

CANCER CONTROLLING EXPERIMENTS WITH ANTI-CANCER DRUG EMULSIONS AND INFLAMMATION CAUSATIVE POLYSACCHARIDES

by

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INTRODUCTION

A number of anti-cancer drugs have been reported. However, none has yet been proved to give conclusive therapeutic effects which are enough to take the place of surgical operations.

The purpose of this research is not to compare the effect of these anti-cancer drugs, but to clarify the following two points :

- 1) Is it possible to intensify the therapeutic effect of the anti-cancer substances, by administering in the form of emulsion?
- 2) Is it surely possible to arrest the growth of cancer by using starch grains and bacterial polysaccharides?

EXPERIMENT I

(I) Experiment Preparing Emulsion of Anti-Cancer Drug

It is presumed that, if certain anti-cancer drugs are given as a form of emulsion, their absorption may be much slower than when it is given as an aqueous solution. Therefore, the toxicity of the drug can be lowered, and it may be convenient to keep the effective blood concentration for considerable period of time.²²⁾³⁰⁾ If this presumption is acceptable, the same principle may be applied widely to any drug, though, at the present, only certain drugs could be used as a form of *dépot* to prolong the effective period.

1) Materials and methods

For the preparation of emulsion,¹⁶⁾ 7 volumes of liquid paraffin, 3 volumes of aqueous solution of drugs, and a small amount of Tween 80, the surface active agent, were used. At first, Tween 80 was put into a glass homogenizer, a stirring rod was connected to a motor, then stirring was done for 3 minutes with 2000 rotations per minute. Following this, the stirring was continued while liquid paraffin was added gradually until the contents became pasty. 3000 to 4000 rotations per minute of stirring is necessary for about 10 minutes. This pasty content is hot, due to friction heat, therefore, it had to

be cooled down to room temperature, and then, aqueous solution of the drug was mixed gradually, while still stirring, to make the emulsion. By this method, the emulsion obtained will be stable for at least 7 days in an incubator of 37°C. The size of particles in emulsion is between about 0.2 μ to 50 μ in diameter¹⁶⁾ (Photo. 1).

Next, in order to see the state of particles in the emulsion when it is diluted by water, 0.2cc of this emulsion was injected intraperitoneally into mice in which EHRlich ascites carcinoma had been transplanted, when a sufficient accumulation of ascites was noted 6 days after the transplantation. Then, ascites were drawn out periodically, and particles of the emulsion were examined microscopically.

In order to study the concentration of absorption in the blood and the urine of these emulsions and aqueous solutions, a healthy adult dog which weighed 10kg was given 5 drops of LUGOL's solution for 5 days, to block effect to the thyroid gland; then an emulsion which contained 30 μ c of I¹³¹ was injected⁴⁾ into the gluteal muscles. 1 cc each of blood was taken periodically, from the left femoral vein and I¹³¹ concentration in the blood was measured with a scintillation counter. At the same time, all the urine was obtained periodically and counted its activity in the same manner. For the control study, 30 μ c of I¹³¹ aqueous solution was injected into the same dog on later days, and blood concentration and urinary excretion rate of I¹³¹ were measured in the same manner.

Next, in order to see the effect of repeated injections of this emulsion, a healthy adult dog which weighed 12kg was injected intramuscularly with 30 μ c of I¹³¹ daily for two days with the emulsion and the aqueous solution. The periodic blood concentration of I¹³¹ was determined and this was compared to the previous study.

In order to observe the drug concentration in the body fluid at the site of injection when drug was injected into a body cavity in a form of emulsion, Ehrlich ascites carcinoma was transplanted into mice intraperitoneally and after 6 days, when the ascites accumulation was found to be enough, 5 μ c each of I¹³¹ emulsion was injected intraperitoneally to 3 mice. As for the control group, 5 μ c each of I¹³¹ aqueous solution was given to 3 other mice in the same way. In each case, ascites were withdrawn periodically by punctures and the radioactivity of each sample was measured.

The concentration of drug in the body fluid at the site of injection, when repeated injections of this emulsion were given, was next examined. 10 μ c of I¹³¹ each of emulsion were given daily for two days to mice already transplanted with EHRlich ascites carcinoma. 10 μ c of I¹³¹ each was given in aqueous solutions for control group, and the radioactivity of ascites was measured.

In order to see the accumulation of given emulsion in lymphnodes, 10 mice were given an intraperitoneal injection of 10 μ c of I¹³¹ each after the transplantation of Ehrlich ascites carcinoma. Two mice on each occasion, were killed periodically and sternal lymphnodes were obtained from each of them. Certain portions of them were weighed, and their radioactivity determined. Also 10 other mice were given 10 μ c each of I¹³¹ aqueous solution, as the control group, and examined in the same way.

For the measuring of the radioactive I¹³¹, a well-type scintillation counter was used. To minimize any error in measuring, a certain amount of I¹³¹ in emulsion and in aqueous solution were prepared for the control, and solution of Co⁶⁰ (0.025 μ c) was used as

standard in the measurement of samples.

2) Results

When one sees with a microscope, what became particles of the emulsion in the ascites of mice transplanted with EHRlich ascites carcinoma, the number of particles decreased gradually as time passed and remaining particles were more easily broken down; but there were still a fair number of particles even 24 hours after the injection.

As for the blood concentration and the urinary excretion rate of the emulsion in a dog (Fig. 1 & 2), when emulsion was injected intramuscularly, the blood concentration

Fig. 1

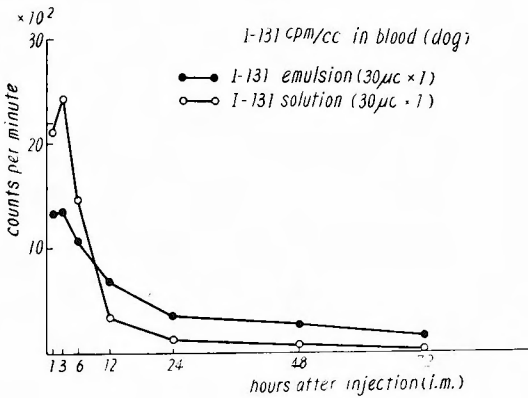
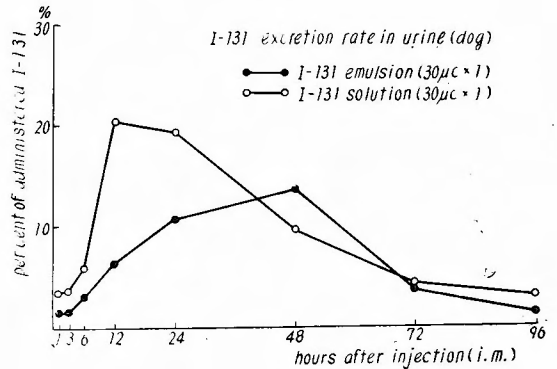
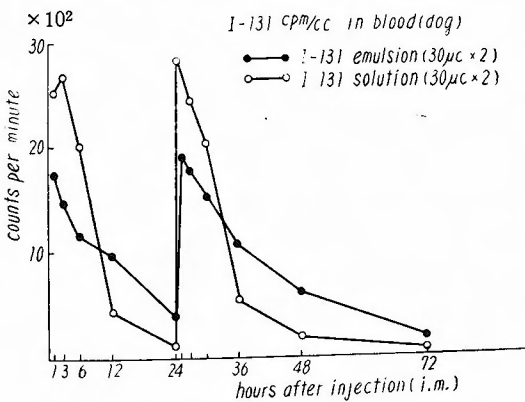


Fig. 2



retained a fairly high level, comparing the case of aqueous solution, even 24 hours after the injection. The decrease of concentration is much slower in the former. On the other hand, the urinary excretion rate of I¹³¹ was 60% of the given amount in 24 hours when it was given as the aqueous solution, but only 27% in the case of emulsion. In the case of repeated intramuscular injections of emulsion to dogs (Fig. 3), the blood concentration,

Fig. 3



I¹³¹ after 12 hours of injection, but there was a remarkable decrease in the group to which aqueous solution was given. In the case of repeated injection (Fig. 5), as in the

same as when it was given only once, decreased slower than it was given in the aqueous solution and retained a considerably high level in each sample of 12 hours, 36 hours, and 48 hours following the injection.

Ascites from EHRlich ascites carcinoma transplanted mice was chosen to examine the drug concentration in the body fluid at the site of injection when the emulsion was injected into a body cavity²⁴⁾ (Fig. 4). The group into which the emulsion was injected retained a considerable amount of

a remarkable decrease in the group to which aqueous solution was given. In the case of repeated injection (Fig. 5), as in the

case of one injection, there was more I^{131} in ascites in the emulsion group than the aqueous group, showing the absorption of I^{131} is slower in the former case.

