

Host Resistance against Cancer after Removal of Primary Tumor

by

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Unexpectedly early recurrence or metastasis in the cases of seemingly early operation and fairly long survival or sometimes spontaneous cure in the cases of mere palliative operation²⁴⁾ have been observed, which has given strange impression to clinicians.

The fact that there can be observed marked fluctuation in the course of tumor arising in a organism can be better explained by possible fluctuation of host resistance than to conceive some alteration in malignancy of the tumor itself. Recently, cancer has come to be investigated under the concept of host-tumor relationship. We also have studied this problem based upon several experiments and clinical experiences.

MATERIALS AND METHODS

1. Experimental animal and experimental tumor: Albino rats of random bred Gifu-strain weighing 100 to 150 gr. were used. Ascites hepatoma AH 130 or Sarcoma Yoshida (from Sasaki Institute, Tokyo) of approximately 5×10^6 cells was implanted subcutaneously in the back or foot-back.

All the animals died of progressive tumor development when the ascites hepatoma AH 130 reached $6 \times 7 \times 8$ mm. in the foot and 10 mm. of diameter in the back within 10 days. In Sarcoma Yoshida, more rapid development was observed.

2. New congo-red index: Concentration of congo-red in serum of 4 minutes after the injection / Concentration of congo-red in serum of 60 minutes after the injection (Adler-Reimann-Sugiyama), and splenic uptake of colloidal radiogold (Stern and Duwelius).

3. Cytotoxic activity of the serum: O'GORMAN's method³⁹⁾ was followed. Well rinsed tumor cells were suspended in a cell density of 30000/mm³ in serum of normal rats diluted to 5 times with Ringer's solution. A series of successive double dilution of the serum to be investigated was prepared with the same solution, which was then mixed with dilution of complement of guinea pig and incubated for an hour at 37°C. Trypan blue-Tyrode solution of 0.05 % was then added to the mixture. After several minutes' staining, cell count of stained cells was performed, which was represented in the term of percentage.

4. Phoretic study of serum protein: Paper electrophoresis was performed.

5. Tanned cell hemagglutination⁷⁾³⁹⁾⁴⁸⁾: The antigen for coating tanned cells was prepared following the method of Zilber and his associates⁴⁷⁾. Namely, homogenate of human cancer tissue was subjected to extraction for an hour with water of pH 7.6 in a freezer. Supernatant was adjusted to pH 6.0 and its precipitant was discarded. Supernatant

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was again adjusted to pH 4.0 and its precipitant was dried in a desiccator. Saline solution of 0.015 to 0.02% of the substance was used.

6. Microscopic preparation: Materials were embedded in paraffin and stained doubly with hematoxylin and eosin.

RESULTS

Experiment 1.: Reticuloendothelial function of tumorbearing animals. Reticuloendothelial function was examined with new congo-red index in subcutaneous inoculation of ascites hepatoma AH 130 in the back of the animals (Tab. 1). Utmost hyperactivity of reticuloendothelial function was observed 8 to 10 days after the inoculation, which gradually fell thereafter until final death of the animals. In other words, reticuloendothelial function is activated in relatively early period of tumor growth, and it is lowered in parallell with development of the tumor thereafter.

Table 1 Reticuloendothelial Function of Tumor-bearing Rats
(Subcutaneous Inoculation of Ascites Hepatoma AH 130)

	Control	Days after Inoculation			
		4	8	12	20
No. of animals	20	19	20	19	17
Splenic uptake of ^{198}Au -colloid	0.38 (0.21-0.64)	0.39 (0.31-0.53)	0.48 (0.24-0.87)	0.47 (0.24-0.77)	0.36 (0.22-0.89)
Congo-red index	1.78 (1.11-2.51)	2.07 (1.29-3.05)	2.76 (2.48-3.44)	2.37 (1.84-3.33)	1.68 (1.13-2.55)

Experiment 2.: Period of metastasis establishment in the regional lymphnodes. In subcutaneous inoculation of ascites hepatoma AH 130 in the back of the foot, it was 10 days after the inoculation that metastasis in the regional lymphnodes was observed constantly (Tab. 2), while in the inoculation of Sarcoma Yoshida, it was 4 days after the inoculation (Tab. 3).

