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Studies on relationship between serum properdin and cancer III. Influence of anticancer agents on the serum properdin level

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Studies on relationship between serum properdin and cancer III. Influence of anticancer agents on the serum properdin level*

Kunzo Orita

Abstract

1. When the various anticancer agents are injected intravenously to normal rabbits and intraperitoneally to normal mice, it seems that the serum properdin levels fall transitorily for some hours after administration with a small dose and then keep rising, but with a massive dose it continues to fall from the beginning. 2. The properdin level is decreased considerably by Thio-TEPA and Carzinophilin; moderately by Mitomycin C; and slightly by M. H. OX-substance hardly changes the level and 8-azaguanine rather has a tendency to raise the level. 3. The administration of most anticancer agents seems to suppress the properdin system. 4. The influence of these agents on human serum properdin is similar to that of rabbits. 5. The properdin levels keep at high titers in the group to which the agents act effectively on the cancer, but the levels fall down more rapidly and animals die earlier in the group to which the agents act ineffectively on the cancer as compared with the control group.

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STUDIES ON RELATIONSHIP BETWEEN SERUM PROPERDIN AND CANCER

III. INFLUENCE OF ANTICANCER AGENTS ON THE SERUM PROPERDIN LEVEL

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In Part II it was found that properdin system, one important factor of host natural immunity, can be one barrier against cancer and it changes in an inverse proportion to the aggravation of tumors.

One of the greatest difficulties in the treatment of malignant tumor lies in its metastasis. Recently it has become clear that cancer cells are in the blood stream of cancer patients^{1,2,3,4,5}, sometimes these cells flow into the blood stream in such a great population as to be called canceremia, and it is an undeniable fact that cancer cells in the blood are responsible for metastasis or metastatic recurrence. This fact indicates that surgical operations and X-ray radiation have reached a certain limit. Since cancer is not only localized but spread all over the body, it is natural that we seek much from chemotherapy of cancer. The chemotherapy has yielded but little satisfactory results, so that the natural resistance to cancer in the host should be re-evaluated in order to stamp out cancer. Against the most widely supported theory that cancer starts as a localized disease, it spreads with the lapse of time to the regional lymphnodes, and eventually throughout the body, there is another theory called by Ian Mac DONALD⁶ "biologic predeterminism" that each cancer has certain biologic characteristics which tend to stay at more or less definite state throughout its life. In the latter theory it is the type of cancer and the resistance of the host rather than time that largely determines the spread of cancer. Gerald O. McDONALD⁷ went so far as to declare that host resistance is an important key to the cure of cancer.

If anticancer agents should greatly decrease the host natural resistance without much injury to cancer cells, they act in reality as the cancer-growth stimulants. Accordingly, when we administer various kinds of anticancer agents to healthy or cancer bearing individuals, it is of utmost importance to find out what effect they will have on the properdin system.

MATERIALS AND METHODS

The experimental animals used were comparatively young adult rabbits, weighing approximately 2 kg, and mature female Cb strain mice, weighing about 20 g. The experimental tumors transplanted were Brown-Pearce carcinoma for rabbits and Ehrlich ascitic carcinoma for mice.

Brown-Pearce carcinoma was transplanted into the liver of rabbits through portal vein and in mice, 7—10 day old Ehrlich ascites was aseptically implanted into the peritoneal cavity, as was described in Part II.

The anticancer agents used were as follows:

As anticancer antibiotics, Mitomycin C, Carzinophilin and Sarkomycin.

As anticancer chemicals, 8-azaguanine, Thio-TEPA (Triethylene thiophosphoramide) and M. H. (mercury complex salt of hematoporphyrin).

As an anticancer physical agent, OX-substance (a highly unsaturated fatty acid which was extracted by YAMAMOTO from the bone marrow and liver of the rabbit after the total body X-irradiation).

All the anticancer agents were injected into the marginal veins of rabbit ear on one side and blood sample was taken periodically from the veins of the contralateral ear, and in the mice the agents were intraperitoneally injected and blood was taken from 3 or 4 mice of each group by cardiac puncture periodically before and after the injection. In man the anticancer agents were intravenously administered to cancer patients before operation and blood was collected from the elbow vein.

The separated sera were stored at -30°C in the sealed tubes till the completion of the blood collection in a series.

Properdin levels of all the samples were measured at least within a month after the blood collection.

The method of the properdin assay, Rp and R3 used for this assay were previously described.

RESULTS

A. Influences of several anticancer agents upon serum properdin levels in normal condition.

1. Influences of several anticancer agents upon serum properdin levels in normal rabbits.

Groups of 3 rabbits each were used.

Group I. The group to which Mitomycin C was administered.

a. The group to which 1 mg/kg Mitomycin C was administered once. Mitomycin C was injected in the dilution of 5 ml with saline solution. Three hours after the injection the properdin level rather fell, 2—3 days later it tended

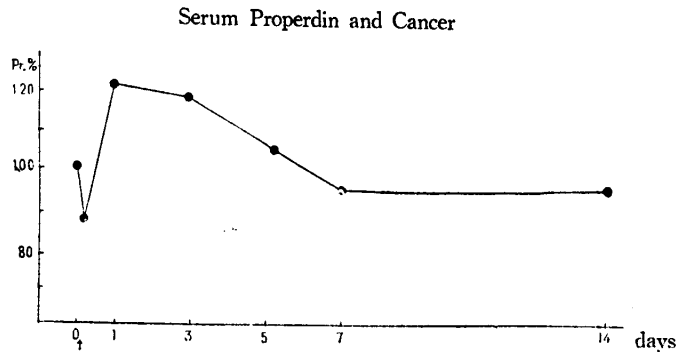


Fig. 1. Mean effect of a single injection of Mitomycin C (1mg/kg) on the properdin levels in rabbits.