Fig. 4

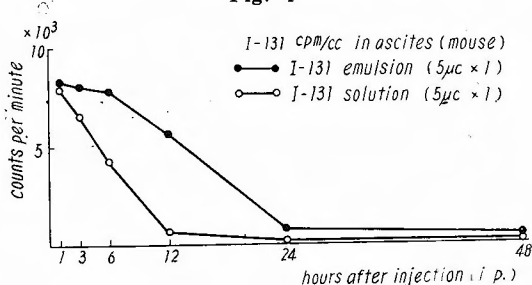
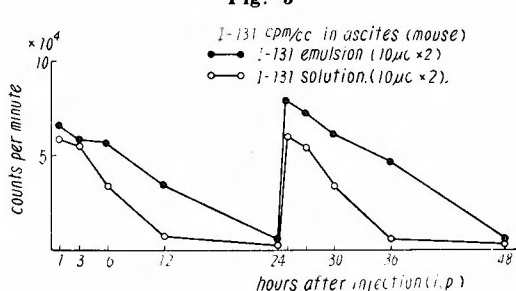


Fig. 5



Of the accumulation of emulsion particles in lymphnodes of EHRlich ascites carcinoma transplanted mice (Fig. 6), the radioactivity of sternal lymphnodes was always larger in the emulsion given group than in the aqueous solution given group.

3) Comments

Using I^{131} as an indicator, we took into consideration the blood concentration and urinary excretion rate of emulsion in dogs and also the decreasing rate in ascites and the activity of regional lymphnodes to the given emulsion in mice. As a result, when drugs were given in the form of emulsion, the absorption and the excretion were slower than when they were given as aqueous solution. It was also found that the emulsion conveniently retains certain concentration in the body; it was likewise presumed that there was a tendency of the accumulation of emulsion into the regional lymphnodes.

(II) Experiments on Cancer Control

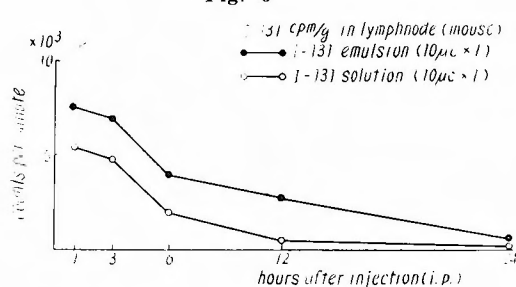
From above preliminary experiments concerning emulsion, it is convenient to have certain concentration retained in the body and subsequently, to give continuous treatment for cancer, if anti-cancer substances were given in the form of emulsion. Moreover, it is considered that, since the emulsion has a tendency to accumulate in regional lymphnodes, it will have a better effect on the treatment of malignant neoplasms. With these presumptions, the following animal experiments and clinical experiments on cancer control were attempted.

(A) Animal experiments

1) Materials and methods

As for anti-cancer substances, radioactive P^{32} , Mitomycin C and Trespamin were selected, and each were made into emulsion preparations; then, the anti-cancer effects of these preparation were compared. Used P^{32} was imported from England as diluted hydrochloric acid solution of orthophosphoric acids.⁴⁾ Mitomycin ($^{14}28$) is an anti-cancer drug which was separated and prepared from a culture filtrate of a new actinomyces strain by Dr. HATA et al. in KITAZATO Research Laboratory. And this substance is

Fig. 6



presumed to arrest cancer cell divisions by inhibiting, D. N. A. synthesis specifically. LD₅₀ of Mitomycin C in the intraperitoneal injection to mice is 5.2mg/kg. Tespamin⁵⁾ (Thio-TEPA) is an alkyl preparation with active ethylene imine link and reacts on active hydrogen of radicals such as -SH, -NH₂, -COOH etc. which are in nucleic acids or other ground substances that participate in the metabolism of tumor cells, and it is considered that it will inactivate metabolically the hydrogen. The LD₅₀ of Tespamin in the intraperitoneal administration is 17mg/kg.

Female mice of d-d strain, 40 to 50 days old, weighing about 20 grams were selected for the experiment. 8 mice were set as a group and a control group was set for each experiment. EHRLICH ascites carcinoma was used as the tumor and 1,000,000 cancer cells were transplanted intraperitoneally into each mouse.

Cancer control experiments were usually started on the 5th day after the tumor transplantation, that is when cancer cells in ascites are in a purely cultured state. All drugs used were directly injected into the peritoneal cavity. The amount of administration was 0.1cc each at a time both in the emulsion and in the aqueous solution and each drug was used without any combination.

For criteria of cancer control effect, the surviving effect⁽¹²⁾⁽²⁹⁾⁽³¹⁾ was taken as the first mark, then combined were the appearance of the distension of abdomen due to ascites accumulation²⁹⁾, the increase of body weight¹⁷⁾ and cell finding in smear preparations stained with Giemsa stain which were obtained from ascites aspiration³¹⁾ periodically.

The emulsion was made with 7 volumes of liquid paraffin, 3 volumes of physiological saline solution and a small amount of Tween 80. 0.1cc of it was injected intraperitoneally into the healthy d-d strain mice, once daily for 14 days, and all of them lived well. Thus it is confirmed that this emulsion itself had no toxic effect at all.

2) Results

(1) Mitomycin C administered group

(From now on, Mitomycin C will be abbreviated as Mit. C, Emulsion as Emul. and aqueous solution as Sol.)

(i) Group I : Mit. C Emul. 10γ 7 times every 24 hours.

Group II . Mit. C Sol. 10γ 7 times every 24 hours.

Group III : Mit. C Emul. 20γ 3 times every 48 hours.

Group IV : Mit. C Sol. 20γ 3 times every 48 hours.

Group V : Mit. C Emul. 40γ once.

Group VI : (Control). Emulsion with physiological saline sol. 0.1cc 7 times every 24 hours. (This emulsion was made with 3 volumes of physiological solution, 7 volumes of liquid paraffin and Tween 80.)

As is shown in the figure (Fig. 7 & 7'), the vertical axis represents the survival rate in percent and the horizontal axis represents the number of days following to the tumor transplantation.

The 50% survival period of the control group was 12 days, but in contrast to this, the 50% survival period of Group I was 39 days, and 33 days in Group II. Moreover, all the control groups died of tumor in 9 to 16 days after the transplantation, but in Group I, 3 out of 8 mice and in Group II, one out of 8 mice survived. Retransplantation

Fig. 7

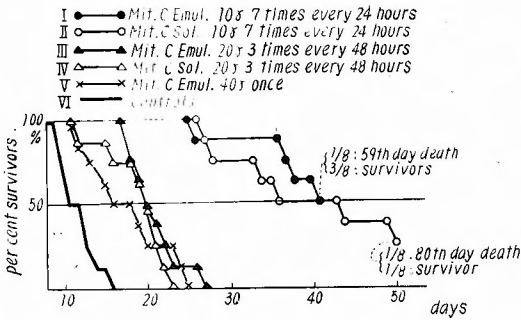
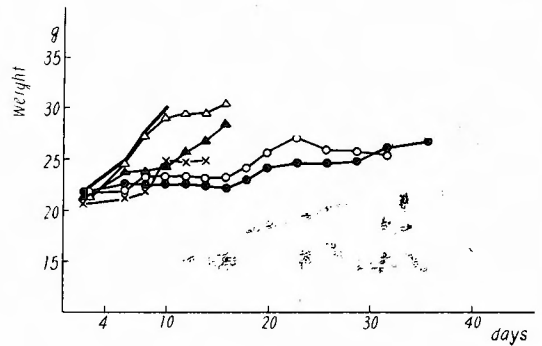


Fig. 7'



was done to all these survivors, 100 days after the first tumor transplantation, and that there were no insusceptibility in animals was ruled out.

The accumulation of ascites was estimated by measuring the mean body weight, compared to the control group, and there were marked inhibitory effects of the ascites accumulation both in group I and II.

The 50% survival period in Group III and IV was 20 days and they all died of tumor. The inhibitory effect on ascites accumulation was noted in Group III but not in Group IV. A large amount of injection was given to Group V, but there were only 5 days of 50% survival period increase and no inhibitory effect on ascites accumulation was recognized. They all died of tumor.

(ii) Group VII: Mit. C Emul. 10γ 7 times every 24 hours.

Group VIII: Mit. C Sol. 10γ 7 times every 24 hours.

Group IX: (Control). Emul. with physiological saline sol. 0.1cc 7 times every 24 hours.

(All started 48 hours after tumor transplantation)

Fig. 8

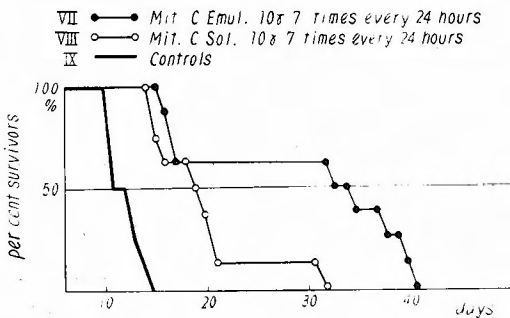
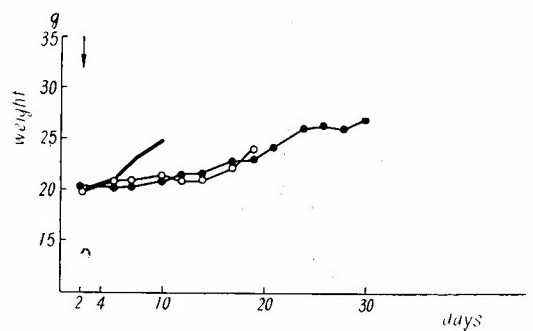


Fig. 8'



In Group VII, VIII and IX (Fig. 8 & 8'), the administration of drug was started 48 hours after tumor transplantation and intended to make a comparison to Group I and II in which drugs were given 4 days after the transplantation and showed a marked cancer control effect. The control group all died of tumor in 10 to 15 days and its

50% survival period was 12 days. The 50% survival period was 34 days in Group VII and 20 days in Group VIII. In neither group, contrary to presumption, none survived. But there was a marked inhibitory effect of ascites accumulation.

