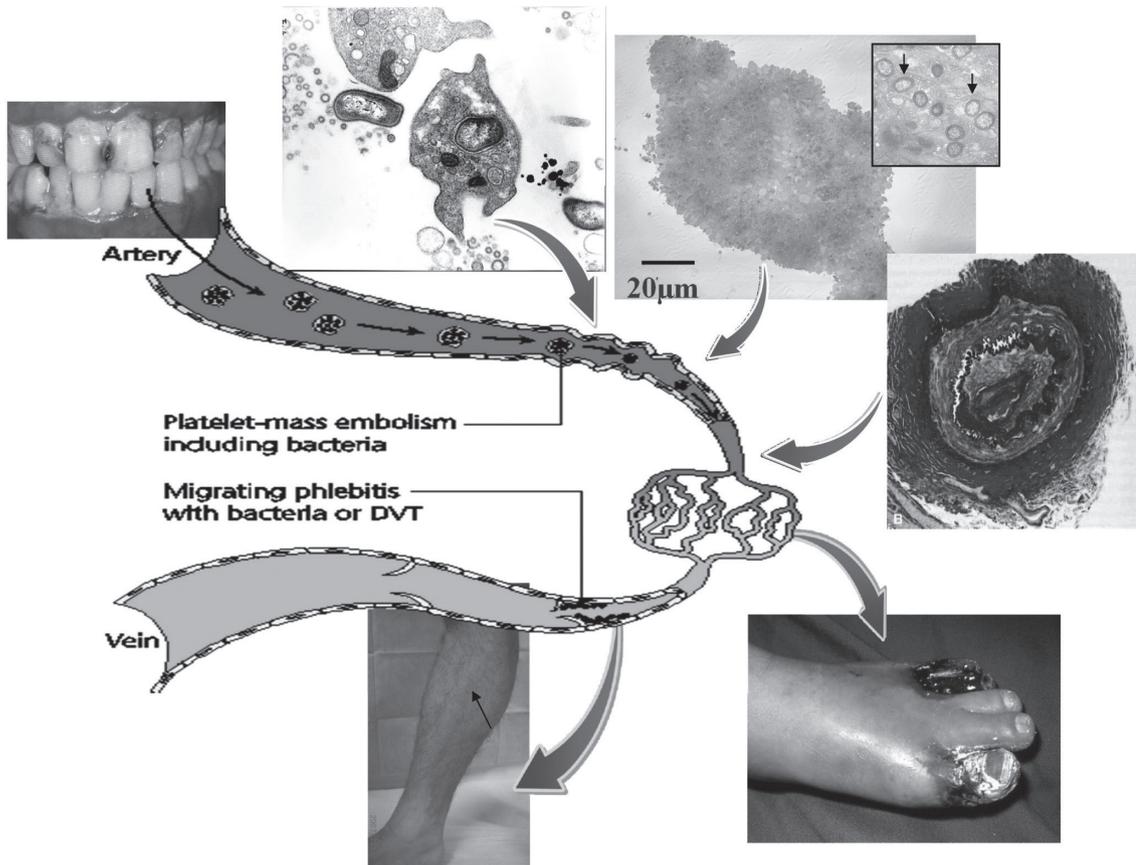
In an animal model, rats developed a small arterial thrombus within 2 weeks or receiving an intravenous infusion of the oral bacteria (*P. Gingivalis*). After sacrificing the rats 2–4 weeks after finishing the IV, the thrombosed arteries showed a 50% positive rate of oral bacteria DNA (**Fig. 1**).<sup>9)</sup>

### HYPOTHESIS

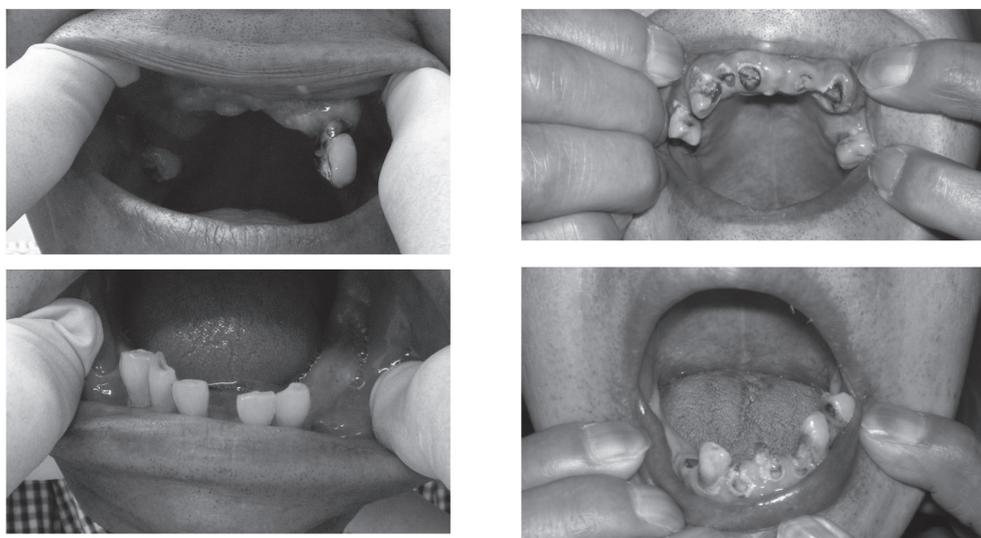
**Figure 2**<sup>10)</sup> shows the scheme of our hypothesis. Multiple