to rise and 1—2 weeks later reverted to the value before injection (Fig. 1).

b. The group administered with (1 mg/kg) Mitomycin C for 7 days successively. The properdin level fell after the first injection and later gradually rose and reached its peak (150%) on the fifth day, and suddenly fell after that (Fig. 2). Two rabbits died, one on the ninth and the other on the tenth day, respectively. The tendency of the rise in the properdin level was not indicated in one surviving rabbit after one week.

c. The group administered with 2 mg/kg Mitomycin C successively. Three hours after the first injection the properdin level rather fell, but after 24 hours suddenly it rose to over 170 per cent of the value before injection and suddenly fell after that, and finally fell to 50 per cent on the third day. Two rabbits died, one on the fourth and the other on the fifth day, respectively (Fig. 3).

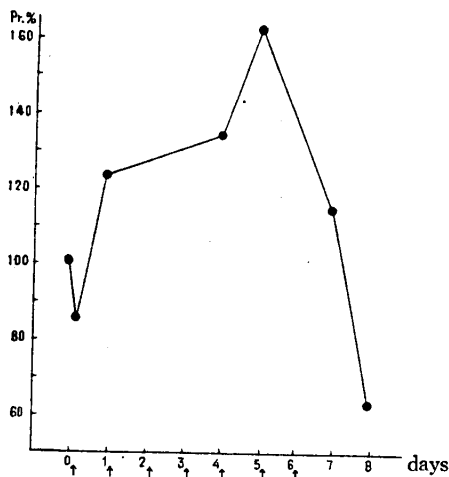


Fig. 2. Mean effect of 7 injections of Mitomycin C (1mg/kg) on the properdin levels in rabbits.

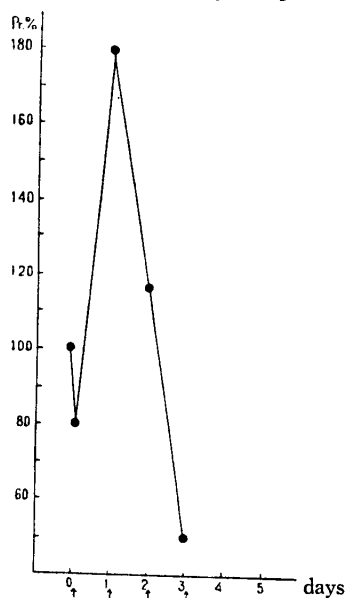


Fig. 3. Mean effect of multiple injections of Mitomycin C (2mg/kg) on the properdin levels in rabbits.

d. The groups administered with Mitomycin C 0.5 mg/kg and 0.1 mg/kg successively for 7 days. No rabbit died in the two groups. About 3 days after the first administration the properdin level reached its peak and fell afterwards. It showed a tendency to recover after the seventh injection, but 2—3 weeks later it still remained at rather a low level (Fig. 4).

e. The groups administered with Mitomycin C 0.5 mg/kg and 0.1 mg/kg for 11 days. It was much the same as in group d, but it did not show any tendency of rising in 2—3 weeks after injection (Fig. 5). No rabbit died.

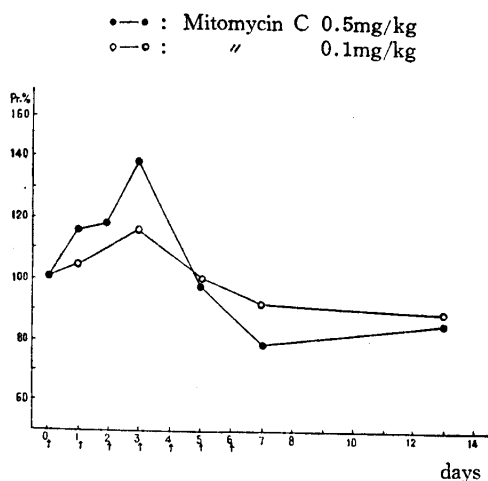


Fig. 4. Mean effect of 7 injections of Mitomycin C (0.5mg/kg; 0.1mg/kg) on the properdin levels in rabbits.

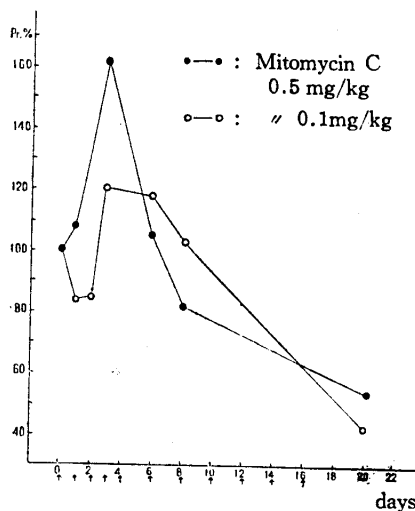


Fig. 5. Mean effect of 11 injections of Mitomycin C (0.5mg/kg; 0.1mg/kg) on the properdin levels in rabbits.

Group II. The group administered with Carzinophilin.

a. The group administered successively with 25 γ /kg Carzinophilin.