(iii) In the cytological study of ascites (Photo. 2 & 3), in the Group I and II in the Giemsa stain preparation of ascites, at first on the second day (6 days after the transplantation) of Mit. C Emul. administration (Photo. 4), the number of cancer cells was smaller than that of the control group and there was no grouping of cells. No ordinary cell division was seen. And there were a considerable number of polynucleic cells. All cancer cells were generally and fairly swollen, and there were found the pictures of degeneration, such as vacuole formation, small processes of cytoplasm, and even the collapse of cells in some parts. On the fourth day of administration of drugs (Photo. 5), there were more collapsed cells, and polynucleic cells increased. On the tenth day (Photo. 6), nearly all the cells were either collapsed or about to collapse, and no cell division was found. When aqueous solution was given (Photo. 7), same as in the case of emulsion, the cell collapse was increased and polynucleic cells were increased as time passed. There was no appreciable cytological difference between cases of Mit. C emulsion and aqueous solution.

(2) P^{32} administered group

(i) Group I: P^{32} Emul. $5\mu\text{c}$. 3 times every 48 hours.

Group II: P^{32} Sol. $5\mu\text{c}$. 3 times every 48 hours.

Group III: P^{32} Emul. $20\mu\text{c}$. once.

Group IV: P^{32} Sol. $20\mu\text{c}$. once.

Group V: (Control). Normal saline Emul. 0.1cc 3 times every 48 hours.

Fig. 9

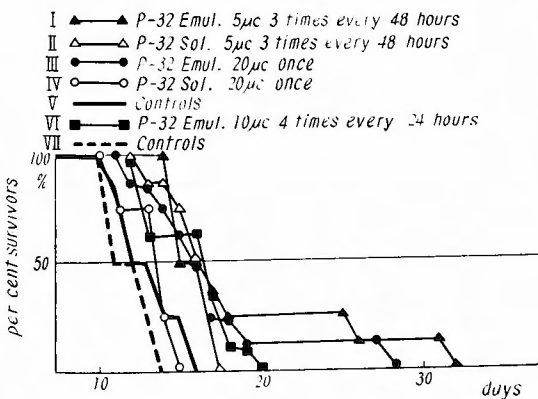
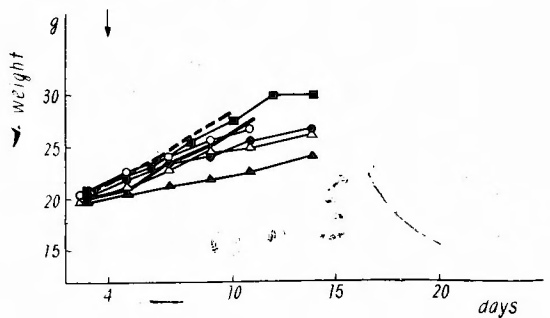


Fig. 9'



The control group all died of tumor in 10 to 16 days (Fig. 9 & 9'). 50% survival period was 13 days. In Group I and II, there was only 4 days more of 50% survival period against the control group. So, there was nearly no increase of survival period. The inhibition to ascites accumulation was noted in Group I. In Group III, there was 4 days more of 50% survival period but none in Group IV. There was no actual effect on survival period in Group III and IV, and there was also no inhibition to ascites accumulation.

(ii) Group VI: P^{32} Emul. $10\mu\text{c}$ 4 times every 24 hours.

Group VII: (Control). Normal saline Emul. 0.1cc 4 times every 24 hours.

50% survival period of the control group (Fig. 9 & 9') was 12 days and there were 6 more days increase of 50% survival period in Group VI. There was no inhibitory effect on ascites accumulation.

(iii) The cytological findings in Group VI was as follows: 2 days after the P^{32} Emul. administration (6 days from tumor transplantation) (Photo. 8), the number of cells was somewhat decreased and there was no grouping of cancer cells which was seen in the control group, but cell divisions were noted in some part. There was no appearance of polynucleic cells. In some of the cancer cells, signs of slight degeneration were noted showing small vacuole formations or mild swellings of cell body. Ten days after the initial drug administration (Photo. 9), most of the cancer cells showed a normal form and on the 16th day (Photo. 10), they also had cancer cell groupings and cell divisions. That is, cytologically speaking, P^{32} arrested the growth of cancer cells up to a certain degree, but it did not cause severe damage to cells as it was seen in Mitomycin C.

(3) Tespamin administered group

Group I: Tespamin Emul. 30γ 7 times every 24 hours.

Group II: Tespamin Sol. 30γ 7 times every 24 hours.

Group III: (Control). Normal saline Emul. 0.1cc 7 times every 24 hours.

All of the control group died of tumor in 8 to 15 days and 50% survival period was 11 days (Fig. 10 & 10'). There were only 4 days each of increase of 50% survival period in Group I and II, but 25% survival period was 21 days in Group I against 14 days in the control group which showed a considerable increase of survived days. There was no inhibition to ascites accumulation in any of these groups. The cyto-

Fig. 10

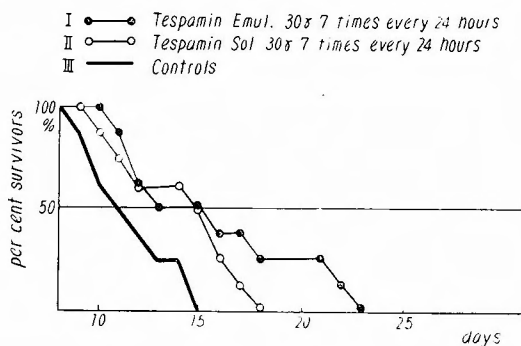
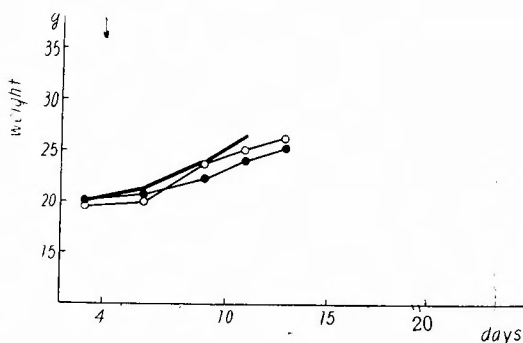


Fig. 10'



logical findings (Photo. 11) were nearly same in both groups and there was only partial and mild degeneration of cells.

(B) Experiences in the clinical application

The emulsion was prepared mixed with Mit. C $1\sim 2\text{mg}$ and P^{32} $1\sim 2\text{mc}$ and this was injected directly into the tumor of several patients who had cancer of the breast.

In all cases, 2 to 5 days following the injection, the removal of tumor and axillary lymphnodes was performed. In the same manner, another case of cancer of the breast

was selected as a control and mixed aqueous solution of Mit. C and P^{32} was injected to the tumor before the operation. Tumors and lymphnodes in each case were studied and pathological findings of these were compared to the others. Histologically, in the tissue of breast cancer, surrounding the portion where drugs were directly injected (Photo. 12 & 13), severe necrosis of tumor cells and stroma were observed, both in the case of emulsion and aqueous solution. But toward the peripheral portion, apart from the site of injection, normal tumor structures were preserved and there was no histological difference in the effect of these drug preparations to the tumor itself (Photo. 14 & 15).

However, there was a considerable difference in histological findings of lymphnodes between the case of emulsion and aqueous solution. That is, in the case to which emulsion was injected, the entire lymphnodes showed a considerable degree of degeneration, and hemorrhage and inflammatory reaction were also noted (Photo. 16 & 18); but in the case to which aqueous solution was used, lymphnodes preserved their structure fairly well and there was no degeneration (Photo. 17 & 19).

(III) Considerations

When anti-cancer agents are used in the treatment of malignant tumor, these agents are expected to have a selective collection in the tumor, through the abnormally increased metabolic processes of these tumor tissue.³⁾²⁷⁾ When these drugs are directly administered into a body cavity or the tumor, it is especially desirable that they meet the following conditions: first, they should stay in the tumor for a long time with high concentration; and there should be the necessary concentration in the regional lymphnodes; and also, they should retain an effective concentration in the blood for a certain period.

Anti-cancer agents in use at the present time, however, have no such satisfactory selective metabolic incorporation with the malignant tumor tissues.

For the purpose of local application, colloidal radioactive isotopes, such as radiocolloid gold or chromic phosphate, have been used; however, there is difficulty in keeping them all the time, because of their short half-life and the expense involved.

We prepared the emulsion adding a relatively simple process to an arbitrary anti-cancer agent and used them expecting as much as the higher concentration of drugs in cases of tumor. At the same time, we expected that these drugs would be taken in with high concentration to a wide area of serosal surface or regional lymphnodes through the local reactive vital phenomena such as phagocytosis by histiocytes. In other words, this is a more surgical way of anti-cancer agent administration than the way which had been applied.

