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<th>Protective Effect of Vitamin E against Immunosuppression Induced by Adriamycin, Mitomycin C and 5-Fluorouracil in Mice</th>
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<td>Author(s)</td>
<td>YASUNAGA, TOSHIMI; OHGAKI, KAZUHISA; INAMOTO, TAKASHI; KAN, NORIMICHI; HIKASA, YORINORI</td>
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Kyoto University
Protective Effect of Vitamin E against Immunosuppression Induced by Adriamycin, Mitomycin C and 5-Fluorouracil in Mice

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Introduction

There have been many reports concerning the protective effect of vitamin E against ADR-induced cardiotoxicity\(^2\). It is said that lipid peroxidation may play an important role in ADR-induced cardiotoxicity and that vitamin E functions as free radical scavenger\(^14\,20\).

On the other hand, vitamin E has been shown to have immunostimulatory effects, but nearly all of the reports concern humoral immunity\(^8\,21\) and few concern cellular immunity\(^16\,19\). We manifested that vitamin E stimulated cellular immunity by the method of lymphoproliferative assay in mice\(^25\).

The purpose of the present study is to find out whether coadministration of vitamin E can prevent immunosuppression induced by anticancer agents as measured on the basis of lymphoproliferative assay, regardless of their production of free radicals. We chose three representative anticancer agents utilized clinically, i.e., Adriamycin (ADR), Mitomycin C (MMC) and 5-Fluorouracil (5FU). It is said that ADR and MMC participate in the generation of free radicals and 5 FU does not\(^1\,7\).

Materials and Methods

Animals: 7 to 10-week old male inbred BALB/c mice were purchased from the Shizuoka Agricultural Cooperative Association for Laboratory Animals, and they were fed by commercial solid feed which contains 5 mg of vitamin E/100 g.

Tumor: Meth-A, methylcholanthrene induced fibrosarcoma of BALB/c origin was main-
tained by intra-peritoneal transplantation in adult BALB/c mice. Tumor cells were washed three times and adjusted to desired numbers in RPMI 1640 before implantation. Tumor cells were implanted in the right footpad. The thickness of footpad was measured by calipers and tumor growth was calculated as follows:

tumor growth = the thickness of footpad implanted tumor — the thickness of the opposite footpad.

Chemicals: [dl]α-tocopherol as vitamin E and HCO 60, solvent of [dl]α-tocopherol, as placebo were used. Both were obtained from the Eisai Pharmaceutical Corp., Tokyo. ADR, MMC and 5 FU were obtained from the Kyowa Hakko Co. Ltd., Tokyo. Each was diluted in saline solution to the desired concentration and 0.5 ml was inoculated into the intra-peritoneal cavity (i.p.) or back subcutaneous space (s.c.).

Spleen Cell Preparation: The mice were sacrificed by cervical dislocation and their spleens were removed aseptically. After measuring the spleen weight, single cell suspensions were severally prepared by gently pressing each spleen through a #200 mesh stainless steel screen. Erythrocytes were lysed with Tris-buffered ammonium chloride, and then the spleen cells were centrifuged and washed three times. The single cells adjusted to 5 × 10⁶/ml were resuspended in RPMI 1640 containing 10% heat-inactivated fetal calf serum and 0.1 mg/ml Gentamycin. (Shionogi Pharm. Co. Ltd. Tokyo)

Lymphoproliferative Assay to Mitogens: Cultures were set up in triplicate in Falcon Microtest II No. 3040 microtiter plates (Falcon Plastics Oxnard, Calif. USA). 5 × 10⁵ spleen cells/0.1 ml and 0.1 ml of RPMI 1640 supplemented with 20% fetal calf serum were placed in each well. Purified Phytohaemagglutinin (PHA 0.13 μg/0.01 ml/well: Wellcome, USA) and Concanavalin A (Con A 0.33 μg 0.01 ml/well: Wako Junyaku, Tokyo) were used to assess T-cell responses. Escherichia coli lipopolysaccharide (LPS 3.3 μg 0.01 ml/well: Difco, USA) was used to assess B-cell proliferation. The plates were incubated for 48h at 37°C in 5% CO₂ in a humidified atmosphere. 16hr prior to culture termination, 0.5 μCi of tritiated thymidine (³H-TdR: New England Nuclear, Boston: specific activity 21.8 Ci/mM) was added to each well. After 64hr of culture, the cells were harvested on a glass fiber filter using an automatic multiple cell harvester (LM 101 LABO MAC11: Labo Science Co. Tokyo) and the incorporation of ³H-TdR was determined by a liquid scintillation counter (Isocap 300, Nuclear Chicago Co.). We calculated the mean count per minute (cpm) of the triplicate cultures, and expressed Δcpm as follows.