Carzinophilin was injected in the dilution of 5 ml with saline solution. Three hours after the first injection the properdin level rapidly fell to 50 per cent of the level before administration and changed through subsequent injections, generally continuing to fall (Fig. 6). One rabbit out of three died of lack of appetite and emaciation on the fifth day. As the two remaining indicated the sign of emaciation, the injection was stopped after five injections.

b. The group administered successively with 5 γ /kg Carzinophilin for 7 days.

None indicated the sign of lack of appetite and debility in this group. Three hours after the first injection the properdin level fell to approximately two thirds of the level before injection, and stayed at low level for 2 or 3 days after that, and a week after the seventh injection it reverted to only two thirds of the original level (Fig. 7).

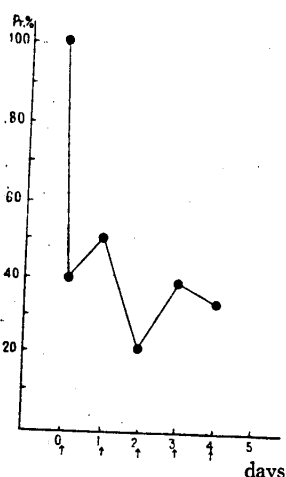


Fig. 6. Mean effect of multiple injections of Carzinophilin (257/kg) on the properdin levels in rabbits.

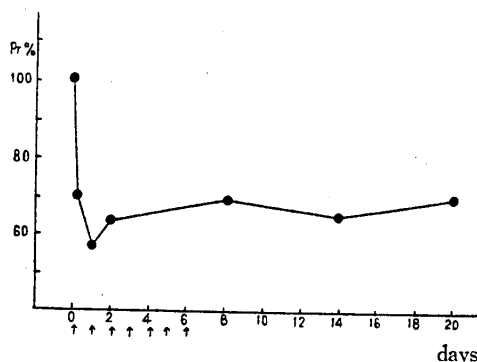


Fig. 7. Mean effect of 7 injections of Carzinophilin (57/kg) on the properdin levels in rabbits.

c. The group administered with 5 γ /kg Carzinophilin for 11 days.

It was the same as in group b, but a week after the completion of injection the properdin level did not tend to rise. No rabbit died in this group (Fig. 8).

Group III. The group administered successively with 35 mg/kg 8-azaguanine for 7 days.

8-azaguanine was injected in the dilution of 5 ml with saline. Three hours after the first injection the properdin level fell to approximately 60 per cent of the value before injection, but in 24 hours it showed a higher level than the original, and it gradually decreased afterwards, but 24 hours after the seventh injection it showed approximately the same level as before administration and showed the tendency of rising after that (Fig. 9). No change was seen in the general conditions of the rabbits.

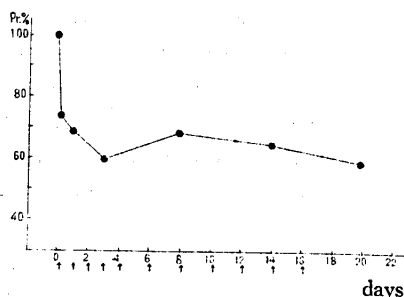


Fig. 8. Mean effect of 11 injections of Carzinophilin (57/kg) on the properdin levels in rabbits.

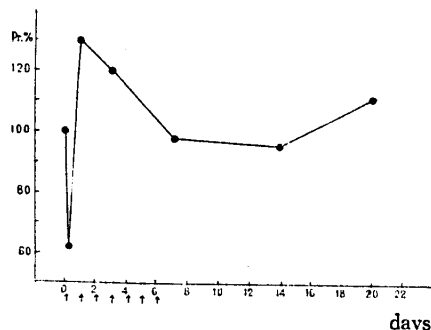


Fig. 9. Mean effect of 7 injections of 8-azaguanine (35 mg/kg) on the properdin levels in rabbits.

Group IV. The group administered with Thio-TEPA.

a. The group administered successively with 4 mg/kg Thio-TEPA.

Five ml of Thio-TEPA diluted with saline was injected at a time. With repeated injections the properdin level kept falling, and when it fell to approximately 40 per cent of the original level, one of the three rabbits died (Fig. 10). After the fourth injection three rabbits languished so that injection was discontinued.

b. The group administered with 2mg/kg Thio-TEPA successively for 7 days.

Three hours after the first injection the properdin level did not fall, but rather rose and later fell and showed the lowest value 3—5 days later. In a week after the injection was finished, the properdin level stayed at rather lower level than before (Fig. 11).

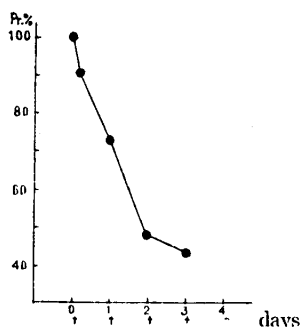


Fig. 10. Mean effect of multiple injections of Thio-TEPA (4mg/kg) on the properdin levels in rabbits.

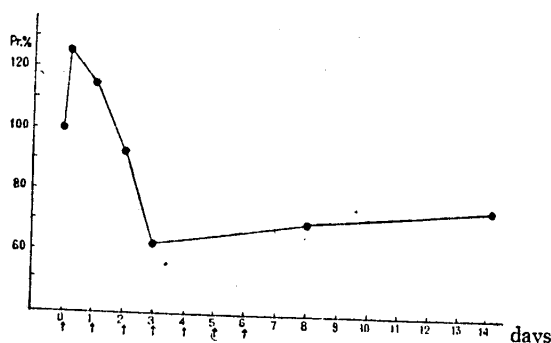


Fig. 11. Mean effect of 7 injections of Thio-TEPA (2mg/kg) on the properdin levels in rabbits.