Anti-cancer agent Mitomycin C and Tespamin, radioactive isotope P^{32} were prepared as emulsions. Each case was compared with the effects when aqueous solution was administered to each of these. As a result, when these drug were used as emulsions, they had larger anti-cancer effect than when they were used in aqueous solutions. Clinically, from the view point of histological findings of axillary lymphnodes in the patient of breast cancer to whom local injection of these drugs were given, there was a marked degeneration in cases where emulsion had been used. Considering the higher radioactivity in lymphnodes of mice treated with I^{131} emulsion than mice treated with I^{131} aqueous solution, it is considered that emulsion is collected into lymphnodes relatively well.

EXPERIMENT II

The effects of inflammatory reaction on cancer growth ;

STEWART¹¹⁾ reported a case of uterine myosarcoma who developed high fever and generalized urticaria of unknown cause, and when these symptoms were subsided the tumor rapidly became smaller and this patient lived for 11 more years. In our department, we experienced a similar case : a patient who had cancer of the pancreas and developed similar episodes with marked regression of the tumor.¹⁵⁾ For the explanation of these phenomena we studied the effect of starch grains and bacterial polysaccharide on the growth of EHRLICH ascites carcinoma.

(I) Starch Grains

(A) Positive chemotactic reaction⁹⁾¹⁰⁾ of polynucleic leukocytes ;

Positive chemotactic reaction of polynucleic leukocytes against starch grains was studied.

1) Materials and methods

A thin piece of frog spleen was put in the depression glass then physiological saline solution was added as medium.

At first, powder of arrowroot as starch grains was smeared lightly and dried on the inner surface of a deck glass. Then, the depression glass was covered with this deck glass and left in room temperature for one hour and a half. As the control, the same procedure was carried out with the deck glass, but with no starch grains, and left also one hour and a half. Both cultured contents were studied with a phase contrast microscope.

Next, at one corner of the depression glass, a piece of thin frog spleen was placed and a tiny glass tube was put in the other corner. To this glass tube, the mixed solution of ascites from EHRLICH ascites carcinoma transplanted mice and physiological saline solution, and powder of arrowroot as starch grains were filled in. As for the control, a similar thing, but which does not contain starch grains, was prepared. Both were put in physiological saline solution as the medium and kept in room temperature for 50 minutes : then contents were studied with a phase contrast microscope.

2) Results

When starch grains were smeared on deck glass, many leukocytes which moved out from the spleen into the medium appeared around the smeared starch grains (Photo. 20). But in the control in which starch grains were not smeared, only very few leukocytes were seen (Photo. 21).

Then, when starch grains were put into a small glass tube, there was around the opening of the tube, a collection of many leukocytes which had emerged (Photo. 22) : but in the control only a few leukocytes appeared (Photo. 23).

(B) Anti-cancer experiments

1) Materials and methods

Arrowroot was used as starch grains. The size of each grains was between 50μ to 500μ in diameter. Before use, the starch grains were drily sterilized in 150°C for one hour, and just before the injection, 15% suspension of it was prepared with RINGER's solution.

D-d strain mice, females, weighing 20 grams, were used. EHRLICH ascites carcinoma, 1,000,000 cancer cells to each mouse, was transplanted. 8 mice were set in one group and intraperitoneal injections were started on the 5th day of tumor transplantation. For the criteria of anti-cancer effect, survival period, accumulation of ascites and Giemsa stained ascites smear preparation findings were examined.

This starch grain preparation was also injected intraperitoneally into healthy mice, 0.2cc, 7 times every 24 hours, but no appreciable side effect developed.

2) Results

(i) Group I : Starch grains 0.2cc 7 times every 24 hours.

Group II : (Control). RINGER's solution 0.2cc 7 times every 24 hours.

All in control group died of tumor in 10 to 15 days after the transplantation, 50% survival period was 12 days (Fig. 11 & 11'). The 50% survival period was 4 days longer in Group I but all of them died in 20 days after the transplantation of tumor. After about the second starch grain injection, generally, mice became inactive, lost their appetite and became emaciated. After injections were completed, gradually they grew

Fig. 11

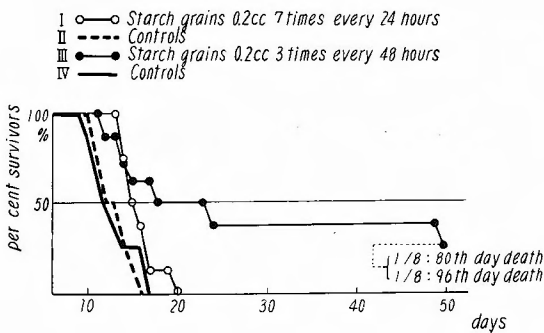
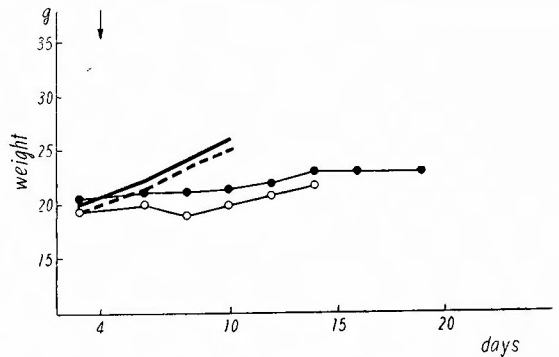


Fig. 11'



active, but at the same time, the accumulation of ascites became eminent.

(ii) Group III : Starch grains 0.2cc 3 times every 48 hours.

Group IV : (Control). RINGER's solution 0.2cc 3 times every 48 hours.

In Group III, there was no emaciation as was seen in Group I (Fig. 11 & 11'). They were all well and accumulation of ascites also was inhibited while injections had been given. Even after the completion of injection, there was inhibition of ascites accumulation and 50% survival period was nearly twice as much as that of the control group: 23 days in Group III against 12 days in the control group. 3 mice out of 8 in Group III survived for 50 days, 80 days and 96 days each. In these long survival cases, ascites accumulations were remarkably inhibited while they were living, and in only a few days before their death, ascites accumulation reached a high grade rapidly.

(iii) Giemsa stained ascites smear preparations in Group III were studied microscopically (Pho. 24). After the second injection of starch grains (7th day of tumor transplantation), the number of cancer cells was small and there was almost no cell division. Cells underwent generally mild degeneration and thus the growth of cancer cells was

arrested. Starch grains were scattered among cancer cells, and many polynucleic cells had moved out and were gathering around the starch grains.

(II) Bacterial Polysaccharide

1) Materials and methods

The original filtrate from *Bacillus Coli Communior* was used as bacterial polysaccharide. Anti-cancer experiment was carried out with d-d strain mice, 20 grams of weight, which were transplanted with 1,000,000 EHRLICH ascites carcinoma cells each. 8 mice were set in one group, and 0.1cc of preparation was injected intraperitoneally starting on the 5th day of tumor transplantation.

2) Results

(i) Group I : Bact. Polysaccharide 0.1cc 14 times every 24 hours.

Group II : Bact. Polysaccharide 0.1cc 7 times every 24 hours.

Group III : (Control). Physiological saline 0.1cc 7 times every 24 hours.

All in the control group died of tumor in 10 to 15 days of transplantation (Fig. 12 & 12'). 50% survival period was 12 days. In Group I and II while injection had been continuing, there was inhibition of ascites accumulation which had gone well, but

Fig. 12

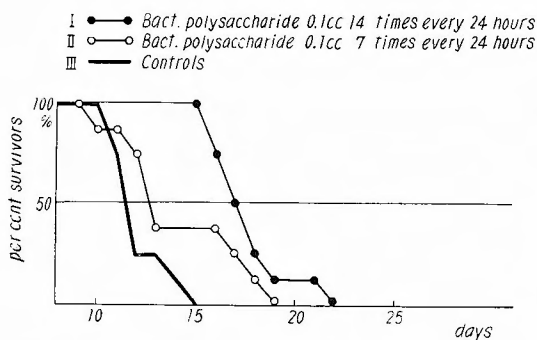
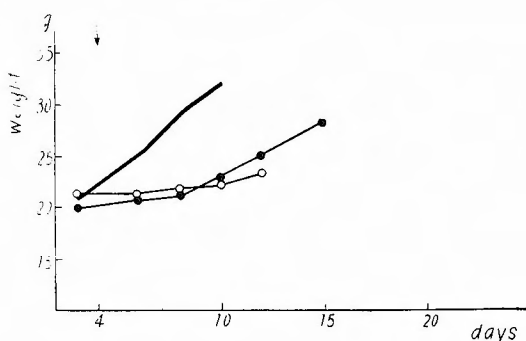


Fig. 12'



after the completion of injection, there was a rapid ascites accumulation and all died. In few cases, there was a high grade of ascites accumulation, even while injections was being carried on.