Δcpm = mean cpm of mitogen stimulated culture of the triplicate — mean cpm of unstimulated culture of the triplicate.

Statistics: We determined the lymphoproliferative assay for each spleen of each mouse respectively, and the mean Δcpm ± standard deviation was calculated from the Δcpm in each experimental group. The results were evaluated by Student’s t-test.

Results

Effect of Vitamin E against Subacute Toxicity induced by ADR.

It is recognized that vitamin E is effective against acute ADR-induced cardiotoxicity. We
studied the effect of vitamin E against daily i.p. injection of ADR in BALB/c mice. 2.5mg/kg/day of ADR was injected i.p. daily until death. 20 IU/kg/0.5 ml/day of vitamin E, its solvent equivalent or 0.5 ml/day of saline solution was also injected i.p. daily including 3 daily pretreatments before ADR inoculation. Each group consisted of 5 mice. As a result, the total doses of ADR received until death were 72.5±14.4 mg/kg in the vitamin E coadministration group, 49.5±11.8 mg/kg in the placebo group (p < 0.05) and 43.5±17.1 mg/kg in the saline solution group (P<0.05). The cumulative mortality and the total doses of ADR received are shown in Figure 1.

Immunopotentiating Effect of Vitamin E.

The various doses of vitamin E, i.e., 5, 10, 20, 40 and 80 IU/kg/0.5 ml/day, placebo equivalent to 20 IU/kg/0.5 ml/day of vitamin E or 0.5 ml/day of saline solution were inoculated i.p. daily for 14 days after which the mice were sacrificed and the lymphoproliferative assay was studied. Each group consisted of 4 BALB/c mice. The lymphoproliferative responses, especially to PHA and LPS, were significantly enhanced in the group treated with 5 to 20 IU/kg day of vitamin E and the serum tocopherol level was elevated to about twice the control in this condition, which was measured from the pooled serum in each group by the method of Kato10. On the other hand, this immunopotentiating effect disappeared in the group treated with 40 IU/kg/day of vitamin E, and the mitogen responses were suppressed contrarily in the group treated with 80 IU/kg/day of vitamin E. The response to Con A showed the similar pattern though not significant. The placebo did not affect the mitogen responses as compared with the control group treated with 0.5 ml of saline solution. The results are represented in Table 1.

Coadministration of Vitamin E and Anticancer Agents.

The possibility of an immunoprotecting effect of vitamin E against anticancer agent-induced immunosuppression was studied in BALB/c mice. We chose ADR, MMC and 5 FU from among clinically utilized anticancer agents. Of these three chemicals, ADR and MMC participated in the generation of free radicals and 5 FU did not.

![Fig. 1](image)

Fig. 1. Survival Percentage Rate after Daily i.p. Injection of ADR. 2.5 mg/kg/day of Adriamycin was injected i.p. daily from day 0 until death. Coadministration of 20 IU/kg/0.5 ml/day of [Dl]α-tocopherol (——), solvent equivalent to it (———) or 0.5 ml/day of saline solution (⋯⋯⋯) was done i.p. daily from day −3 until death. Each group consisted of 5 BALB/c mice. The total doses of ADR received until death was 72.5±14.4 mg/kg in the vitamin E coadministration group, 49.5±11.8 mg/kg (P<0.05) in the placebo group and 43.5±17.1 mg/kg (P<0.05) in the saline solution group.
Table 1. Effect of Vitamin E on Lymphoproliferative Responses