**Fig. 1** In an animal model, rats developed small arterial thrombosis after intravenous infusion of oral bacteria for 2 weeks.



**Fig. 2** Our hypothesis.<sup>10)</sup>



**Fig. 3** 100% of the patients have suffered from periodontal disease from a young age. 64%: severe form.<sup>10)</sup>

species of oral bacteria, which are weak, easily enter the bloodstream from the venous angle in the neck via lymph vessels around the mouth. They stay alive in the platelets for more than one hour at minimum. Platelets are an ideal home because they like the anaerobic conditions and the iron. Simultaneously or soon afterward, strong platelet aggregation is induced. The aggregated mass reaches over 100 micrometers in vitro.<sup>5)</sup>

The embolic phenomenon is the principle of Buerger disease that was emphasized by Dr Buerger.<sup>11)</sup> Distal areas such as the big toe or little toe are common targets of necrosis. Passing beyond the capillary, the oral bacteria touch the venous valve, which will be destroyed or will adhere to the venous lumen forming deep vein thrombosis.<sup>12)</sup>

Pathological studies suggest that the oral bacteria must enter the vaso vasorum or sympathetic nerve under the same mechanism. The results of these studies form the basis of our hypothesis.

### SMOKING AND ORAL CONDITION

One hundred percent of Buerger patients have suffered from periodontal disease from a young age. Of those, 64% were at an advance stage (**Fig. 3**).<sup>4,10)</sup> Cigarette smoking clearly worsens the periodontal condition as reported in several papers.<sup>13-16)</sup> The fact that periodontitis worsens the endothelial function was reported in the New England Journal of Medicine in 2007.<sup>17)</sup>

### ANGIOGRAPHIC FINDINGS AND ARTERIAL OCCLUSION

Arterial occlusion seems to start from the toe or finger and presents as an embolic phenomenon as Dr Buerger clearly stated in his text book published in 1924.<sup>11)</sup> Early-stage angiography shows distal or tip occlusion, which was mentioned by Japanese doctors<sup>18,19)</sup> as well as Dr. Buerger (**Fig. 4**). Buerger disease is not only a foot and a hand arterial occlusive disease, but also a whole body arterial occlusive disease. Cerebral, coronary, visceral and generalized involvements were reported,<sup>20)</sup> and more than 40 papers (in English) mention it. Our reports include the superior mesenteric artery occlusion,<sup>21)</sup> the right gastric artery occlusion,<sup>22)</sup> and the distal gastric arteries occlusion as shown below.

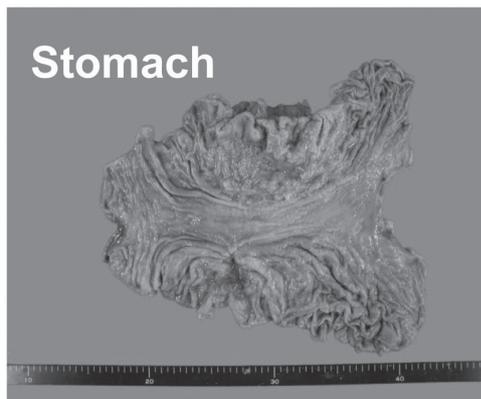
A case report: A 57 year-old male underwent a gastrectomy because of gastric cancer. The splenic and right gastric arteries demonstrated normal arterial structures, but half of the distal gastric arteries showed complete occlusion and recanalization in the thrombus site. The vein was patent and normal (**Fig. 5**).