Group V. The group administered with M. H.

a. The group administered successively with 10 mg/kg M. H.

M. H. was dissolved with 5 % glucose solution and 5 ml of it was injected at a time. Three hours after the first injection the properdin level fell to two thirds of the level before injection and rose or fell to some extent since then, and on the fourth day one of three rabbits died, and two remaining ones on the sixth day with copious bloody diarrhea. Owing to the severe debility of the total body of the rabbits the injection was discontinued after five injections (Fig. 12).

b. The group administered successively with 2 mg/kg M. H. for 7 days.

Three hours after the first injection the properdin level did not show a fall but inversely a transitory rise. Twenty-four hours after the seventh injection the level was rather lower than that before injection, after 3—4 days it reverted to the level before injection, but later rather tended to rise (Fig. 13).

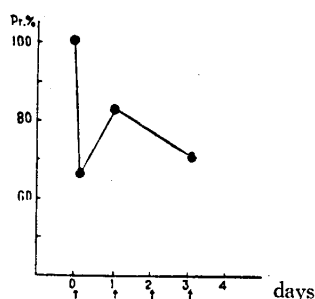


Fig. 12. Mean effect of multiple injections of M.H. (10mg/kg) on the properdin levels in rabbits.

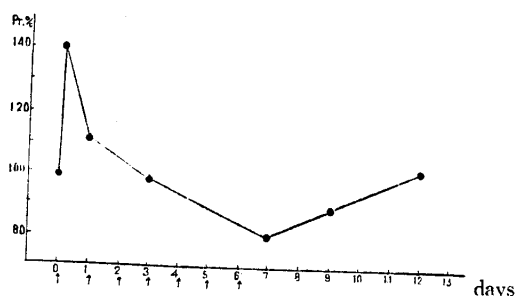


Fig. 13. Mean effect of 7 injections of M.H. (2mg/kg) on the properdin levels in rabbits.

Group VI. The group administered successively with 20 mg/kg OX-substance for 7 days.

Five ml of OX-substance diluted with saline was injected at a time. Four to five days after the first injection, the properdin level tended to rise to some extent but the changes were insignificant (Fig. 14).

Control group. The groups to which physiological saline solution 5 ml/rabbit and 5% glucose solution 5 ml/rabbit were administered successively for 7 days.

In all cases there was no perceptible change of the properdin level (Fig. 15).

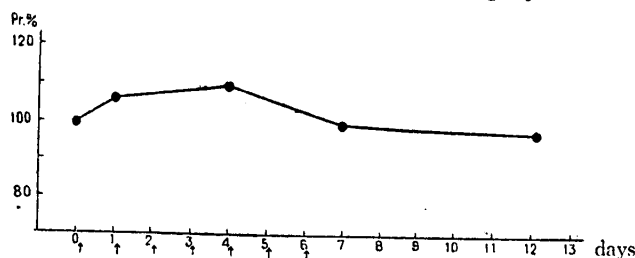


Fig. 14. Mean effect of 7 injections of OX-substance (20mg/kg) on the properdin levels in rabbits.

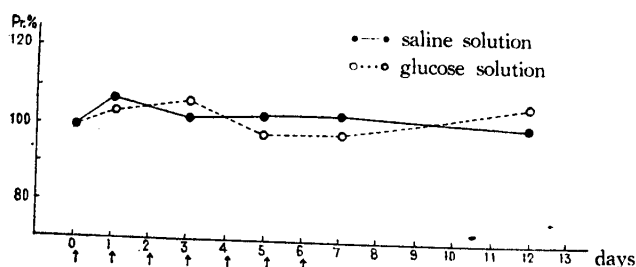


Fig. 15. Mean effect of 7 injections of physiological saline solution (5 ml/rabbit) and of 5% glucose solution (5ml/rabbit) on the properdin levels in rabbits.

2. Influences of administering several anticancer agents upon serum properdin levels in man.

As anticancer agents can not be administered to normal persons, they are administered to cancer patients before operation and changes in the properdin value are followed. Accordingly, the examination of the level through a long period after administration is not possible. In the cases of intravenous injection of 10 mg Mitomycin C for 4 days, 50 γ Carzinophilin for 7 days, 3 g Sarkomycin for 7 days, and 15 mg Thio-TEPA for 7 days respectively; similar phenomena were observed as in the cases of rabbits as in Figure 16. a—d. In the case of administration of 100 mg OX-substance for 7 days, no change was found in the properdin levels as in the case of rabbits (Fig. 16. e). With 70 mg 8-azaguanine for 3 days, it tended to rise higher than the level before injection (Fig. 16. f).