(ii) Cytological findings of ascites of Group I on the 6th injection (10 days after the transplantation) revealed that generally, the number of cancer cells became small and few polynucleic cells appeared (Photo. 25). Though there were some cancer cells with a degenerative change, on the other hand, cell divisions were also seen and thus in this case, the arrest of cancer cell growth was seemingly, not so remarkable.

(III) Considerations

In the process of malignant neoplasm, a spontaneous regression or a disappearance of tumor and a marked remission of symptoms by unexplainable causes have been reported by STEWART¹¹⁾, IMAI¹⁵⁾, LEVIN¹⁸⁾, MORTON²¹⁾ and PENNER²³⁾. McCARTY¹⁹⁾, MOORE²⁰⁾ and BLACK⁶⁾⁷⁾⁸⁾ had discussions on the relationship between the postoperative survival period and pathological picture of cancer of stomach, breast, and rectum, and mentioned that the higher the degree of lymphatic cell infiltration into cancer nests exists, the prognosis

is better. YOSHIDA³¹⁾ made an observation in an animal experiment, that in a case of intraperitoneal transplantation of YOSHIDA's sarcoma, which was insusceptible to certain animals, there was a continuous moving out of neutrophilic leukocytes and macrophages (monocytes) into ascites and their infiltration was remarkable. He also mentioned that this is a picture of inflammation of ascites sarcoma. We selected starch grains and bacterial polysaccharide as the substance which induce an adequate inflammatory reaction to the animal body. And we administered them intraperitoneally to mice which had been transplanted with EHRLICH ascites carcinoma. We made a study of what may be the effect of the change in the body fluid, in association with inflammation over the growth of cancer.

ROBERT and C. G. GRAND⁹⁾¹⁰⁾ reported that when starch grains are injected into the tumor, a marked collection of leukocytes developed around the tumor and this collection definitely disturbed the growth of the tumor and then by the aseptic necrosis and its absorption, the tumor became necrotic and regressive. PAVLOVSKY and WIDAKOWICH¹⁰⁾ mentioned that when leukocytes accumulation developed, eosinophilic cells have a destructive action on tumor cells. We prepared 15% arrowroot suspension of RINGER's solution as starch grains and injected it intraperitoneally into EHRLICH ascites carcinoma transplanted mice, and observed the appearance of many polynucleic cells in ascites and inhibition of cancer cell growth. Thus, considerable increase in survival period was obtained.

Next, according to ALGIRE et al.¹⁾²⁾ (1947, 1952), they produced necrosis of tumor (L-Sarcoma, Sarcoma 37) by intraperitoneal injection of bacterial polysaccharide and mentioned that this is due to anemia and circulatory disturbances caused by hypotension.

YOSHIDA³¹⁾ obtained a good therapeutic effect to YOSHIDA's sarcoma by direct intraperitoneal injection of bacterial culture filtrate, but mentioned that the mechanism is still unknown.

We made continuous intraperitoneal administration of 0.1cc daily of bacterial polysaccharide prepared from *Bacillus Coli Communior* to EHRLICH ascites carcinoma transplanted mice for 7 days and 14 days. While the injection was being given, there was some degree of inhibition to ascites accumulation and seemingly, acting as anti-cancer substance. However, soon after the completion of administration, they developed ascites accumulation and died. Therefore, its anti-cancer effect is seemingly, not as powerful as starch grains.

It is quite noteworthy that we can arrest the growth of EHRLICH ascites carcinoma in certain degree by changing the general and local internal circumstances, using substances such as starch grains or bacterial polysaccharide which seem to have no direct effect on cancer cells.

EXPERIMENT III

On the combined administration of anti-cancer agents ;

An attempt was made to accelerate the anti-cancer effect by several ways of the combined administration of anti-cancer agents which were used alone in Experiment I and II.

1) Materials and methods

Emulsion and aqueous solution of Mitomycin C, P¹² emulsion, starch grains (15%

arrowroot RINGER's solution suspension) and bacterial polysaccharide (filtrate obtained from *Bacillus coli communior*) were used in different combinations. As for the animals, d-d strain, female mice with 20 grams of body weight were used. 8 mice were set in one group and each were given 1,000,000 EHRLICH ascites carcinoma cells transplantation. Drug administration was started on the 5th day of transplantation and criteria of anti-cancer effect was set on the change in survival period, the accumulation of ascites and the findings of Giemsa stained ascites smear preparations.

2) Results

(i) Group I : P^{32} Emul. $10\mu\text{c}$ with Mit. C Emul. 10γ 4 times every 24 hours then followingly, Mit. C Emul. 10γ 3 times every 24 hours.

Group II : (Control). Physiological saline 0.1cc 7 times every 24 hours.

All in the control group died of tumor in 9 to 16 days. 50% survival period was 12 days (Fig. 13 & 13'). The 50% survival period in Group I was 20 days, and there

Fig. 13

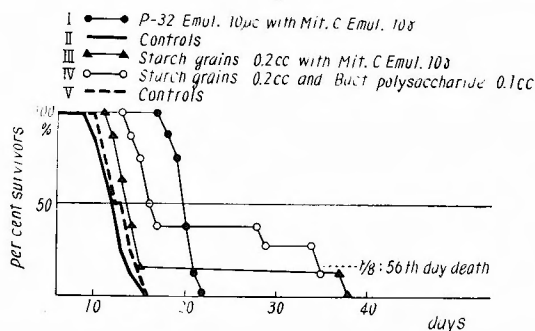
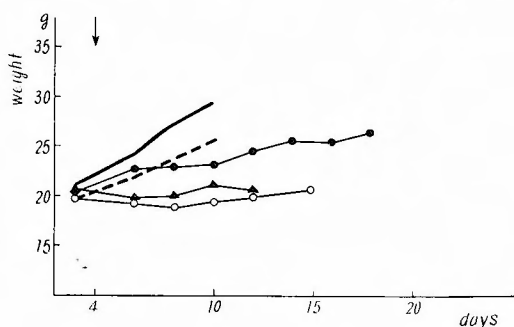


Fig. 13'



was positive inhibition of ascites accumulation, but none survived. This result is less good than that of Mit. C Emul. 10γ 7 times administered group in Experiment I in survival effect but better than that of single P^{32} Emul. $10\mu\text{c}$, 4 times administered group.

(ii) Group III : Starch grains 0.2cc with Mit. C Emul. 10γ twice every 24 hours then followingly Mit. C Emul. 10γ 5 times every 24 hours.

Group IV : Starch grains 0.2cc and bacterial polysaccharide 0.1cc were given alternately 5 times.

(The first, third and fifth administrations were starch 0.2 cc, the second and fourth were bacterial polysaccharide 0.1cc)

Group V : (Control). Emul. of normal saline 0.1cc 7 times every 24 hours.

All in the control group died of tumor in 10 to 16 days after the transplantation (Fig. 13 & 13'). The 50% survival period was 12 days.

Mice in Group III became weak and emaciated on the second day of the injection (6th day of transplantation). Ascites accumulation was slight but no survival effect was seen. Mice in Group IV also became somewhat weak on the second day of the injection but after the completion of injection, they recovered. There was inhibition of ascites accumulation. There were only 5 days of increase in 50% survival period, but 3 mice out of 8 survived 28 days, 35 days, and 56 days each. All of these developed a large accumulation of ascites and finally died of tumor.

(iii) Group VI: Mit. C Emul. 10 γ 7 times every 24 hours, then after 3 days, starch grains 0.1cc was given once.

Group VII: Mit. C Sol. 10 γ 7 times every 24 hours then after 3 days, starch grains 0.1cc was given once.

Group VIII: (Control). Physiological saline Emul. 0.1cc 7 times every 24 hours.

In Group VI and VII, starch grains were administered in the last injection (Fig. 14 & 14'). In both of groups 50% survival period increased twice as much as that of the control group which was 11 days. There was an inhibition of ascites accumulation but

Fig. 14

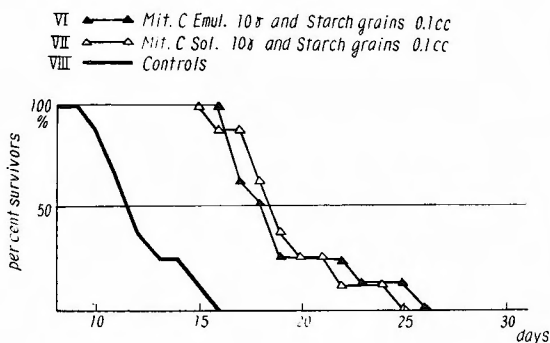
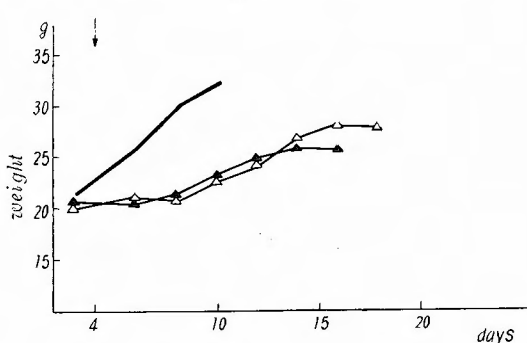


Fig. 14'



none survived. There was no recognizable differences of anti-cancer effect between emulsion and aqueous solution. Compared to the group which received Mit. C 10 γ alone for 7 times in Experiment I, these starch combined groups had less survival effect.