### IMMUNOHISTOCHEMICAL AND INFLAMMATORY CHANGES

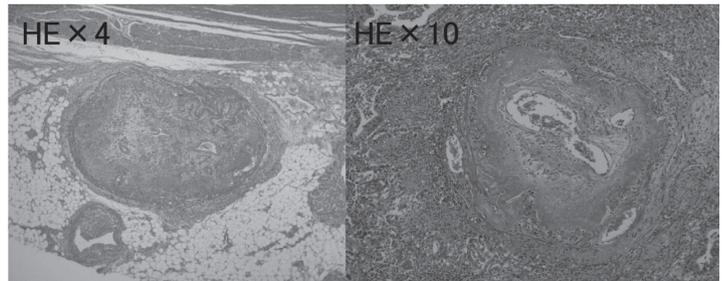
From our hypothesis, immunohistochemical changes will be imagined in the intimal layer or internal elastic lamina, adjacent to the infectious thrombus. Several papers discuss this.<sup>23,24)</sup> We know that the infectious



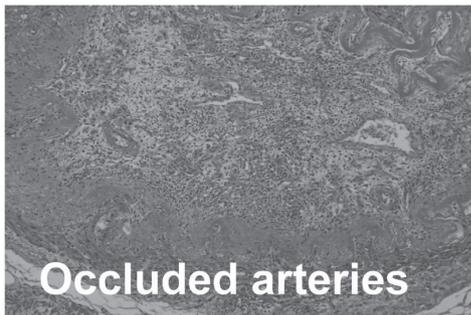
**Fig. 4** Arterial occlusion seems to start from the toe or finger and presents as an embolic phenomenon.



**Stomach**

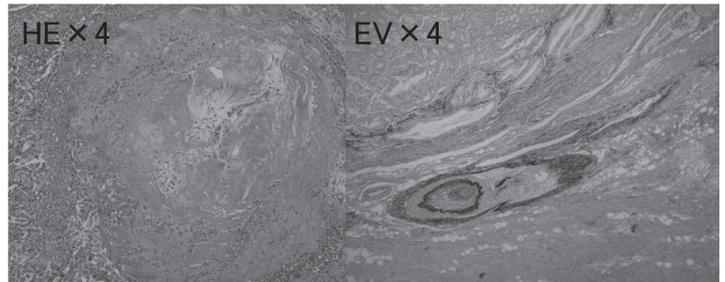


**Splenic, & rt gastric art. are normal**



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**Half of the arteries are occluded  
showing recanalization: Intact vein**

**Fig. 5** 57 year male Buerger disease (Shionoya criteria) Gastric cancer→gastrectomy.

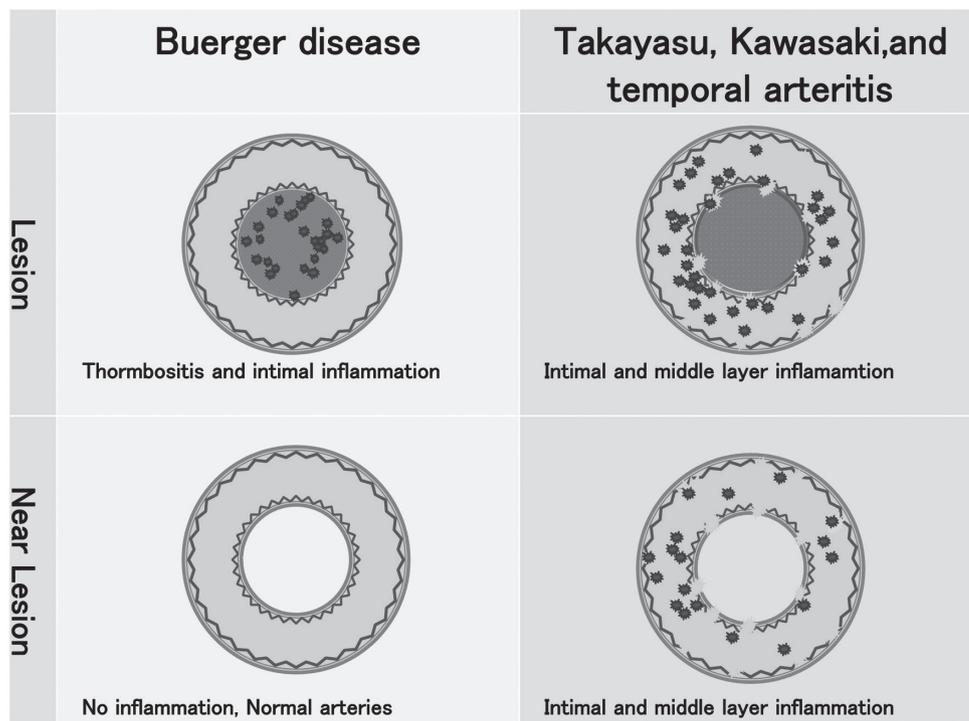


Fig. 6 Immunohistochemical and inflammatory changes.

thrombus influences the surrounding layers.

Also, it is very important to note that Buerger disease is completely different from other types of arteritis. Buerger disease only shows an inflammatory reaction in the thrombus and around the thrombus. The proximal patent site of the thrombus is free from the disease. On the other hand, the more typical types of arteritis such as Takayasu's, Kawasaki's or temporal arteritis show all layer inflammation in all layers, even in the patent region (Fig. 6). Steroid therapy is not effective in Buerger disease. This is a big difference from the above-mentioned types of arteritis.

