On Characteristic Antiinflammatory Effects of Several Antileprosy Drugs

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As for the question why the efficacy of DDS can extend over several diseases of exudative but non-infectious such as *Herpes dermatitis*, *Erythema elevatum diutinum*, Impedigo in sublayer of *Stratum corneum*, Schönlein-Henoch type anaphylactic Purpura, Gougerot-Ruiter type allergic Angitis in corium, and Parapsoriasis by daily dosage of 50-150 mg of DDS could not be explained before Katabira, *et al.* of Japan dermatological field found out a clue to discovery of its inhibitory effect on Carrageenin-induced rat acute edema^{1,2)}.

In leprosy field, the endeavor for drug screening has laid emphasis on the result how to be possible to decay the growth of bacilli as foci in mouse footpad method. Already in 1972, Evans and Levy had mentioned the remain of leprosy bacilli localized in inflammatory cells even in the case of mouse footpad method³⁾. While, as the result of drug screening employing nearly all the types of antibiotics, no one except Rifampicin (RFP) enough effective to leprosy bacilli could be searched out.

Even though this regrettable process can be explained by the partially elucidated but possibly peculiar *in vivo* metabolism of leprosy bacilli^{4,5)}, the inefficacy of s-DDS in both of mouse footpad method and clinical trial in Kuriu Rakusen-en⁶⁾ could not be explained by single sulfonamide-type inhibition, because it is the deacetylate of Promacatin and its action area was known to be resemble to that of DDS but far superior to that of Promacatin. This report is to offer the details in the results of pharmaco-dynamic studies on antileprosy and the relating drugs hitherto examined.

Experimental Methods

1. Carrageenin-induced rat acute edema (CRAE).

Experimental animal was male rat (Wistar, weighing about 100 g, 5 weeks after the birth). Always, 6 rats per group were used. Edema was made as follows: A λ -carrageenin (Pasco-International Co.) was triturated well in an agate mortar with saline under aseptic state and it was preserved in a vial for a night at 4°C. Then, 0.1 ml (1 mg of λ -carrageenin) was subcutaneously injected to right hind footpad. Dose: At 1 hour before the injection of carrageenin solution, all the drugs shown in Fig.1 were dosed by a catheter after triturated well with tween-80 water. The water without drug was dosed to control group. After 5

days, the experiment was repeated by left hind footpad. Measuring the swelling of rat paw : by a liquid paraffin-mercury system, the swelling volume below *Malleolus lateralis* was measured. Always, the swelling rates by 12 foot paws of 6 mice were averaged.

2. Skin test.

Male guinea pigs (Hartley weighing about 200 g, 6 weeks after the birth) were used. After spreading depilation cream onto the wet furs cut previously, the cream was washed away well with warm water and the skin was protected by 0.01 % Tetracycline ointment. Two or 3 guinea pigs per group were fasted from food for a night. The drugs were given by catheters and 1 hour later, they were labelled by gradual injection of 0.8 ml of 4 % Pontamine Sky Blue 6B/PBS solution directly into their hearts. Further 30 minutes later, 0.1 ml of 0.4 % Histamine diphosphate (Tokyo Kasei Company) or 0.1 % Serotonin creatinine sulfate (the same)/PBS solution including 0.1 % of drug (but in the case of Indomethacin (IDM)-glutarate, TV 1322, Bayer Pharmaceutical Industry, it was 0.01 %) was intracutaneously injected to 5-6 sites of the depilated skin of each guinea pig.

Copy of spots : The indistinct spots were excluded. Each spot was copied through semi-transparent section paper and was transcribed onto a thickend alumi foil (10 layers piled up, averaged weight ; 0.42 mg/mm²). As the areas of blue spots by Serotonin cases were generally small, in some cases, it was copied after photographed and enlarged.

However, in the case of Bradykinin skin test, male rabbits weighing 2.0-2.5 g were used. The pigmental labelling was done by injecting 2 ml of 4 % Pontamine Sky Blue 6B/PBS, pH 7.0 into auricular vein.