Table 2 Time of Regional Node Metastasis
(Inoculation of Ascites Hepatoma AH 130 in the Back of the Foot)

Time of slaughter	No. of case	No. of metastasis
5 days after inoculation	3	0
7 days after inoculation	8	3
9 days after inoculation	10	9
10 days after inoculation	10	10
12 days after inoculation	5	5

Table 3 Time of Regional Node Metastasis
(Inoculation of Sarcoma Yoshida in the Back of the Foot)

Time of slaughter	No. of case	No. of metastasis
3 days after inoculation	8	4
1 days after inoculation	8	8
5 days after inoculation	5	5

Experiment 3.: Behavior of metastasized regional lymphnodes after the excision of primary growth. As metastasis in the above, initial metastasis in the regional lymphnodes was constantly observed 10 days after the inoculation of ascites hepatoma AH 130, which, at the same time, corresponds to the period of utmost hyperactivity of reticuloendothelial function. The primary tumor was removed at this stage and the behavior of metastasized

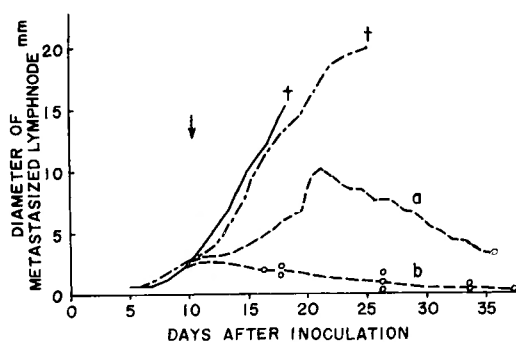


Chart 1

Behavior of Regional Metastasized Lymphnodes after Removal of Primary Tumor (Subcutaneous inoculation of ascites hepatoma AH 130 in the back of the foot). Group of 10th day amputation of the foot. Solid line represent non-treated group (32/32), chain line animals died (30/40) and broken line animals showed regression (a : 1/40, b : 9/40) in group of amputation. Arrow represent time of amputation.

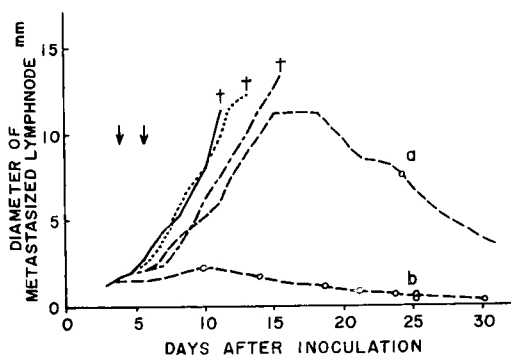


Chart 2

Behavior of Regional Metastasized Lymphnodes after Removal of Primary Tumor (Subcutaneous inoculation of Sarcoma Yoshida in the back of the foot). Solid line represent non-treated group, chain line animals died (43/53) and broken line animals showed regression (a : 2/53, b : 8/53) in group of 4th day amputation and dotted line group of 6th day amputation. Arrow represent time of amputation (4th day and 6th day).

lymphnodes was pursued thereafter (Chart 1). Regression of metastatic tumor was observed in amazingly high percentage as 25%, histological study of which revealed a characteristic appearance, that is, tumor cells were surrounded by newly appearing reticulum cells (Fig. 1) and finally the former was displaced with the latter (Fig. 2), whereas in control animals no reactive finding was observed, allowing progressive growth of tumor cells (Fig. 3). The regression occurred in 9.5 % (2/21) when the primary tumor was removed 13 days after the inoculation, what was more, these 2 cases of regression were those of retarded development of the primary tumor.

In the similar experiment using Sarcoma Yoshida, if the primary tumor was removed 4 days after the inoculation, when the initial metastasis was observed constantly in the regional lymphnodes, regression of the metastasized lymphnodes occurred in 20.7%. If the excision was performed 6 days after the inoculation, all the animals died of tumor growth, showing no regression of the metastatic tumor (Chart 2).

Experiment 4.: Cytotoxic activity of the serum after the excision of the primary tumor and its fraction. When the primary tumor was removed 10 days after subcutaneous inoculation of ascites hepatoma AH 130 in the back, cytotoxic activity showed higher value and maintained for long in the group of regression in metastatic tumor which then restored to normal as it regressed further, whereas, in control animals and in the animals died of over-

whelming growth of metastatic tumor despite the excision of the primary tumor, the activity remained within normal range until the death (Chart 3).