(iv) Cytological study was done on the Giemsa stained ascites smear preparation. In Group I on the 6th injection (Photo. 26), the number of cancer cells was small and signs of degeneration were remarkable. Also the appearance of polynucleic cells was remarkable. This is mostly the picture of change in cancer cells by Mitomycin C.

There was a high degree of degeneration in Group III (Photo. 27), as that seen in Group I. There were collections of polynucleic cells around the starch grains. Here, the picture of changes in cancer cells due to Mitomycin C and starch grains were mixed.

The cell degeneration was slight in Group IV but the number of cancer cells was small and there was nearly no cell division (Photo. 28). There were collections of polynucleic cells around starch grains and some of the grains were taken into polynucleic cells.

In Group VI and VII, there were noticeable changes in the appearance of ascites due to Mitomycin C and starch grains.

(3) Considerations

In 1949, SKIPPER²⁶⁾ applied nitrogen mustard and urethane to the leukemia of mice and reported their effect. Ever since, there have been a number of discussions concerning the combined use of many drugs.¹³⁾²⁵⁾ The reason why many discussions on combined therapy have been brought up is a countermeasure against the appearance of tolerance of tumor to drugs, acceleration of effects, and the decrease of side effects. We attempted to

increase the effects more in a combined use of those drugs which were fairly effective when applied alone in Experiments I and II. However, we could not get good effects in their combined use as we had expected. Especially, in the combination of starch grains and Mitomycin C as used in Group III, the effect seemed to decrease more in the combined use than in the sole use of each drug. Therefore, when more than two anti-cancer agents are used together, a careful consideration should be made not only of their working mechanism but also on the dosis and method of application.

SUMMARY AND CONCLUSIONS

I. For the purpose of local application of anti-cancer agents against tumor, and to obtain higher anti-cancer effects, emulsion preparations were produced. Injection of emulsions was followed by slower absorption and excretion than when the aqueous solution retain higher blood concentration and to accumulate in regional lymphnodes.

Emulsion preparation of P³², Mitomycin C and Tespamin were made and they were injected into the peritoneal cavity of EHRlich ascites carcinoma transplanted mice, and tumor of human breast cancer, to study the anti-cancer effect. As a result, when they were administered in the form of emulsion they had somewhat greater anti-cancer effect than when administered in aqueous solutions. When emulsion was injected directly into the tumor of breast cancer, there was a marked picture of degeneration in the axillary lymphnodes.

II. A study was made on the effect of inflammatory reaction over the growth of EHRlich ascites carcinoma, administering starch grains and bacterial polysaccharide.

In the group which was administered with 0.2cc of starch grains (arrowroot) 3 times every 48 hours, there was an apparent inhibition of cancer growth.

There was some grade of cancer arresting effect while bacterial polysaccharide had been administered; however, as soon as the administrations were discontinued animals died of tumor quickly.

III. In the combined use of anti-cancer agent, the effect was much less than what had been expected.

On the termination of this paper, I am deeply and most grateful to professor CHISATO ARAKI who has been giving me kind advices and directions, and to Dr. SHOZO ISHII, who has been offering a cordial guidance throughout the achievement of this research.

I am also very much obliged for the help I have received from The ROCKFELLER Foundation as a part of the expense incurred in doing this work.

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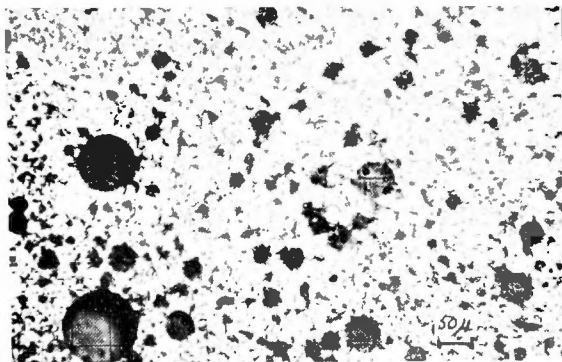


Photo. 1 Particles in emulsion.
x100

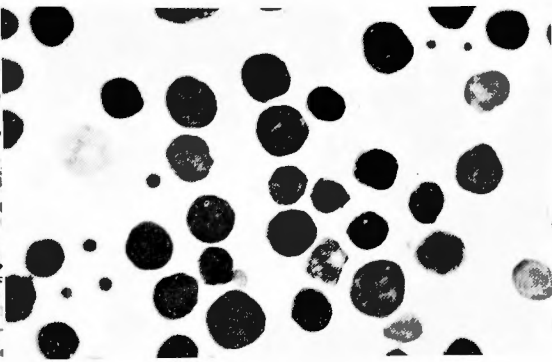


Photo. 2 Controls : 4 days after the transplantation of EHRlich ascites carcinoma (the Giemsa stain preparation of ascites).
x450

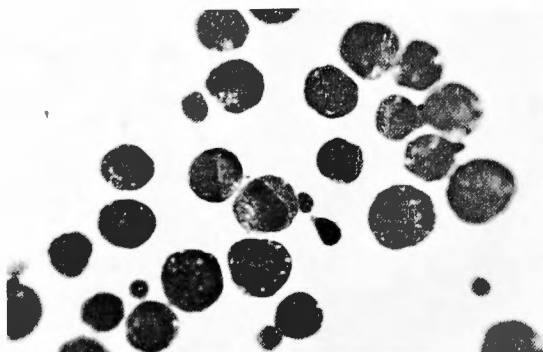


Photo. 3 Controls : 8 days after the transplantation.
x450

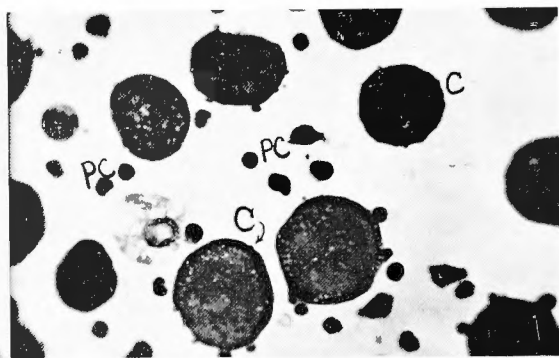


Photo. 4 Mit. C Emul. $10\gamma 7$ times every 24 hours : the 2nd day of Mit. C Emul. administration (6 days after the transplantation). x450
C : Cancer cells, PC : Polynucleic cells

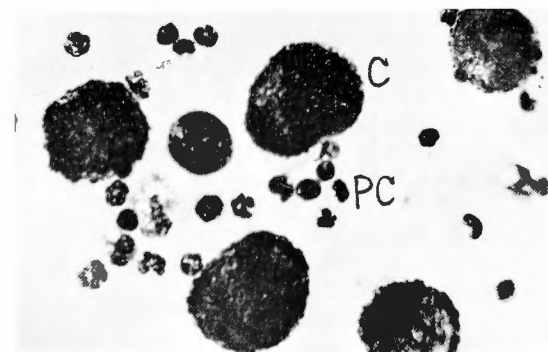


Photo. 5 Mit. C Emul. $10\gamma 7$ times every 24 hours : the 4th day of Mit. C Emul. administration (8 days after the transplantation). x450
C : Cancer cells, PC : Polynucleic cells

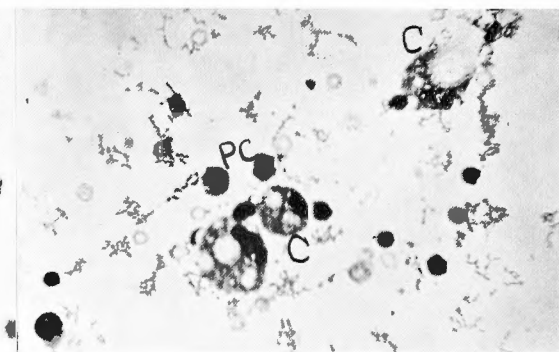


Photo. 6 Mit. C Emul. $10\gamma 7$ times every 24 hours : 10 days after the initial drug administration (14 days after the transplantation). x450
C : Cancer cells, PC : Polynucleic cells

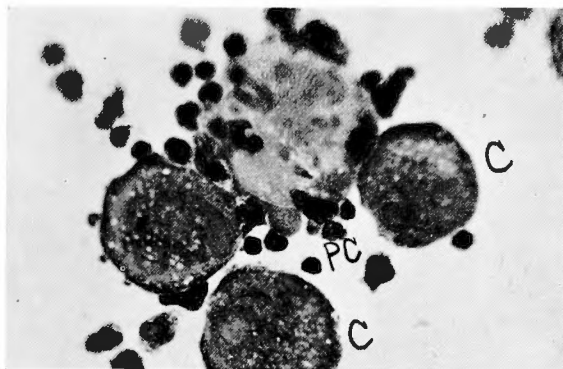


Photo. 7 Mit. C Sol. 10γ 7 times every 24 hours : the 4th day of Mit. C Sol. administration (8 days after the transplantation). x450
C : Cancer cells, PC : Polynucleic cells