3. Tests of some stabilizing effects

Stabilizing of rat erythrocytes membrane. The fresh erythrocytes collected from rat femoral artery were washed twice with 0.015M phosphate buffered saline, pH 7.4 and were added with 19 parts of 0.15M phosphate buffer, pH 7.4. Three ml of the 5 % erythrocytes suspension was mixed with 3 ml of 0.015 M phosphate buffer including drug of various concentrations lower than 10⁻³ M. It was incubated at 53°C for 20 minutes and cooled immediately in cold water for 5 minutes, and then centrifuged for 40 minutes at 2500 rpm. The supernatant (0.6 ml) was measured at 545 nm by cyanmethemoglobin method. The disturbance by reddish color of B 663 was eliminated by the use of specimens including various concentrations of B 663 alone. The drug of low solubility was dissolved by changing pH, rapily diluted with phosphate and immediately used.

Whittle test. To above 10 mice per group (dd-strain, male, weighing about 20g fasted from food for a night), 100 mg/kg of DDS, B 663, Thalidomide, or 3 mg/kg of Indomethacin (IDM) was given *via* catheter, and at 1 hour later, 0.1 ml of 4 % Pontamine Sky Blue 6 B solution was injected into tail vein followed by intraperitoneal injection of 0.4 ml of 0.75 % acetic acid. Twenty minutes later, they were sacrificed by neck bone puncture, and after several minutes for coagulation, the blue ascite was washed out to adjust 10 ml. It was measured at 620 nm after excluding some specimens which color changed into green-dark green by the contamination of hemoglobin.

Heat denaturation of albumin and IgG: The drug solutions of various concentrations (1/5000–1/40000 M) were mixed with 0.375 % bovine serum albumin or 0.2 % human IgG purified/0.2M phosphate, pH 5.3, and the mixture heated at 67°C for 3 minutes or at 80°C for 5 minutes respectively and immediately cooled in water for 5 minutes. Then its turbidity was measured at 600 nm. Except IDM, no inhibition could be detected in DDS, DADDS, Thalidomide, and Clindamycin (CLM).

4. CMC pouch method.

Animals used were male rats (SLC, 150–200 g). Always, 7 rats (TV 1322, 5 rats) per group were used. CMC pouch: Ten ml of air was subcutaneously injected into the depilated back of rat and was fasted from food for a night. At 24 hours later, 5 ml of 2 % CMCNa/saline including 100 µg/ml (TV 1322, 10 µg/ml) of drug was injected into air pouch. Dose: Just before injecting CMCNa solution, drugs were dosed by catheters. ³H-DDS: It was synthesized by catalytic reduction of a mixture consisted of tri- and tetra-bromo DDS which was got by dropping of bromine into DDS solution (HCONMe₂-AcOH mixture) followed by UV irradiation. Counting of leucocytes: The pouch fluid (0.1 ml) was stained with 3 ml of 0.05 % Brilliant Cresyl Blue/saline. The pouch fluid was taken out employing a needle for blood transfusion after well picked the CMC pouch. Measuring of protein: Total amount of protein components exudated into 0.1 ml of CMC pouch was measured by Lowry's method.

The next points must be recognized.

(i) This method can not distinguish whether the drug possesses action on leucocytes themselves or on any other types of cells.

(ii) Since it is an *in vivo* experimental form, the indirect action on PMN can be expressed far exactly than the experiment by Boyden chamber.

(iii) A strict care must be necessary when taking out 0.3 ml of viscous CMC pouch fluid, because any scratch wound inside of pouch surface can be causal to a side-inflammation. The rats were preserved under 0.005 % Tetracycline water and subcutaneous injection of 10⁵ units of Penicillin-G immediately after injecting air.

5. Adjuvant-induced arthritis.

Animals used were male rats (SLC, above 150 g). In each experiment, 6–7 rats (TV 1322, 4–5 rats) per group were used. Sensitization: The lyophilized tubercle bacillus Aoyama B strain was mixed in an agate mortar with liquid paraffin and was once treated by glass homogenizer. It was diluted to 50 mg/15 ml with liquid paraffin, sterilized at 115°C for 20 minutes, and aiming at rat calcaneus, 0.1 ml into footpad and 0.05 ml from upside were injected subcutaneously into each right hind paw. During the first 10 days, 0.005 % Tetracycline water was given. Dose: Drugs were given every day by catheters as fine powder suspensions in tween-80 water. The medium without drug was dosed to the control. Measuring the swelling of rat paw: The swelling volume was measured equally to the case of CRAE. Always, the swelling rate and increasing rate of weight were calculated and averaged, and compared with those of control group. Caused by the severe symptom, the rats of DDS

group often laid down under the incontinence of urine and their lymph nodes from tail to axillae were markedly swollen.