### COLLATERAL CIRCULATIONS

One characteristic finding is rich collateral circulation in the chronic phase. This collateral growth mechanism is achieved by the healthy or pure thrombus. The corkscrew-type of collateral pathway around the original arteries is typical. This collateral system growing mechanism is relatively easy to explain as follows.

In the acute phase, infectious thrombus is mixed with microabscess or giant cells. Bacteria that passed through the capillary network adhere to the venous valves, break the valves, and/or cause the deep vein thrombus. On the

other hand, in the chronic phase, as all of the inflammation settles down, the vasa vasorum or recanalized vessels become increasingly larger to make the corkscrew-type collateral (Fig. 7).<sup>25)</sup> Varicosity also occurs. This verifies that inflammation does not occur in the chronic phase.

### SYMPATHECTOMY AND SYMPATHETIC NERVE

A sympathectomy is effective for a long period. Figure 8 shows the degenerative change of the sympathetic nerve localized around the vaso vasorum. It is suspected that the nerve is also damaged by the scattered oral bacterial infection.

Pain caused by ischemic neuritis is experienced clinically even after restoration of the arterial flow. On the other hand, Dr. Hachisuka observed regeneration of the nerve in the thrombus.<sup>26)</sup> This seems to be present along with the recanalized vessels. The spasm of collateral vessels is caused by the stimulation of the occluded blood vessels. This was Leriche's hypothesis, and it seems to be correct.

### SMOKING CESSATION AND DENTAL CONDITION

Smoking cessation improves the patient's clinical and dental condition. This has been described in several

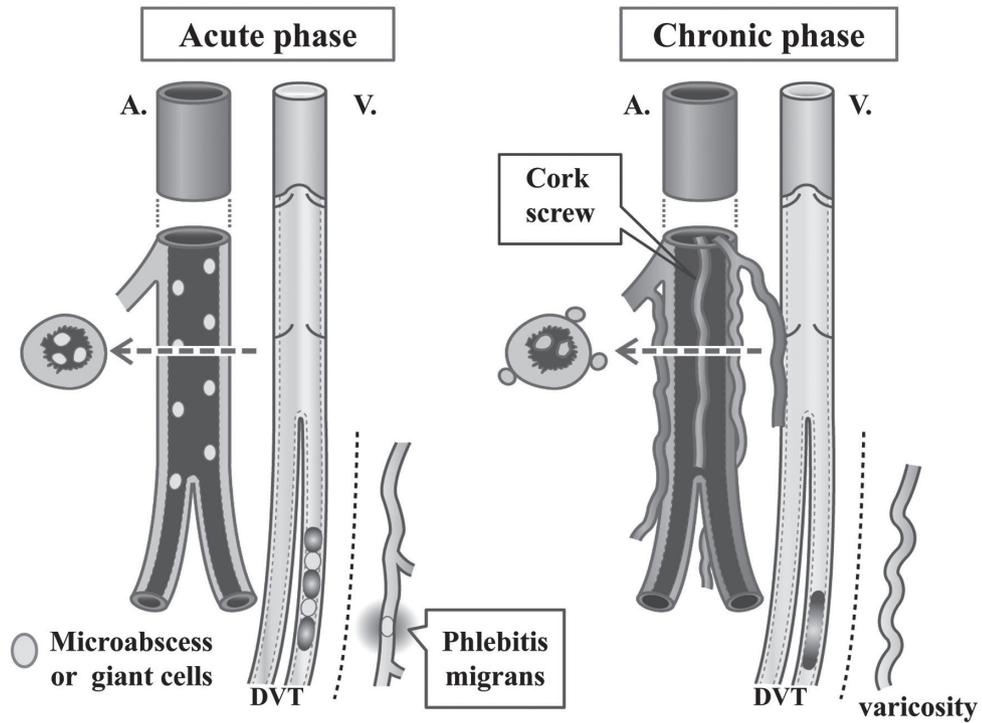


Fig. 7 Mechanism of cork-screw collateral circulation and venous dysfunction.