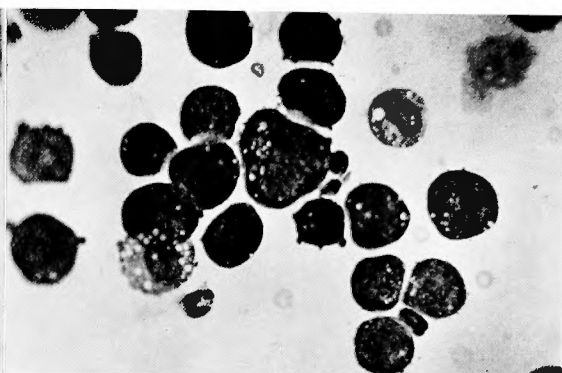


Photo. 8 P^{32} Emul. $10\mu c$ 4 times every 24 hours : the 2nd day of P^{32} Emul. administration (6 days after the transplantation). x450

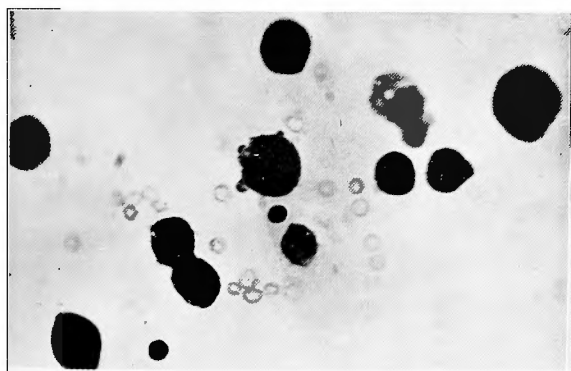


Photo. 9 P^{32} Emul. $10\mu c$ 4 times every 24 hours : 10 days after the initial drug administration (14 days after the transplantation). x450

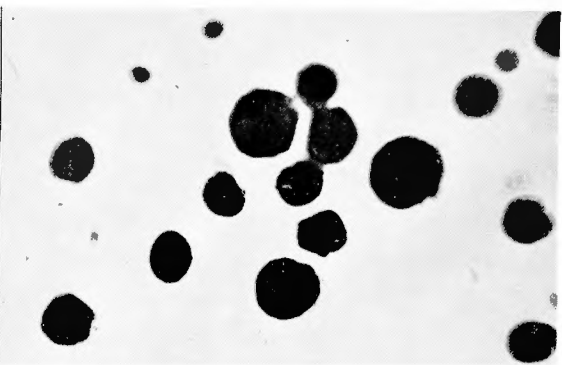


Photo. 10 P^{32} Emul. $10\mu c$ 4 times every 24 hours : 16 days after the initial drug administration (20 days after the transplantation). x450

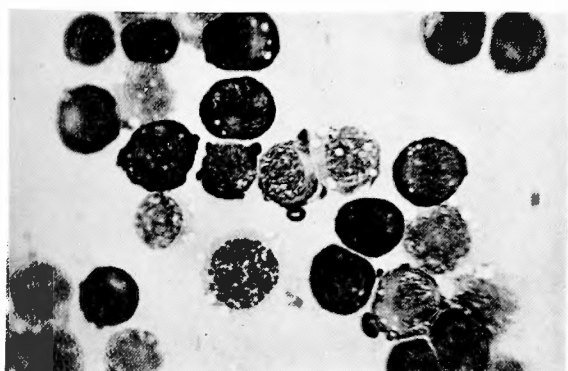


Photo. 11 Tespamin Emul. 30γ 7 times every 24 hours : the 6th day of Tespamin Emul. administration (10 days after the transplantation). x450

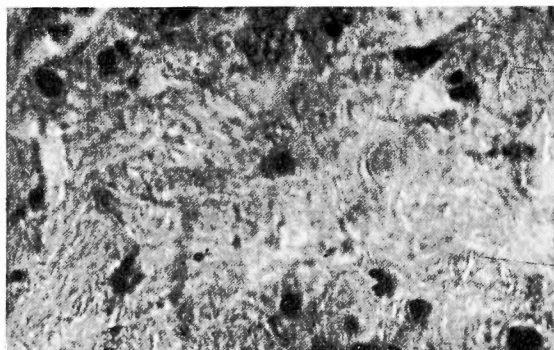


Photo. 12 The tissue of breast cancer : the portion where P^{32} and Mit. C Emul. were directly injected. $\times 400$

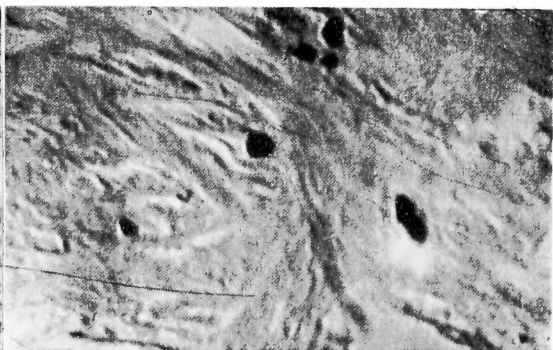


Photo. 13 The tissue of breast cancer the portion where P^{32} and Mit. C Sol. were directly injected. $\times 400$

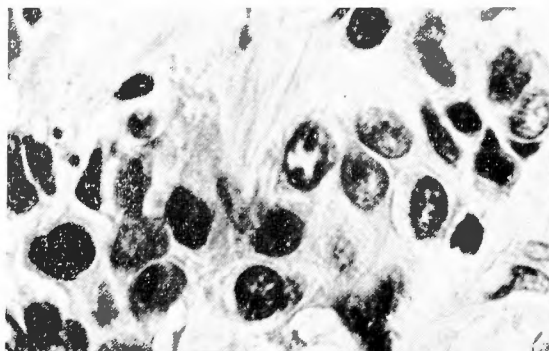


Photo. 14 The tissue of breast cancer : the peripheral portion, apart from the site of P^{32} and Mit. C Emul. injection. $\times 400$

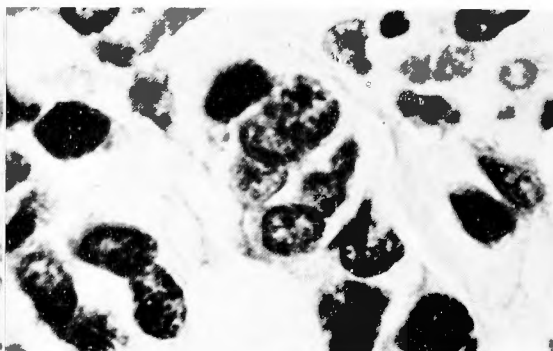


Photo. 15 The tissue of breast cancer : the peripheral portion, apart from the site of P^{32} and Mit. C Sol. injection. $\times 400$



Photo. 16 The tissue of axillary lymphnodes the case of P^{32} and Mit. C Emul. administration. $\times 10$



Photo. 17 The tissue of axillary lymphnodes : the case of P^{32} and Mit. C Sol. administration. $\times 10$

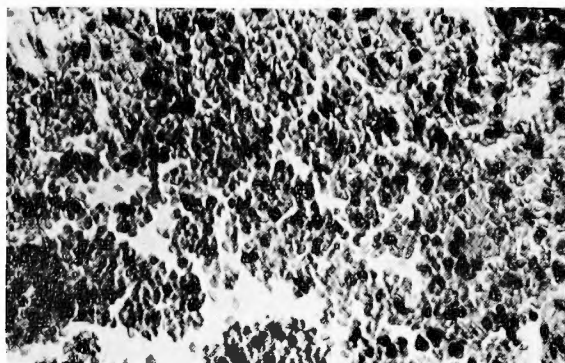


Photo. 18 The tissue of axillary lymphnodes :
the case of P^{32} and Mit. C Emul. administration.
x400

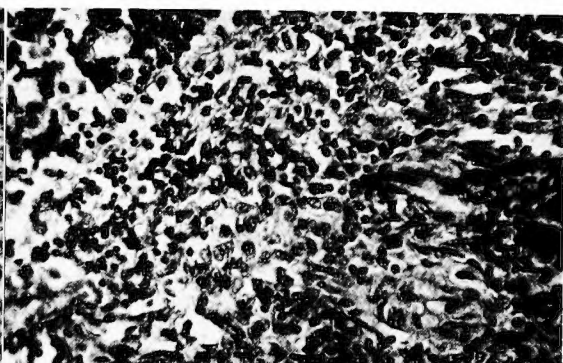


Photo. 19 The tissue of axillary lymphnodes
the case of P^{32} and Mit. C Sol. administration.
x400

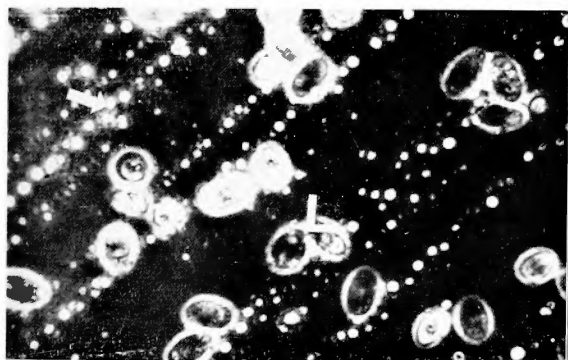


Photo. 20 Starch grains were smeared on deck
glass. x400
→ : Starch grains L . Leukocytes