Results and Discussion

1. Inhibitory effect on CRAE.

The inhibitory effect on CRAE is summarized in Fig. 1. The edema inhibition by DDS could be detected even at the dosage of 4 mg/kg, and it became more clearly above 10 mg/kg. It was nearly comparable to that by IDM of 10 mg/kg. However, by prolonging the measuring time, firstly it was found that when the dosage was increased up to 30 mg/kg and then to 100 mg/kg, as compared with IDM group, the inhibition ratios after 8 hours were gradually lowering, and at 24 hours, on the contrary, it showed the swelling more than the control group.

This phenomenon suggested the excellent inhibition of DDS to acceleration of venular permeability (not to be restricted to mere dilatation) and the subsequent exudation by PMN and/or venular intima of inflamed state such as adhesion by increased viscosity in contrast with the effect of lower or even accelerative especially on the accelerated state of mobility and the subsequently occurred exudation of various mononuclear cells. The sulfonamid-type drugs excluding s-DDS more or less showed inhibition from 3 to 4 hours at the dosage of

Fig. 1 Inhibitory Effect of Antileprosy and the Relating Drugs on Carrageenin-induced Acute Rat Edema

100 mg/kg which is corresponding to Kininins phase. Among them, the effect of Sulfa-dimethoxine which is one of long-acting and of the most reliable in leprosy was found to be the best.

As for the residual drugs, a weak inhibition at 100 mg/kg could be detected in Thalidomide and B 663 especially at 1 hour later which is corresponding to Histamine phase, but that of the latter was very slight and must be said to be within error. While, s-DDS seemed to exacerbate the edema, perhaps be due to the manifestation of its cellular toxicity in high dosage.

2. Inhibitory effect on the exudation examined by skin tests

Originally, it is said that Kinins play the most important part in CRAE and Histamine in yeast-induced edema. As for Histamine cases, the clear inhibition could not be noticed except TV 1322 group. On the contrary, the intricately extended spots in RFP were noticed. It is said that various antibiotics of high dosages enhance exudation and this phenomenon is never caused by the increase of freed pigment through competitive adsorption between pigment and antibiotics on the surface of protein molecule⁷⁾. While in Serotonin cases, the antiexudation by DDS could be detected nearly comparably to that by TV 1322 of 3 mg/kg. Moreover, in Bradykinin cases, the antiexudation by drugs became more clearly detectable. On the depilated rabbit skin it could be shown as clear blue pigmental spots enough to be capable of transcription. The results are summarized in Table I.

These results remind us of the fact that the numerous cases of plantar ulcer in leprosy patients could be treated by the dose of Anginin which is a strong kinins inhibitor and a drug for arteriosclerosis by its strongly preventive effect on thrombus (Anginin: 2,6-pyridine dime-thanol bis-(N-methylcarbamate)). In addition, it is an interesting finding that the plasma Kininogen content of armadillo was about 3 times higher than that of human (9.3 $\mu\text{g/ml}$) and was the highest (33.1 $\mu\text{g/ml}$) among the tested animal species⁸⁾.

3. Stabilization effect on rat erythrocytes membrane from heat and hyposmotic hemolysis

The fresh rat erythrocytes can be a favorable substitute for lysosomal membrane. Thus, the stabilization effect of antileprosy drugs on the erythrocytes membrane toward heat and hyposmotic hemolysis was examined. As shown in Fig. 2., a stabilization by B 663 proportional to the increase of concentration was detected, but it was quite weak in comparison with IDM. In the case of CLM, inversely, a weak hemolytic action was seen. While in the case of Thalidomide, with higher concentration than 1/4000 M, the stabilization became clear with the increase of concentration, and with lower concentration than 1/4000 M, inversely, the slight hemolysis at 1/4000 M gradually diminished with the lowering of concentration. However, since above 1/4000 M of Thalidomide is calculated to be higher than 64.5 $\mu\text{g/ml}$, merely based on this result, the stabilization effect of Thalidomide on lysosomal membrane could not be discussed. The influence of DDS was within error.