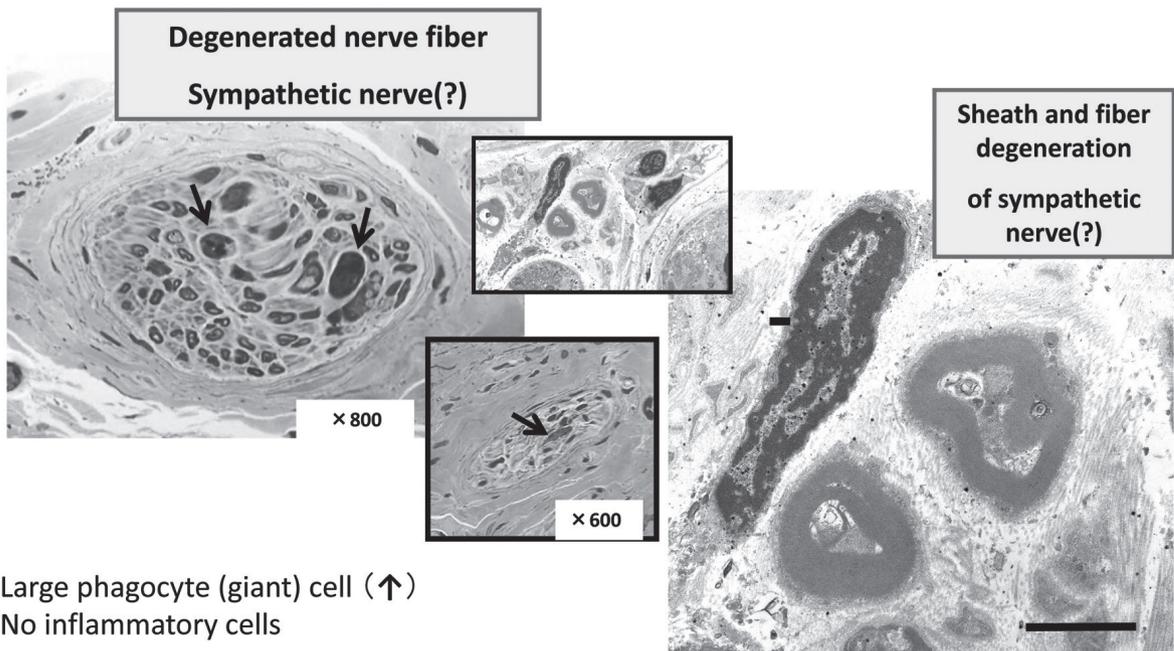


Fig. 8 Sympathetic denervation is effective for a long period.

**Basic data for stratification analyses of disease-associated genetic factors in the susceptibility to Buerger Disease**

DRB1*1501	DPB1*0501	CD14-TT	Patients (n = 131)	Controls (n = 227)	Odds Ratio
+	+		32	16	<b>12.57</b>
+		+	15	6	<b>7.12</b>
	+	+	43	36	<b>4.72</b>

**Chen Z, Takahashi M, Naruse T, Iwai T et al. Hum Genet 2007; 12: 367-72**

**Fig. 9** The intensity of the disease is different in each person. Synergistic contribution of CD14 and HLA loci in the susceptibility to Buerger disease.

papers.<sup>27,28</sup>) Smoking worsens the oral infection. There are minimum blood count and blood chemistry changes,<sup>29</sup> and no peculiar markers are found. Precise pathological observation has revealed that Buerger disease is not an all-layer arteritis. Steroids are not effective. Thrombus with microabscesses disappears soon; only in the very acute phase are the CRP, WBC, platelet, serotonin, or cytokine changes seen.<sup>30</sup>)

### INTENSITY OF THE DISEASE IN EACH PERSON

The intensity of the disease is different in each person. This is shown in our paper that reported the synergistic contribution of CD14 and HLA loci in the susceptibility to Buerger disease (**Fig. 9**).<sup>6</sup>) You can see that the odds are very high with each combination.

### HOW TO DETECT THE ORAL BACTERIA

It is impossible to detect the bacteria with a standard culture. We detect it using the PCR method,<sup>31</sup>) which is well established. This will detect the DNA whether the bacteria is dead or alive. Oral bacteria are strictly anaerobic so they can't survive a long time in the artery or vein. We announced this new discovery in our paper on the study of Buerger disease<sup>4</sup>) that appeared in the Journal of Vascular Surgery in 2005.

### REDUCTION OF BUERGER DISEASE PATIENTS

The disease is not prevalent in modern, developed countries<sup>32,33</sup>) and even appears to be decreasing in North