Comment: 1. When the substances that combine with properdin *in vitro* are administered to experimental animals intravenously, it seems that these substances interact with properdin *in vivo* and change their properdin levels. Immediately after these substances are injected, the serum properdin level falls to low levels, but reverts to more than normal values within 2—3 days^{8,9,10}. LANDY, *et al.*¹¹ injected bacterial lipopolysaccharides into the peritoneal cavity of a mouse and showed that properdin level was changed two or three hours after injection. As for the time and dose relation in the case of injection of 100 μ g, the properdin level fell in 12—24 hours and later showed notable rise lasting for at least 5 days. In the case of injection of 10 μ g, the level rose in only 6 hours and in 24 hours reached double the value before injection, and lasted for 72 hours, and this elevation occurred without the prior fall in the properdin level. They inferred that this might, therefore, be due to a direct stimulation of the synthesis or release of properdin rather than to a mechanism which represents overcompensation "rebound" on the part of the host. In the case of 1 μ g, it was the same as in the case of 10 μ g. In the case of 0.1 μ g it was the same as in the case of the injection of saline solution. HOFF¹² saw that the change in the properdin system was nonspecific and was found in the cases of impulse of central nervous system and artificial fever, and that in artificial fever in man the properdin level showed the lowest value in the third hour when the fever reached its peak after the injection of pyrogene lipopolysaccharide and 1—2 days later it rose to approximately double the value before injection.

The relation between the administration of anticancer agents and the serum properdin level can not be understood because there are still such unsolved problems as whether or not anticancer agents combine with properdin *in vivo*, how long anticancer agents remain in blood stream after administration, what organs or cells of living beings are injured by anticancer agents, where properdin is produced, and the adequate dose, time, and frequency of administration of

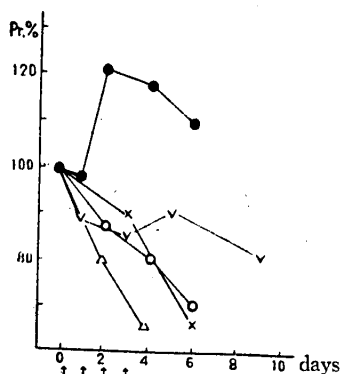


Fig. 16. a. Effect of 4 injections of Mitomycin C 10mg on the properdin levels in man.

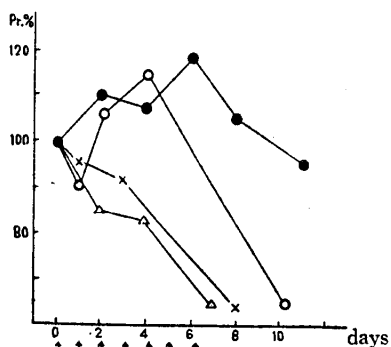


Fig. 16. b. Effect of 7 injections of Carzinophilin 507 on the properdin levels in man.

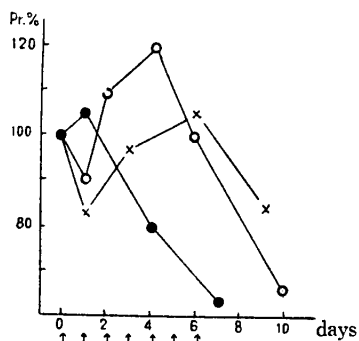


Fig. 16. c. Effect of 7 injections of Sarkomycin 3g on the properdin levels in man.

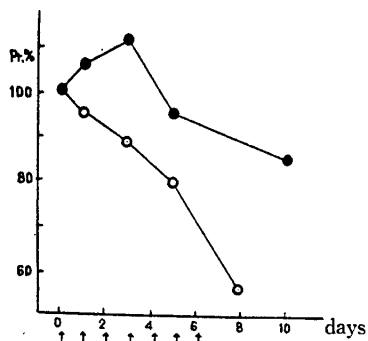


Fig. 16. d. Effect of 7 injections of Thio-TEPA 15mg on the properdin levels in man.

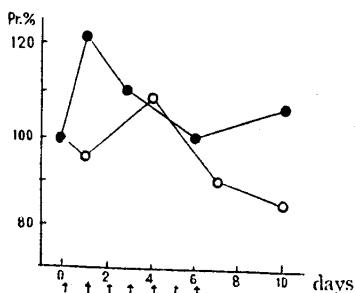


Fig. 16. e. Effect of 7 injections of OX-substance 100mg on the properdin levels in man.

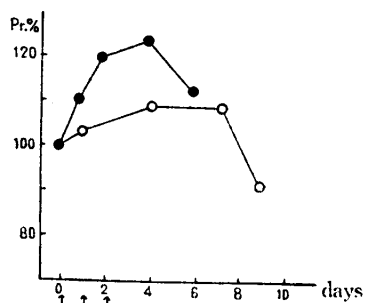


Fig. 16. f. Effect of 3 injections of 8-azaguanine 70mg on the properdin levels in man.

anticancer agents. Accordingly, it is not always justified to attach too much importance to the relation between the two, but it seems that properdin falls transitorily for some hours after administration of a small dose and then keeps on rising, but it keeps falling from the first in the case of administering a massive dose. It is very difficult to evaluate precisely the effect of each anticancer agents as the dose administered differs in each case, but it seems that Thio-TEPA and Carzinophilin lower properdin levels considerably; Mitomycin C, moderately; and M. H. slightly; that OX-substance hardly changes the levels as in the case of administration of saline and glucose solution, and that 8-azaguanine rather tends to raise its levels. We must await future investigations to see by what mechanisms these anticancer agents lower the properdin levels or interfere with properdin zymosan assay, but these agents seem to have undesirable effects upon the properdin system which is an important factor of host natural resistance.

2. It is uncertain whether anticancer agents have the same effect upon a normal person as upon a cancer patient, but it can be assumed that anticancer agents have a considerable effect upon human serum properdin levels.