Besides this experiment, the inhibitory effect on the exudation of pigment into peritoneal cavity was examined and a weak inhibition by B 663 was detected also in this test form,

Table I The Summarized Results of Skin Tests

animals	chem. mediat. μg in 0.1ml of PBS intracutaneously	drug, μg contained in intracutaneous injection					
guinea pigs	Histamine $\cdot$ 2PO ₄ 400	100 (TV 1322, 10)					
"	Serotonin $\cdot$ C $\cdot$ S 100	"					
rabbits	Bradykinin $\cdot$ 3Ac 0.4	—					
Oral Dosage: 100mg/kg (TV 1322, 3mg/kg)							
Averaged Areas of Blue-Pigmental Skin Spots (mm ² +mm ²)							
	DDS	B 663	Thalidomide	TV 1322	RFP	Control	
Histamine	3 hrs.	36.5±11.8	70.5±21.4	52.3±20.6	23.9± 4.7	100.7±24.3	46.8±18.0
Serotonin	2 hrs.	12.3± 3.7	21.3± 6.0	16.9± 5.2	16.0± 3.0	—	24.0±11.0
	4 hrs.	19.4± 4.8	32.3± 9.2	25.9± 6.8	28.4± 5.8	—	31.1±12.4
Bradykinin	(the 1st experiment)						
	1 hr.	50.3± 9.9	76.1±22.7	52.1± 8.7	57.4± 8.4	—	63.3±13.3
	2 hrs.	42.3± 5.1	66.5±16.9	45.7± 9.1	52.6±10.1	—	76.4±17.6
	3 hrs.	60.1±12.2	70.2±14.8	54.2±13.0	62.4±12.3	—	99.7±28.1
	4 hrs.	66.1±13.8	80.7±18.9	66.6±10.0	78.1±14.1	—	123.3±30.5
	(the 2nd expersment)						
	1 hr.	46.7±11.5	62.0±18.8	44.1± 7.0	60.5± 9.0	—	108.6±23.7
	2 hrs.	52.4±10.5	71.8±22.2	54.2± 8.6	74.5±17.8	—	120.8±16.1
	3 hrs.	54.5±10.5	71.7±20.6	68.5±17.5	75.1± 9.2	—	139.3±18.6
	4 hrs.	69.4±19.0	105.3±19.5	75.0±18.7	89.3±12.2	—	142.8±27.2
	10 hrs.	62.3±13.1	95.4±24.3	89.3±20.1	109.4±11.7	—	153.2±22.1

Fig. 2 Stabilization Effect of Rat Erythrocytes Membrane from Heat and Hyposmosis-induced Hemolysis

even though it was far inferior to that by IDM. While neither DDS nor Thalidomide showed inhibition by this test.

4. CMC pouch method⁹⁾. To find out a difference between DDS group and the control, the experiments were repeated 4 times. As the result, the followings were concluded.

(a) The maximum concentration of the exudated ^3H -DDS per 1 mg of protein which exudates together into CMC pouch was found to be at 4 hours.

(b) Until 4 hours, a slight inhibition by

DDS to both exudation of protein and emigration of leucocytes into CMC pouch could be detected.

(c) Thalidomide: Inhibition to emigration of leucocytes alone could be detected.

(d) No inhibition could be detected in B 663 and Clotrimazole (Bayer Pharmaceutical

Fig. 3 Inhibitory Effect of Several Antileprosy Drugs on the Exudation of Pigment into Peritoneal Cavity Induced by Intraperitoneal Injection of Acetic Acid in Mice (Whittle Test)

Fig. 4 Inhibitory Effect of Several Antileprosy Drugs on Leucocytes Emigration and Protein Exudation Examined by CMC Pouch Method

Industry).

Summarizing the results in 3. and 4., it may be suspected that DDS does not possess strong action on cells themselves such as mobilizing cells or stabilizing membrane.

5. Inhibitory effect on adjuvant-induced arthritis (AIA).

The method is known to be a suitable model to search for effective substance to rheumatic diseases among several experimental arthritis. At least 10 rats are said to be necessary for enough reliable result. Therefore, two series of experiments were averaged under comparison with the respective control groups and the important part of the results are shown in Fig. 5.