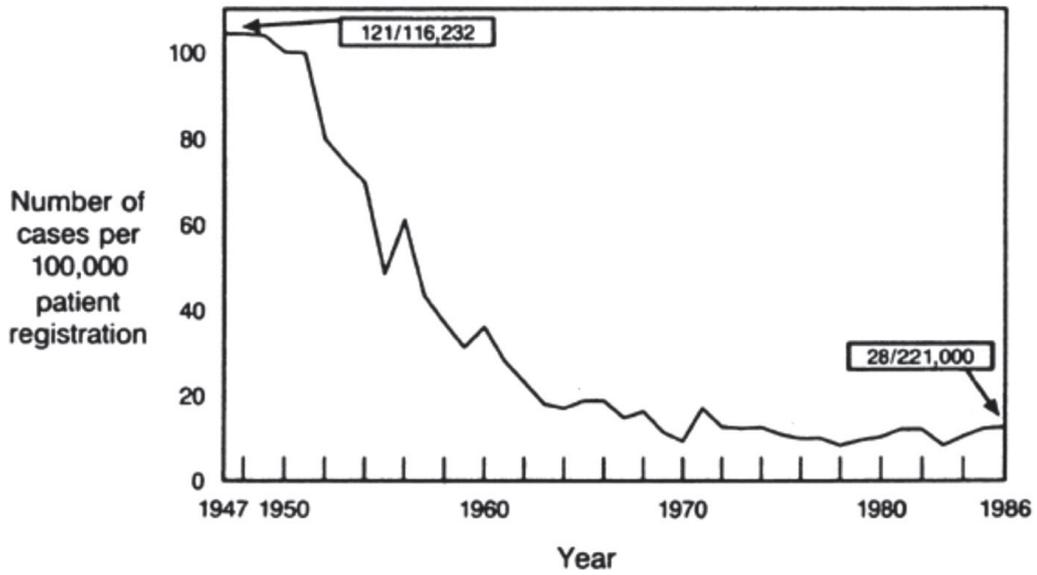
America, western Europe, parts of South Asia, Korea and Japan.<sup>34</sup>) The cause seems to be a reduction in smoking among the general population.

Mayo Clinic data showing the reduction in the number of patients is seen in **Fig. 10**. The past four decades have seen a decline. This trend holds true in Japan as well, but there is a 20 years gap in the data between the two countries. The U.S. data started from 1950, and the Japan data started from 1970. It is interesting that the Ministry of Health recommended gingival brushing 45 years ago in Japan.<sup>35</sup>)

### PHLEBITIS MIGRANS

Dr Buerger emphasized the presence of the phlebitis migrans in the disease.<sup>36</sup>) The hypothesis states that a periodontal bacterial infection passing through the valve region will result in phlebitis migrans or vein incompetence.<sup>10</sup>) Phlebitis migrans appeared in clinical practice, in 40% of the cases.

A case report: A 41 year-old male. Onset at age 39 with a right toe ulcer and IC. A heavy smoker for 25 years. Very poor dental condition; gingivitis in the gums and had no molars. No other atherosclerotic factors were present. There was phlebitis migrans along with GSV (great saphenous vein). Occlusion of the GSV occurred in the same area that had redness (**Fig. 11**). Angiography showed typical Buerger disease with right SFA (superficial femoral artery) and distal popliteal arterial total occlusion. A big toe ulcer was present (**Fig. 12**). We found the oral bacteria DNA in the phlebitis migrans samples<sup>10</sup>) and also in the primary varicose veins.<sup>37</sup>)



Prevalence trend of the diagnosis of Buerger's disease among patients registered at the Mayo Clinic, 1947–1986.

Fig. 10 Mayo Clinic data.