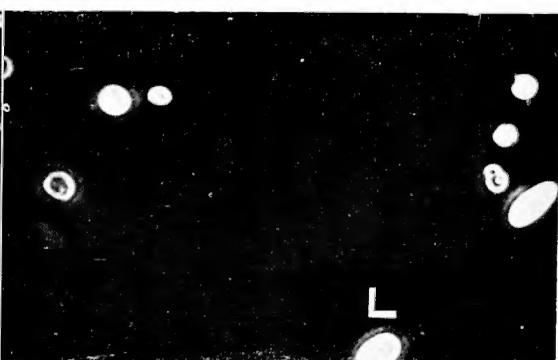


Photo. 21 Starch grains were not smeared on
deck glass. x400
L . Leukocytes

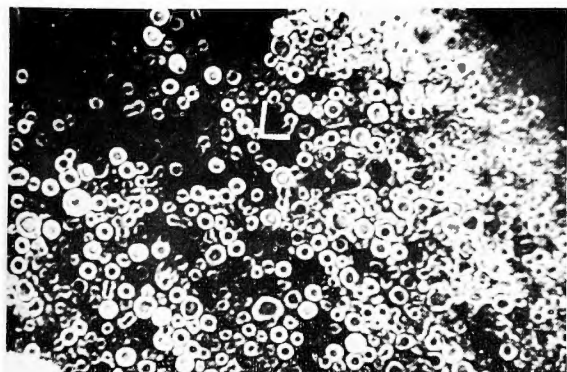


Photo. 22 Starch grains were put into a small
glass tube. x100
L : Leukocytes

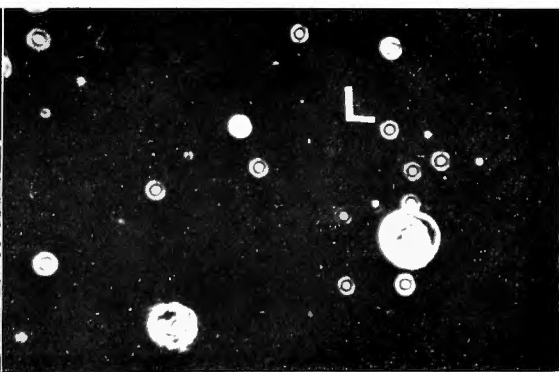


Photo. 23 Starch grains were not put into a small
glass tube. x100
L : Leukocytes

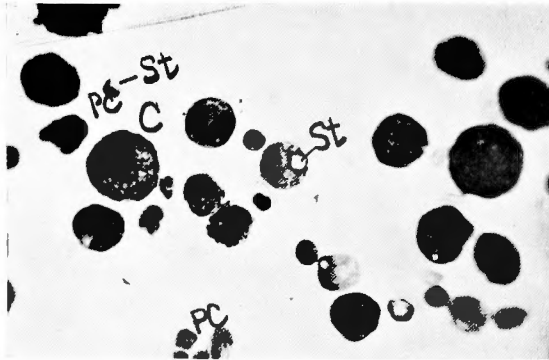


Photo. 24 Starch grains 0.2cc 3 times every 48 hours: the 2nd injection of starch grains. x450
St: Starch grains, C: Cancer cells,
PC: Polynucleic cells

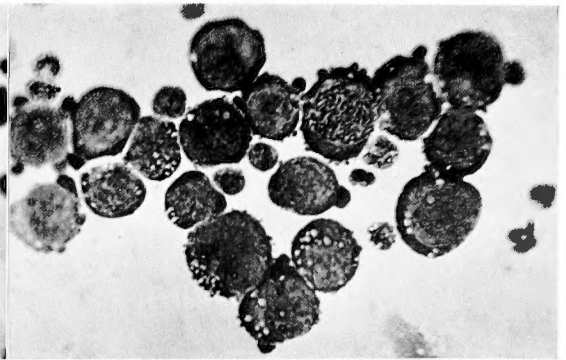


Photo. 25 Bact. polysaccharide 0.1cc 14 times every 24 hours: the 6th injection of bacterial polysaccharide. x450

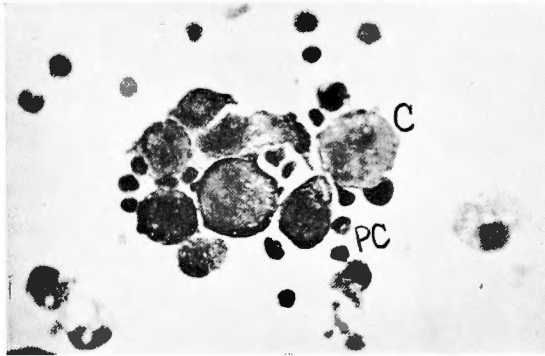


Photo. 26 P^{32} Emul. 10 μ c with Mit. C Emul. 10 γ : the 6th injection (10 days after the transplantation). x450
C: Cancer cells, PC: Polynucleic cells

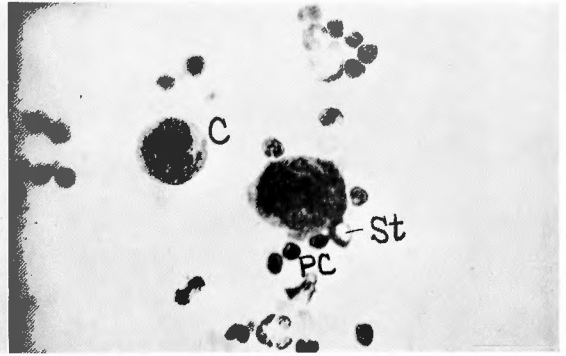


Photo. 27 Starch grains 0.2cc with Mit. C Emul. 10 γ : the 6th injection (10 days after the transplantation). x450
C: Cancer cells, PC: Polynucleic cells, St: Starch grains

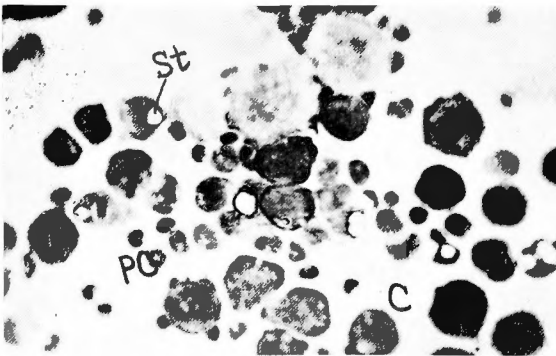


Photo. 28 Starch grains 0.2cc and Bact. polysaccharide 0.1cc: the 6th injection (10 days after the transplantation). x450
C: Cancer cells, PC: Polynucleic cells, St: Starch grains

和 文 抄 録

制癌剤乳濁液及び催炎性多糖類による制癌実験

京都大学医学部外科学教室第1講座(指導:荒木千里教授)

岡 田 芳 彦

(I) 制癌剤を腫瘍に局所使用して制癌効果を高める目的で乳濁液(Emulsion)を作成した。

まず乳濁液を生体に注射した場合、その吸収、排泄、血中濃度及び淋巴節への集積度を放射性同位元素 I^{131} を指標として、犬及びマウスで検討したが、対照水溶液注射例と比較し、注射局所、所属淋巴節により長期間とゞまり、又高い血中濃度を持続した。

次にマイトマイシンC、テスパミン及び放射性同位元素 P^{32} の各乳濁液をつくり、エールリッヒ腹水癌移植マウスに於て、腹腔内直接注射を行つて、その制癌効果を検討した。その結果、乳濁液として投与すれば水溶液として投与した場合よりも幾分制癌効果が大きかった。又臨床的に乳癌腫瘍内にマイトマイシンC及び P^{32} の混合乳濁液を直接注射して、剔出腫瘍及び腋窩

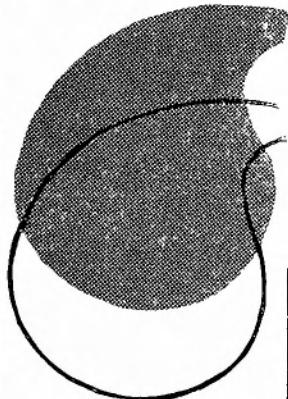
淋巴節の所見を検討したが、乳濁液注射例に於ては腋窩淋巴節に変性の像が著明であつた。

(II) 炎症性反応がエールリッヒ腹水癌の発育に如何なる影響を及ぼすかを、Starch grains及びBacterial polysaccharideを使用して検討した。即ちStarch grainsとして Arrowrootを用い、そのリンゲル氏液15%浮游液を調製して、エールリッヒ腹水癌移植マウス腹腔内に注射し、癌発育阻止作用を若干認めた。

Bacterial polysaccharide としては大腸菌濾液を使用した。その制癌効果はStarch grainsに比べて劣つて居り、投与期間中は癌発育は或る程度阻止されるようであるが、投与終了後全例速かに腫瘍死した。

(III) 制癌剤及び催炎性多糖類の併用投与を行つたが、期待した程の制癌効果は得られなかつた。

点滴静脈注射用 脂肪乳剤



健 保 適 用



大阪市東区道修町 3-25
大日本製薬株式会社

フアトゲン

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