<table>
<thead>
<tr>
<th></th>
<th>PHA</th>
<th>Con-A</th>
<th>LPS</th>
<th>serum tocopherol level (µg/ml)</th>
<th>spleen weight index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>controla)</td>
<td>10222</td>
<td>1938</td>
<td>27010</td>
<td>3.55</td>
<td>4.65</td>
</tr>
<tr>
<td>placebob)</td>
<td>8662</td>
<td>20561</td>
<td>27323</td>
<td>3.48</td>
<td>4.80</td>
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<tr>
<td>5Ec)</td>
<td>28614</td>
<td>42226</td>
<td>50517</td>
<td>5.39</td>
<td>4.62</td>
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<tr>
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<td>52241</td>
<td>40309</td>
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<tr>
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<td>44911</td>
<td>42399</td>
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<td>28909</td>
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<td>3584</td>
<td>20580</td>
<td>1711</td>
<td>21.91</td>
<td>6.37</td>
</tr>
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</table>

a) control: 0.5 ml/day of saline solution.
b) placebo: solvent equivalent to 20 IU/kg/0.5 ml/day of [dl]-α-tocopherol.
c) E: 1 IU/kg/0.5 ml/day of [dl]-α-tocopherol.
d) Blood was drawn from heart and the serum tocopherol level was measured from pooled serum in each group by the method of Kato.
e) spleen weight index was calculated as follows: \( \frac{\text{mean spleen weight (mg)}}{\text{mean body weight (g)}} \)

Various doses vitamin E, solvent or saline solution were injected i.p. daily from day 1 to day 14, and lymphoproliferative assay, serum tocopherol level and spleen weight index were studied on day 15. Each group consisted of 4 BALB/c mice.

\* P<0.1  ** P<0.05  *** P<0.01 (vs. control group)

These chemicals were injected into back s.c. daily for 5 days. 15 IU/kg/0.5 ml/day of vitamin E, its placebo equivalent or 0.5 ml/day of saline solution was injected i.p. for 11 days which consisted of 6 daily pretreatments and 5 daily coadministration. Mice were sacrificed.

Table 2. Protective Effect of Vitamin E against ADR-induced Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>PHA</th>
<th>Con-A</th>
<th>LPS</th>
<th>spleen weight (mg) (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated Control</td>
<td>28136</td>
<td>45445</td>
<td>21914</td>
<td>99.0 ± 1.1</td>
</tr>
<tr>
<td>ADRa)</td>
<td>23005</td>
<td>12568</td>
<td>5667</td>
<td>71.5 ± 3.5*</td>
</tr>
<tr>
<td>+ Saline solutionb)</td>
<td>23005</td>
<td>12568</td>
<td>5667</td>
<td>71.5 ± 3.5*</td>
</tr>
<tr>
<td>ADRc)</td>
<td>25799</td>
<td>15669</td>
<td>7101</td>
<td>71.3 ± 4.1*</td>
</tr>
<tr>
<td>+ Placeboa)</td>
<td>25799</td>
<td>15669</td>
<td>7101</td>
<td>71.3 ± 4.1*</td>
</tr>
<tr>
<td>ADRd)</td>
<td>42122</td>
<td>17758</td>
<td>13233</td>
<td>77.3 ± 4.5</td>
</tr>
<tr>
<td>+ Vitamin Ee)</td>
<td>42122</td>
<td>17758</td>
<td>13233</td>
<td>77.3 ± 4.5</td>
</tr>
</tbody>
</table>

a) ADR: 1.5 mg/kg/0.5 ml/day of Adriamycin.
b) saline solution: 0.5 ml/day.
c) placebo: solvent equivalent to vitamin E.
d) Vitamin E: 15 IU/kg/0.5 ml/day of [dl]-α-tocopherol.
Saline solution, solvent or vitamin E was injected i.p. daily from day 1 to day 11, and ADR was injected into back s.c. daily from day 7 to day 11. Lymphoproliferative assay was studied on day 12. Each group consisted of 5 BALB/c mice.