Both of the inhibition by B663 and the final exacerbation by DDS could clearly be obse-

Fig. 5 Inhibitory Effect of Several Antileprosy Drugs on Adjuvant-induced Arthritis

rved in every experiment at the every day's dosage of 10, 30, and 100 mg/kg. It became more marked with the increase of the dosage. However, since the decrease of body weight by the progress of symptom was enhanced by the toxicity of DDS, the decreasing rate of body weight was to be somewhat lowered when it was used too much high dosage. While, Thalidomide did not show any inhibition. Clotrimazole was developed as an antifungal agent and its effects on both of malarial and rheumatic diseases were interested. However, as it is excreted under metabolic elimination of its imidazole ring, presently, it is tested by external route alone. By oral intake of 50 mg/kg of Clotrimazole, rat feces were greenly colored during the first 2 weeks but this phenomenon gradually diminished. While, the color of the footpads was always somewhat deeply reddish. At the dosage of 10 mg/kg, the inhibition to the primary reaction was not clear. Clotrimazole inhibited only slightly the growth of leprosy bacilli in mouse footpad at the drug content of 0.005% while DDS inhibited completely at this drug cotent. The details will be published in other report.

The pharmaco-dynamic spectra of main tested drugs are summarized in Table II.

It may be noticed that the antiinflammatory spectra of antileprosy drugs are a sort of partial inhibition in comparison with that of the representative antiinflammatory one, IDM.

The explanation of mechanism of DDS efficacy is very complicated. Returned to CRAE, generally speaking, the inhibitory effect of basic non-steroidal antiinflammatory drugs on emigration of PMN, especially on that of monocytes is said to be weaker than that of acidic non-steroidal ones. Previously, Palekar, *et al.*¹⁰⁾ reported the stabilizing effect of DDS on lysosomal membrane based on the result of enzymatic measurent by clinical routine work. However, when thinking about these finding such as its weak inhibition to emigration of

Table II Summarized Pharmacodynamic Spectra of Tested Drugs

		DDS	B 663	Thali domide	Indomethacins
Carrageenin edema		markedly inhibited	not detectable	weak	markedly inhibited
	Histamine	slight or non	non	not detectable	inhibitory
Skin test	Serotonin	inhibitory	"	inhibitory	"
	Bradykinin	"	weak	"	"
Stabilizing erythrocytes membrane		non	"	weak	markedly stabilized
	Whittle test	"	"	non	"
Heat denaturation of protein		"	non	"	"
CMC	Leucocytes emigration	slight	"	inhibitory	inhibitory
pouch	Protein exudation	"	"	not detectable	"
Adjuvant-induced arthritis		exacerbate	inhibitory	non	markedly inhibited

cells by the case of CMC pouch method its antiexudative effect must become regardful of another mechanism of efficacy of DDS, that is, since the adhesion of these types of cells and platelets to venular intima play an important part in the inflammation process, the mutual reaction between the exposed collagen and the completely symmetrical but polar structure of DDS can be imagined. Indeed, Avila, *et al.*¹¹⁾ proposed their comments to the report by Palekar, *et al.* Generally speaking, the antiinflammatory drugs possess more or less immunosuppressive effect. Beiguelman, *et al.*¹²⁾ reported this effect of DDS which was examined by phytohemagglutinin-induced lymphocytes transformation. The following experience in pharmacological field must be remembered that too much *in vivo* accumulation of immunosuppressive drug contrarily exacerbated the symptom of AIA. This general experience also suggests us a possible immunosuppressive effect of DDS.

However, practically, DDS is mainly effective to the general symptom of leprosy and B 663 to ENL. So far as the precedent reports are concerned¹⁴⁻¹⁹⁾, B 663 and Thalidomide themselves seem to be immunosuppressive.

Although the simultaneous measuring of analgesic and antipyretic effects of B 663 on AIA could not be performed, the resemblance of B 663 to antirheumatic drugs, and though vaguely, the connection between B 663 and some antimalarial antipyretics may together be suspected when looking over its characteristic pharmacodynamic spectra.

Hastings, *et al.*²⁰⁾ reported the stabilizing effect of Thalidomide on lysosomal membrane. However, looking over these findings, another mechanism is necessary for enough explanation of Thalidomide efficacy on ENL. Indeed, recently, they published the inhibitory effect of Thalidomide on antibody synthesis²¹⁾.