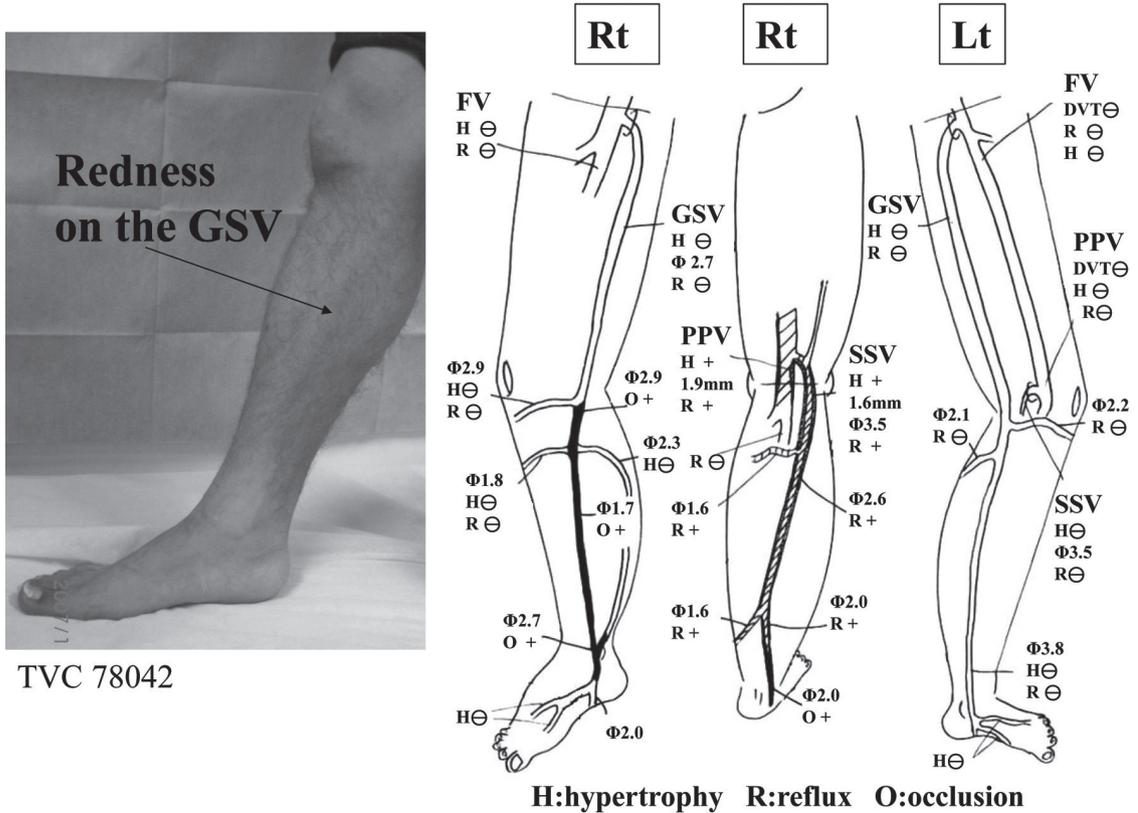
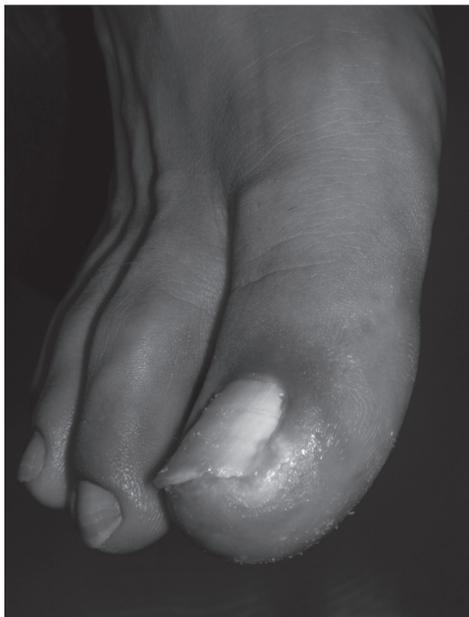


Fig. 11 A 41 year-old male. Reflux or thrombosis of the saphenous system.



**TVC: 78042**



**Fig. 12** A 41 year-old male showing a big toe ulcer and his angiography.

However, patients who take care of themselves can engage in sports. Four of our patients are now enjoying skiing.

### CONCLUSION

All previous studies and clinical course are well explained by our hypothesis.

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### DISCLOSURE STATEMENT

All authors have no conflict of interest.

### REFERENCES

- 1) Winiwarter F. Uber eine eigenthumliche Form von Endarteriitis und Endophlebitis mit Gangrue des Fusse. Arch klin Chir 1879; **23**: 202-26.
- 2) Buerger L. Is thromboangiitis obliterans an infectious disease? Surg Gynecol Obstet 1914; **19**: 582-8.
- 3) Allen EV, Brown GE. Thromboangiitis obliterans. A clinical study of 200 cases. Ann Intern Med 1928; **1**: 535-49.
- 4) Iwai T, Inoue Y, Umeda M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg 2005; **42**: 107-15.
- 5) Li X, Iwai T, Nakamura H, et al. An ultrastructural study of Porphyromonas gingivalis-induced platelet