\* P<0.05  ** P<0.01  *** P<0.001 (vs. vitamin E coadministration group)
Table 3. Protective Effect of Vitamin E against MMC-induced Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>mitogen response (mean Δcpm±S.D.)</th>
<th>spleen weight (mg) (mean±S.D.)</th>
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<tbody>
<tr>
<td></td>
<td>PHA</td>
<td>Con-A</td>
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</table>

a) MMC: 0.5 mg/kg/0.5 ml/day of Mitomycin C.
b) saline solution: 0.5 ml/day.
c) Placebo: solvent equivalent to vitamin E.
d) Vitamin E: 15 IU/kg/0.5 ml/day of [dl]-α-tocopherol.
Saline solution, placebo or vitamin E was injected i.p. daily from day 1 to day 11, and MMC was injected into back s.c. daily from day 7 to day 11.
Lymphoproliferative assay was studied on day 12. Each group consisted of 5 BALB/c mice.

next day and the lymphoproliferative assay was studied. Each group consisted of 5 mice. The results are represented in Tables 2-4. The daily dosages of anticancer agents were decided from about one-twentieth of LD 50 in BALB/c mice, that is, ADR was 1.5 mg/kg/0.5 ml/day, MMC was 0.5 mg/kg/0.5 ml/day and 5 FU was 20 mg/kg/0.5 ml/day.

Vitamin E and ADR

Mitogen responses to PHA, Con A and LPS were significantly suppressed by treatment with 1.5 mg/kg/day of ADR as compared with the non-treated control group. In the group coadministered with 15 IU/kg/day of vitamin, E, response to PHA was significantly enhanced even

Table 4. Protective Effect of Vitamin E against 5FU-induced Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>mitogen response (mean Δcpm±S.D.)</th>
<th>spleen weight (mg) (mean±S.D.)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PHA</td>
<td>Con-A</td>
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</table>

a) 5FU: 20 mg/kg/0.5 ml/day of 5-Fluorouracil.
b) Saline solution: 0.5 ml/day.
c) Placebo: solvent equivalent to vitamin E.
d) Vitamin E: 15 IU/kg/0.5 ml/day of [dl]-α-tocopherol.
Saline solution, solvent or vitamin E was injected i.p. daily from day 1 to day 11 and 5FU was injected into back s.c. daily from day 7 to day 11.
Lymphoproliferative assay was studied on day 12. Each group consisted of BALB/c mice.

* P<0.05 ** P<0.01 *** P<0.001 (vs. vitamin E coadministration group)
compared with the non-treated control group, and immunosuppressions induced by ADR were significantly protected for the response to PHA and LPS, but no effect was recognized for the response to Con A. The loss of spleen weight induced by ADR injection was also protected significantly by coadministration of vitamin E. (Table 2)

**Vitamin E and MMC**

Mitogen response to PHA was significantly suppressed by treatment with 0.5 mg/kg/day of MMC and the suppression was protected by coadministration of vitamin E as compared with the saline solution plus MMC group, but there was no statistical significance between the placebo group and the vitamin E group. Response to Con A was not affected by this dose of MMC-injection as compared with the control and the saline solution plus MMC groups, and there was no effect by coadministration of vitamin E. Response to LPS was suppressed and spleen weight decreased significantly in the group treated with MMC plus saline solution or placebo, but the suppression of response and loss of spleen weight were restored to the control levels by coadministration of vitamin E. (Table 3).

**Vitamin E and 5-FU**

Response to PHA was not affected by the treatment with 20 mg/kg/day of 5-FU in the coadministration of saline solution or placebo group as compared with the non-treated control group, but remarkable enhancement was shown by the coadministration of vitamin E. Response to

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**Fig. 2.** Anti-tumor Effect of ADR for Meth-A.

1.5 mg/kg/0.5 ml/day of ADR was injected s.c. daily for 5 days.

- o-o control group, o-o placebo plus ADR group, o-o vitamin E plus ADR group.