B. Influences of administering anticancer agents upon serum properdin levels in cancer bearing animals.

1. Experimental studies by Ehrlich ascitic carcinoma in mice.

When anticancer agents are administered to experimental animals, time from the tumor implantation to its first administration, methods, frequency and the amount of administration are important factors. As it is said that the cancer cell division reaches its peak in 3 days and 5 days after implantation, the administration of anticancer agents was started in 48 hours after implantation. Several anticancer agents were intraperitoneally injected once a day for 7 days in succession.

Group I. The group administered with 10 γ /mouse Mitomycin C for 7 days.

a. The group of normal mice administered with Mitomycin C. The properdin level rather fell after the first injection and later rose. When the seventh injection was finished, it reverted to the level before administration (Fig. 17).

b. The group of ascitic cancer bearing mice administered with Mitomycin C. The weight of mice did not increase in about 15 days after implantation and its abdomen did not swell, but in 20 days they began to die of cancer. Fifty per cent of them survived for 28 days, untreated control group survived for 12 days. As in Fig. 18, the properdin level in this case showed between that of the control group and that of the group of normal mice administered with Mitomycin C, and 20 days after implantation, the properdin level was a little over 40 per

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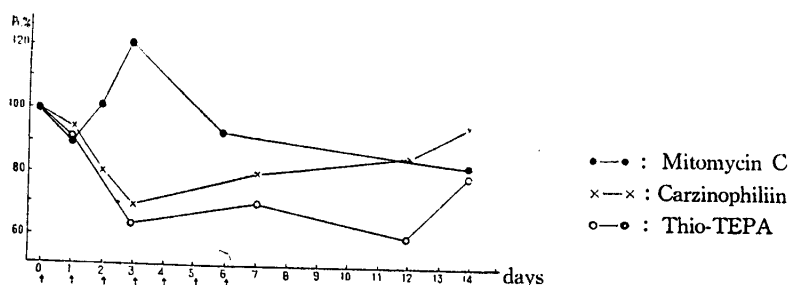


Fig. 17. Mean effect of 7 injections of Mitomycin C (10 γ /mouse), of Carzinophillin (1 γ /mouse) and of Thio-TEPA (90 γ /mouse) on the properdin levels in normal mice.

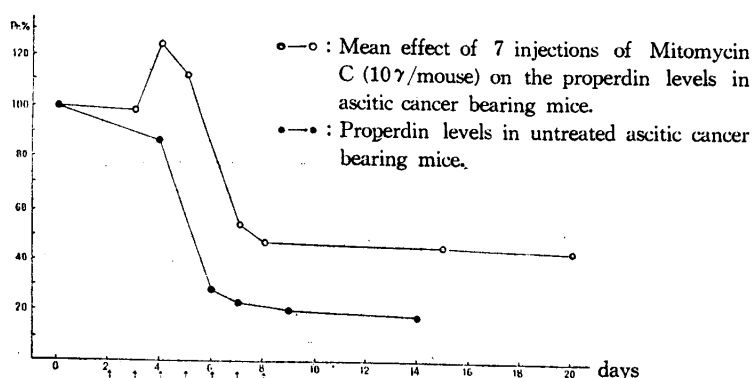


Fig. 18.

cent than that before implantation. Five out of 24 mice survived for more than 100 days and in their postmortem examination, no ascites and tumor metastasis could be seen.

Group II. The group administered with 1 γ /mouse Carzinophillin for 7 days.

a. The group of normal mice treated with Carzinophillin.

The properdin level gradually fell after the first injection, and down to the lowest level after the third injection, and reverted to the normal level in about 14 days after the seventh injection. Its weight rather tended to decrease (Fig. 17).

b. The group of ascitic cancer bearing mice treated with Carzinophillin.

In 3—6 days after implantation the properdin level suddenly fell in the same way as in the untreated control groups. Later the level gradually rose and reverted to that before implantation in about 20 days. They began to die in 3 weeks and 50 per cent of them survived for 35 days and the level began to fall again in the terminal period. In control group 50 per cent survived for 13 days. Four out of 22 cases were completely cured. In 8 cases out of those which died,

their weights ranged 25—30 g, and the storage of a considerable amount of hemorrhagic ascites could be seen, and in 10 cases there was a marked decrease in weight, but ascites and tumor metastasis could not be seen (Fig. 19).

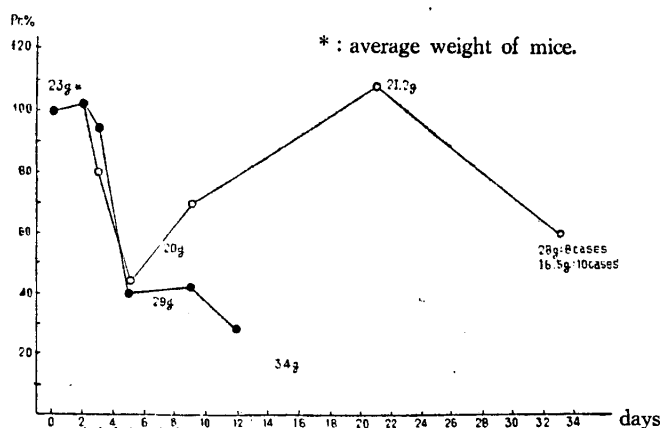


Fig. 19.

○—○ : Mean effect of 7 injections of Carzinophilin (17/mouse) on the properdin levels in ascitic cancer bearing mice.
 ●—● : Properdin levels in untreated ascitic cancer bearing mice.

Group III. The group treated with 90γ mouse Thio-TEPA for 7 days.

a. The group of normal mice treated with Thio-TEPA.