- aggregation. *Thromb Res* 2008; **122**: 810-9.
- 6) Chen Z, Takahashi M, Naruse T, et al. Synergistic contribution of CD14 and HLA loci in the susceptibility to Buerger disease. *Hum Genet* 2007; **122**: 367-72.
  - 7) Chen YW, Umeda M, Nagasawa T, et al. Periodontitis may increase the risk of peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2008; **35**: 153-8.
  - 8) Chen YW, Iwai T, Umeda M, et al. Elevated IgG titers to periodontal pathogens related to Buerger disease. *Int J Cardiol* 2007; **122**: 79-81.
  - 9) Kubota T, Inoue Y, Iwai T, et al. Arterial thrombosis after intravenous infusion of oral bacterium in a rat model. *Ann Vasc Surg* 2008; **22**: 412-6.
  - 10) Iwai T, Sato S, Kume H, et al. Clinical study of phlebitis migrans and incompetence of the leg's superficial vein in Buerger disease. *Ann Vasc Dis* 2012; **5**: 45-51.
  - 11) Buerger L. The circulatory disturbances of the extremities. Edt. Leo Buerger L., Philadelphia: WB Saunders, 1924; pp 218-9.
  - 12) Iwai T. Buerger disease: new evidence. Davies AH, Mitchell AWM edit. *Vascular and endovascular surgery highlights 2008–09*, Oxford: Health press, 2009; pp93-8.
  - 13) Iwai T, Inoue Y, Umeda M, et al. Buerger disease, smoking and periodontitis. *Ann Vasc Dis* 2008; **1**: 80-4.
  - 14) Stoltenberg JL, Osborn JB, Pihlstrom BL, et al. Association between cigarette smoking, bacterial pathogens, and periodontal status. *J Periodontol* 1993; **64**: 1225-30.
  - 15) Hung HC, Willett W, Merchant A, et al. Oral health and peripheral arterial disease. *Circulation* 2003; **107**: 1152-7.
  - 16) Mattila KJ, Pussinen PJ, Paju S. Dental infections and cardiovascular diseases: a review. *J Periodontol* 2005; **76**: 2085-8.
  - 17) Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007; **356**: 911-20.
  - 18) Hirai M, Shionoya S. Arterial obstruction of the upper limb in Buerger's disease: its incidence and primary lesion. *Br J Surg* 1979; **66**: 124-8.
  - 19) Takao K, Ooiwa S, Naiki K, et al. Angiographic findings: with special reference to initial occlusive features. In: Ishikawa K ed. Annual report of the Buerger's disease research committee of the Ministry of Health and Welfare of Japan 1974 pp114-19 (in Japanese).
  - 20) Shionoya S. Lesions outside the extremities. Edit by Shionoya S. *Buerger's disease. Pathology, diagnosis and treatment*. Nagoya: Univ. of Nagoya Press, 1990; pp69-71.
  - 21) Iwai T, Sato S, Yamada T, et al. Identical twin and Buerger's disease. Two cases report showing abdominal angina and the popliteal arterial aneurysms. *Gekachiryō* 1987; **29**: 951-7. (in Japanese)
  - 22) Loh B, Hatano R, Sugihara K, et al. Buerger's disease in the right gastric artery associated with duodenal ulcer and minute gastric cancer. *Nihon Rinsho Geka Gakkai Zasshi* 1980; **13**: 68-72.
  - 23) Eichhorn J, Sima D, Lindschau C, et al. Antiendothelial cell antibodies in thromboangiitis obliterans. *Am J Med Sci* 1998; **315**: 17-23.
  - 24) Kobayashi M, Ito M, Nakagawa A, et al. Immunohistochemical analysis of arterial wall cellular infiltration in Buerger's disease (endoarteritis obliterans). *J Vasc Surg* 1999; **29**: 451-8.
  - 25) Shionoya S. Angiographic findings. In: Shionoya S. *Buerger's disease. Pathology, diagnosis and treatment*. Nagoya: University of Nagoya Press, 1990; pp118-150.
  - 26) Hachisuka K. Histopathological studies on the nerve fibers in the vascular wall in the thromboangiitis obliterans. *Nagoya J Med Sci* 1958; **21**: 190-204.
  - 27) Preber H, Linder L, Bergström J. Periodontal healing and periopathogenic microflora in smokers and non-smokers. *J Clin Periodontol* 1995; **22**: 946-52.
  - 28) Haber J, Wattles J, Crowley M, et al. Evidence for cigarette smoking as a major risk factor for periodontitis. *J Periodontol* 1993; **64**: 16-23.
  - 29) Akar AR, Durdu S. *Thromboangiitis obliterans*. *Rutherford's Vascular Surgery 7th edition*. Philadelphia: Saunders, 2010; pp1169-86.
  - 30) Takahashi M, Furukawa K, Ishimaru S. Blood coagulation in Buerger's disease. In: Ishikawa K ed. Annual report of Buerger's disease research committee of the Ministry of Health and Welfare of Japan, 1973; pp37-41.
  - 31) Ashimoto A, Chen C, Bakker I, et al. Polymerase chain reaction detection of 8 putative periodontal pathogens in subgingival plaque of gingivitis and advanced periodontitis lesions. *Oral Microbiol Immunol* 1996; **11**: 266-73.
  - 32) Shigematsu H, Shigematsu K. Factors affecting the long-term outcome of Buerger's disease (thromboangiitis obliterans). *Int Angiol* 1999; **18**: 58-64.
  - 33) Olin JW, Young JR, Graor RA, et al. The changing clinical spectrum of thromboangiitis obliterans (Buerger's disease). *Circulation* 1990; **82**: IV-3-8.
  - 34) Matsushita M, Nishikimi N, Sakurai T, et al. Decrease in prevalence of Buerger's disease in Japan. *Surgery* 1998; **124**: 498-502.
  - 35) Personal communications with the dentists.
  - 36) Buerger L. The association of migrating thrombophlebitis with thromboangiitis. *Internat Clin* 1909; **19**: 84-105.
  - 37) Kurihara N, Inoue Y, Iwai T, et al. Oral bacteria are a possible risk factor for valvular incompetence in primary varicose veins. *Eur J Vasc Endovasc Surg* 2007; **34**: 102-6.