* P<0.05  ** P<0.02 (vs. control group)

**Fig. 2 to 5.** 15 IU/kg/0.5 ml/day of vitamin E or its placebo equivalent was injected i.p. daily from day 1 to day 11. On day 6, 2×10^4/0.02 ml of Meth A tumor was implanted in the right footpad and s.c. injection of ADR, MMC or 5FU was done daily from day 7 to day 11. As the control group, 0.5 ml/day of saline solution was injected i.p. daily from day 1 to day 11 and into back s.c. from day 7 to day 11. Tumor growth was calculated as written in materials and methods, and mean ± S.D. (mm) were shown. Each group consisted of 10 BALB/c mice.
Fig. 3. Anti-tumor Effect of MMC for Meth-A.
0.5 mg/kg/0.5 ml/day of MMC was injected s.c. daily for 5 days.

- o control group, o--o placebo plus MMC group, o--o vitamin E plus MMC group

* P<0.05    ** P<0.02 (vs. control group)

Con A and LPS were strongly suppressed by 5 FU-injection and its suppressions were significantly protected by coadministration of vitamin E. There was a similar tendency but no significance regarding loss of spleen weight due to 5 FU. (Table 4).

Tumor Growth and Coadministration of Vitamin E.

In order to study the influence on tumor growth by coadministration of vitamin E and anticancer agents, BALB/c mice implanted Meth-A tumor were injected with vitamin E and anticancer agents according to the same schedule. That is, 15 IU/kg/0.5 ml/day of vitamin E or its
placebo equivalent was injected i.p. daily from day 1 to day 11. On day 6, $2 \times 10^5/0.02$ ml of Meth A tumor was implanted in the right footpad and daily s.c. injection of 1.5 mg/kg/day of ADR, 0.5 mg/kg/day of MMC or 20 mg/kg/day of 5FU was done from day 7 to day 11. As the control group, 0.5 ml/day of saline solution was injected i.p. daily from day 1 to day 11, and into back s.c. from day 7 to day 11. Each group consisted of 10 BALB/c mice. The tumor growth was measured 2 or 3 times/week by calipers. As a result, tumor growth was significantly inhibited by the treatment with ADR, MMC or 5FU, and furthermore there was a tendency, though not statistically significant, that the anti-tumor effects of these agents were promoted by the coadministration of vitamin E. These tumor growth curves treated with ADR, MMC and 5FU were shown in Fig. 2, 3, 4, respectively. Notably in the group treated with 5FU, 4 mice died earlier perhaps due to 5FU toxicity and the mean survival days were 26.9 ± 9.6 days in the coadministration of the placebo group as compared with 31.6 ± 2.7 days in the control group. On the other hand, in the coadministration of the vitamin E group, 2 mice which rejected the Meth A tumor lived for over 50 days and the mean survival days were 35.9 ± 8.2 days (P<0.05 v.s. placebo group). Vitamin E may allow protection from 5FU toxicity. The survival percentage rates treated with 5FU are shown in Fig. 5.

**Discussion**

Since Myers's report in 1976\textsuperscript{13}, it has been reported by some investigators that the pretreatment of vitamin E is effective for ADR-induced cardiotoxicity and its effect is due to the function of vitamin E as free radical scavenger. Nearly all of the experiments concerned the lethal dosage of ADR, and the optimal dosage or appropriate administration of vitamin E were not defined.
In order to manifest the protective effect against ADR, Wang et al\(^{(23)}\) administered 200 mg/rabbit of \(\alpha\)-tocopheryl acetate translated from the safe human doses of 2 g/adult. This administration increased the serum tocopherol level to about 2-to 4 fold and the cardiac tocopherol level to about 2 fold in rabbits. Breed et al\(^{(26)}\) used 300 mg/kg/day of vitamin E in rabbits, calculated on the basis of studies done by Myers\(^{(13)}\) in mice, and reported that vitamin E did not protect against the development of cardiomyopathy and contractile decline after chronic exposure to ADR. Sonneveld\(^{(18)}\) mentioned that pretreatment with 3200 IU/kg of [dl] \(\alpha\)-tocopherol 24 hours prior to ADR diminished cardiotoxic effects as judged by ECG changes and histologic changes in rats.

From our studies in mice\(^{(25)}\), doses exceeding about 80 IU/kg/day of [dl] \(\alpha\)-tocopherol are toxic in themselves as judged by decreases in body weight, severe weakness and suppression of cellular immunity assessed by lymphoproliferative assay. It is the appropriate dosage of vitamin E which increases the serum tocopherol level to about 2 fold, i.e., 10 to 20 IU/kg/day of [dl] \(\alpha\)-tocopherol in mice as i.p. administration, and 6 to 12 mg/kg/day of \(\alpha\)-tocopheryl acetate in man as peroral administration.