The properdin level gradually fell after the first administration, and it stayed at rather low level a week after the seventh injection (Fig. 17).

b. The group of ascitic cancer bearing mice treated with Thio-TEPA.

The fall in its properdin level and the increase in its weight were controlled to some extent as compared with the untreated control group. All of the 20 cases died within 14—24 days after implantation. Fifty per cent of them survived for 18 days, while the control group survived for 13 days (Fig. 20).

Group IV. The group treated with 2.5mg/mouse Sarkomycin for 7 days.

a. The group of normal mice treated with Sarkomycin.

The properdin level fell after the first administration and later rose and indicated the highest level for 1—4 days and later fell (Fig. 21).

b. The group of ascitic cancer bearing mice treated with Sarkomycin.

The properdin level was the mean value between the value of untreated control group and that of normal mice treated with Sarkomycin and remained at a high level for a long time as compared with the control group. Fifty per cent of them survived for 20 days, while the control group survived for 16 days. All 15 animals died within 14—25 days after implantation (Fig. 22).

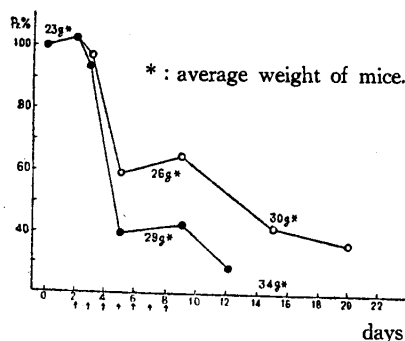


Fig. 20.

- : Mean effect of 7 injections of Thio-TEPA (90 γ/mouse) on the properdin levels in ascitic cancer bearing mice.
- : Properdin levels in untreated ascitic cancer bearing mice.

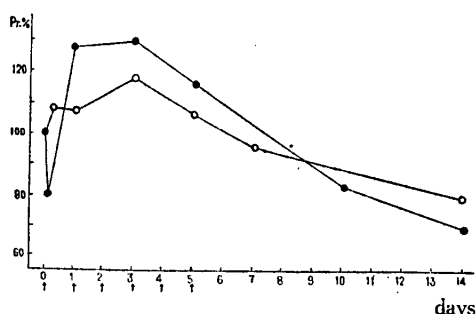


Fig. 21. Mean effect of 7 injections of Sarkomycin (2.5 mg/mouse) on the properdin levels in normal mice (○—○) and Sarkomycin (0.25 mg/mouse) on the properdin levels in normal mice (●—●).

Group V. The group treated with 0.25 mg/mouse Sarkomycin for 7 days.

a. The group of normal mice treated with Sarkomycin.

The properdin level rose after the first injection, but it fell to four fifths of the level before injection in about 7 days after the seventh injection (Fig. 21).

b. The group of ascitic cancer bearing mice treated with Sarkomycin.

The increase in the weight and the storage of ascites were more rapid and so was the fall in the properdin level as compared with the control group. All of

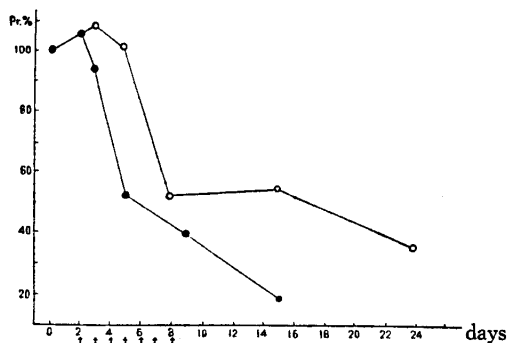


Fig. 22.

- : Mean effect of 7 injections of Sarkomycin (2.5 mg/mouse) on the properdin levels in ascitic cancer bearing mice.
- : Properdin levels in untreated ascitic cancer bearing mice.

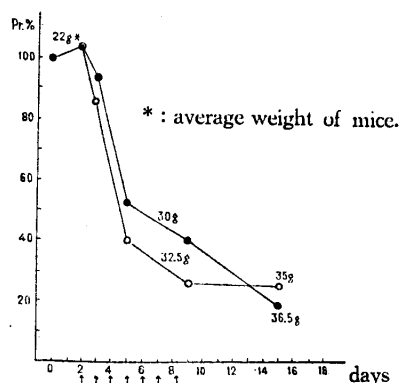


Fig. 23.

- : Mean effect of 7 injections of Sarkomycin (0.25 mg/mouse) on the properdin levels in ascitic cancer bearing mice.
- : Properdin levels in untreated ascitic cancer bearing mice.

the 15 mice died of tumor within 8—17 days after implantation. Fifty per cent of them survived for 14 days, while the control group survived for 16 days. When 0.25 mg/mouse Sarkomycin was administered, it rather stimulated cancer growth (Fig. 23).

2. Experimental studies Brown-Pearce carcinoma in rabbits.

The group treated with 35 mg/kg 8-azaguanine for 7 days after transplantation.

The injection of 8-azaguanine into the vein of the ear was started 72 hours after implantation into the liver through portal vein. In control group, 5 ml of physiological saline was injected in the same way for 7 days.

The properdin level was kept at a little higher level than in the control group, but 3 rabbits died, one 13 days, another 16 days, and the last 18 days after transplantation, respectively, while in the control group one rabbit died in 14 days and 2 rabbits in 16 days. No effect of 8-azaguanine could be recognized (Fig. 24).