Since the causes of inflammation in leprosy disease are imagined to be consisted of various factors including possibly both of immobilizing factors derived from bacilli themselves and the resultant mobilizing and/or immobilizing ones of host, even if the main action of DDS would be antiexudation, the efficacy of DDS on leprosy disease may be more complicated than that in non-infectious diseases.

The addition of pharmacodynamic characters to the classification of antileprosy chemo-

therapeutics is needed, and when based on this concept, DDS and B 663 can be said to be mutually two extreme types. Moreover, suggested by these findings, the relation between the mechanisms of actions of DDS and B 663 and their efficacies on the leprosy symptoms must be considered even as a clue for elucidating the essence of the respective symptoms.

At all events, by the introduction of inflammation view which is known to be the most active part in pharmacological field, the clinical field of leprosy could have a strong base in addition to those by the rapid progress of immunological studies and by the accumulation of experience through the clinical treatment of the reactional phase by various allopathic drugs.

Summary

The pharmaco-dynamic characters of several antileprosy drugs were examined by various pharmaco-dynamic test methods. The results found were as follows:

1. DDS inhibited markedly the carrageenin-induced rat acute edema (CRAE). While, s-DDS, which structure is desacetyl Promacetin and had been found to be ineffective to leprosy, contrarily increased the swelling of rat paws. Promizole and Sulfadimethoxine also showed weak inhibition at its Bradykinin phase. Thalidomide exhibited only a very weak inhibition. While, no inhibition could be found by the dose of B 663.

2. However, the inhibition of CRAE by DDS decreased later than 10 hours with its dosage increased, in comparison with that of Indomethacin as the standard antiinflammatory drug.

3. DDS inhibited the exudation induced by low molecular chemical mediators, especially by Bradykinin, when measured the blue skin spots of animals labeled by Pontamine Sky Blue 6B. A weaker inhibition was found also in the case of Thalidomide but that of B 663 was slight.

4. DDS inhibited the emigration of leucocytes when examined by CMC pouch method. But, later than 4 hours after its dose, the inhibition could not be detected. Thalidomide also exhibited a weak inhibition. But both of them were quite weak if it is compared with that of Indomethacin glutarate (TV 1322).

5. B 663 exhibited weakly the stabilizing effect on rat erythrocytes membrane under heat and hyposmotic shock. Thalidomide weakly showed this effect. But the effect was diphasic and the hemolysis was strongest at 1/4000 M. DDS showed no effect.

6. Among DDS, Thalidomide, and B 663, B 663 alone showed a weak inhibitory effect on the exudation of Pontamine Sky Blue 6B into peritoneal cavity of mice.

7. B 663 strongly inhibited the adjuvant-induced arthritis. While, DDS contrarily exacerbated this arthritis. Thalidomide showed no inhibition. Clotrimazole, which is an anti-fungal agent and was being interested in its antirheumatic effect, also inhibited the arthritis to similar extent as B 663.

Standing on these findings, the mechanisms of actions of DDS and B 663 on the leprosy symptoms were discussed, as mutually two extreme types concerning their pharmaco-dynamic spectra among the tested drugs.

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二、三の治らい剤の特徴的消炎効果について

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DDS, B 663, Thaliclomide のような二、三の治らい剤の消炎効果が種々の薬効学的検査法で調べられ、その結果が非ステロイド消炎剤中代表的な消炎剤であるとして知られる Indomethacin (IDM) またはその glutarate (TV 1322) や抗糸状菌剤だがその抗リウマチ作用が興味を持たれつつあつた Clotrimazole の消炎効果とくらべられた。その結果、これら代表的治らい剤の薬効活性スペクトラは、どの検査法においても活性を示した

IDM や TV 1322 の薬効活性とくらべると部分的なものであることが見いだされた。その上, DDS と B 663 はスペクトラに関し相互に対比的で, DDS はカラゲニン急性ラット浮腫や二、三の発痛物質を皮内注した場合の滲出に対し著明に阻止作用を有するに反し, B 663 はアジュバント関節炎を強く, 膜の不安定化を弱く抑制した。これら発見に基づき, 治らい剤の消炎効果と, らい症状へ及ぼす治効との関係が論じられた。