We confirmed that 3 daily pretreatments with 20 IU/kg/day of vitamin E resulted in an increase of survival days in BALB/c mice treated with single back s.c. injection of 25 mg/kg/day of ADR (unpublished data).

On the hypothesis that vitamin E, if administrated appropriately, protects against both subacute and acute cardiotoxicity caused by ADR, we studied the effect of 20 IU/kg/day of vitamin E against daily i.p. injection of 2.5 mg/kg/day of ADR. As a result, a significant increase of lethal doses of ADR was recognized by coadministration of vitamin E (i.e., 43.5 mg/kg in control group, 72.5 mg/kg in vitamin E group). This result suggests that the maximum cumulative doses of ADR may be increased in man by the coadministration of vitamin E.

Tengerdy et al\(^{(21)}\) reported that vitamin E stimulated humoral immunity and enhanced resistance to bacterial infections. Some studies concerning vitamin E and humoral immunity were reported after that\(^{(4,15)}\) but few concerned cellular immunity\(^{(16,19)}\). If vitamin E participated in permeability and stability of cell membrane\(^{(1)}\), as established in erythrocyte\(^{(17)}\), the same function may be expected to the lymphocyte membrane in the character of potentiator to cellular immunity. Our results that mitogen responses are enhanced by the daily treatment with 5 to 20 IU/kg/day of vitamin E and anticancer agents-induced immunosuppression are protected by the coadministration of vitamin E reveal the function as stimulator or protector of cellular immunity. In addition, it is characteristic that mitogen responses to PHA and LPS are more enhanced or protected than those to Con A by the treatment with vitamin E.

These effects may be resulted from its function as free radical scavenger\(^{(20)}\) or contribution to membrane permeability and stability of lymphocyte\(^{(11)}\). However ADR and MMC are quinone-containing drugs, and interact with microsomes and function as free radical carriers\(^{(15)}\). 5 FU does not participate in the generation of free radicals. Vitamin E protected against the immunosuppression and loss of spleen weight induced by these three anticancer agents regardless of their free radicals participation. On the other hand, there is a probability that vitamin E
stabilizes the tumor cell membrane if it act as membrane stabilizer. Tumor growth were significantly inhibited by the treatment of ADR, MMC or 5 FU, and further there was a tendency that the antitumor effects of these three agents were promted by the coadministration of vitamin E from our studies in BALB/c mice implanted with Meth-A tumor. It was particularly effective in the group treated with 5 FU.

Prostaglandin E₂ may participate in this phenomenon, because it has been recognized that prostaglandin E₂ induces the suppressor T cell⁶ and vitamin E inhibits the biosynthesis⁹. Further examination are necessary to elucidate this problem.

Vitamin E is generally considered to be relatively non-toxic at high doses in spite of being fat-soluble vitamin⁵. In addition, the appropriate dosage to manifest the immunoprotective effect is 300 to 600 mg/day of α-tocopheryl acetate as tablets in man as emphasized in this report, and there is no apparent toxicity under the treatment with 100 to 800 IU of vitamin E daily for a period of three years⁵. We have applied vitamin E clinically in cancer therapy and obtained good preliminary results in immunological studies similar to this experimental data.

Acknowledgement

The authors wish to thank Dr. HITOSHI KATO who measured the serum tocopherol levels, and the staffs of 17th Laboratory of Surgical Department, Kyoto University. We also wish to thank Miss AIKO TAMAKI for her fine technical assistance and Miss AKIKO SHIRA for her preparation of this manuscript.

References


和文抄録
アドリアマイシン，マイトマイシンC，5-フルオロウラシル投与によって生ずる免疫抑制に対するビタミンEの効果—マウスを用いた実験的考察—

京都大学医学部外科学教室第2講座（主任：日笠顕則教授）

安永 敏美，大垣 和久，稲本 俊，菅 典道，日笠顕則