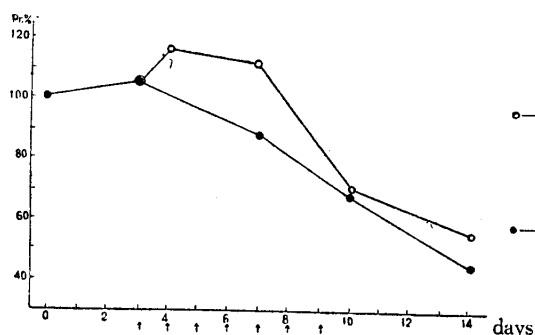


Fig. 24.

○—○ : Mean effect of 7 injections of 8-azaguanine (35 mg/kg) on the properdin levels in cancer bearing rabbits.
●—● : Properdin levels in untreated cancer bearing rabbits.

COMMENT

The same experiment as before with rabbits was attempted by using several kinds of anticancer agents. Though these agents are hitherto reported to act against other malignant tumor effectively, it has been clarified in the present experiment that they are hardly effective against Brown-Pearce carcinoma of rabbit. Therefore, Ehrlich ascitic carcinoma of mice were chiefly employed. When anticancer agents act effectively as observed in the group treated with Carzinophilin and Mitomycin C, the properdin levels are kept for a long time at a higher level than that of the control group. In such instances the properdin level seems to change in inverse proportion to the spread of cancer cells. The properdin levels fell lower and fifty per cent of mice died earlier in the group

treated with 0.25 γ /mouse Sarkomycin than the control, and it seems to suggest that, unless anticancer agents are properly selected for administration, they might stimulate cancer-growth.

Taking the effect of surgical procedure on the host into consideration, it is found that, besides the surgical injury of local tissues, the cells of the liver, the bone marrow and the brain are injured owing to general anesthesia, reduction in blood pressure and anoxia, etc. Chemicals¹⁸ which promote the growth of tissues are mobilized to these injured spots, and these chemicals, together with the decrease in the resistance of these spots, make cancer cells that are scattered in a great number into the blood stream or the lymphatic stream or in the operated region, prone to be implanted to these injured spots. In this connection there are many reports by BEAHRS¹⁴, VINK¹⁶, COLE¹⁶ and many others. On the other hand, it has been explained experimentally that the general anesthesia¹⁷, absorption of necrotic products of tissue^{18,19}, bleeding^{20,21}, and the increase of cortisone^{22,23} following surgical operation, decrease the host resistance against the growth of cancer, but the actual causes are not yet clear. It was described in Part II that the serum properdin level stayed at a low level for a long period after operation in the extended radical operation for gastric cancer. Furthermore, it was explained both experimentally and clinically that, if anticancer agents are administered to living beings, it has undesirable effects upon its properdin. Since cancer is not a local disease but is prone to spread all over body, it is a matter of course that anticancer agents should be administered. Under unfavorable conditions where many cancer cells are evolved in the blood stream after operation, and the host natural resistance is decreased both locally and totally, unless anticancer agents are administered with consideration to its quality and quantity, they will rather enhance the recurrence and metastasis of cancer. When an improper amount of Sarkomycin was administered to cancer bearing mice, it was found that the growth of cancer was promoted and the properdin level fell more rapidly than that of the control. SHEAR²⁴ inferred that the formation of metastasis after removing primary focus was probably caused by the break in the balance between cancer and the properdin system of the host. VINK¹⁵ injected suspension of Brow-Pearce carcinoma cells into the small intestines of rabbits, resected the intestines and then reanastomosed it. He reported that the frequency of recurrence at the anastomosed part in the group treated with Sulphasuxidine and Streptomycin were four times higher than that of the untreated group. This fact seems to have some bearing upon properdin system. Conversely, as was seen in cancer-bearing mice, if the choice of anticancer agents is proper, the properdin level is kept high and the effect of treatment is great. All these facts make us realize the importance of the host natural defense mechanism against cancer, and, moreover, tell us how carefully

anticancer agents must be chosen and how important and urgent it is to establish the reliable screening test for anticancer agents. At the present stage where we still have many unsolved problems about the host resistance against cancer, we have to continue to expand surgical procedures and need not to hesitate to perform radical operation for cancer, but if we take into consideration the fact that metastatic lesions can be found in the distant part from primary focus in necropsy²⁵ even after radical operation for cancer and that cancer cells of the so-called "ruhende metastase"²⁶ or "premetastatische phase"²⁷ begin to grow by surgical manipulation, it seems to be reasonable that surgical operation of suitable extent should be chosen to each cancer patient. In treating cancer patients all the care and consideration be given before we decide for surgical operation and or chemotherapy.

CONCLUSIONS

1. When the various anticancer agents are injected intravenously to normal rabbits and intraperitoneally to normal mice, it seems that the serum properdin levels fall transitorily for some hours after administration with a small dose and then keep rising, but with a massive dose it continues to fall from the beginning.
2. The properdin level is decreased considerably by Thio-TEPA and Carzinophilin; moderately by Mitomycin C; and slightly by M. H. OX-substance hardly changes the level and 8-azaguanine rather has a tendency to raise the level.
3. The administration of most anticancer agents seems to suppress the properdin system.
4. The influence of these agents on human serum properdin is similar to that of rabbits.
5. The properdin levels keep at high titers in the group to which the agents act effectively on the cancer, but the levels fall down more rapidly and animals die earlier in the group to which the agents act ineffectively on the cancer as compared with the control group.

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