Phoretic study of the serum revealed an increase in gammaglobulin in the former serum, and this increase had a close correlation between cytotoxic activity (Chart 4).

Experiment 5.: Change in antibody titer in tanned cell hemagglutination of human serum after excision of the primary tumor. In most of cancer patients, antibody could

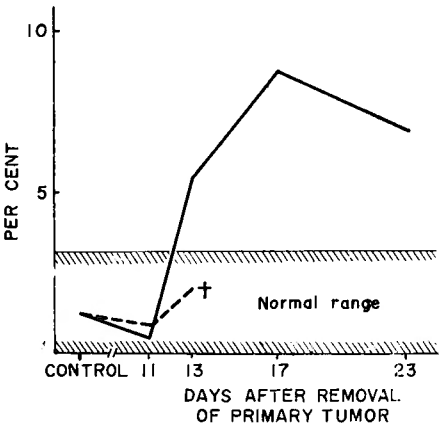


Chart 3

Cytotoxic Activity of Serum after Removal of Primary Tumor (Subcutaneous inoculation of ascites hepatoma AH 130 in the back. Mean value.) Solid line represent animals showed regression, broken line animals died of tumor. Normal range (0 to 3.2%).

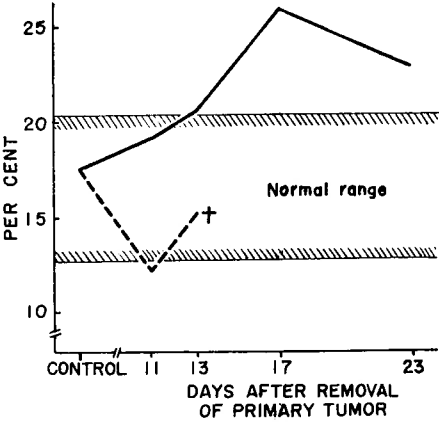


Chart 4

Changes in Gamma-globulin after Removal of Primary Tumor (Subcutaneous inoculation of ascites hepatoma AH 130 in the back. Mean value.) Solid line represent animals showed regression, broken line animals died of tumor. Normal range (12.6 to 20.3%).

not be detected or, if any, showed only low titer in the serum by the use of tanned cell hemagglutination with coating of extract from autochthonous tumor. However, in some cases of relatively favorable prognosis, elevation of antibody titer was sometimes observed after the operation, among which the antibody could be detected to be more than 1000 times dilution (Tab. 4).

Table 4 Tanned Cell Hemagglutination

Degree of cancer development*	Postoperative course**	Before operation	After operation***		
			1st wk.	2nd wk.	3rd wk.
IV	death	5	45	0	0
IV	death	45	0	0	0
IV	death	0	45	0	0
III	death	15	0	0	0
III	favorable	0	0	45	45
II	favorable	15	0	45	45
II	favorable	45	405	1215	1215
I	favorable	0	0	135	45
III	unknown	0	5	0	0
II	unknown	0	15	0	0
II	unknown	15	5	15	5

* Bill of J. S. S. to indicate deggre of tumor development.
** Prognosis within 2 years after operation.
*** Numbers indicate dilution of serum. All cases treated here are stomach cancer

Experiment 6.: Reticuloendothelial function of cancer patient. R. E. S. activity in cancer patient, examined by congo-red test, showed hypofunction as is easily presumed.

There was, however, some cases which showed almost normal level (Tab. 5).

Table 5 New Congo-Red Index in Stomach Cancer

Degree of cancer development*	New congo-red index	Control	New congo-red index
IV	1.44	Appendicitis	1.41
IV	1.48		
IV	1.34	//	1.32
IV	1.32	//	1.47
IV	1.18	//	1.42
III	1.28	Cholelithiasis	1.31
III	1.14		
II	1.45	//	1.31
II	1.39	Gastritis	1.58
II	1.39	//	1.13
II	1.25	//	1.39
II	1.21		
II	1.19		
Mean	1.31	Mean	1.37

* Degree of cancer development is shown similarly to Table 4.

Experiment 7.: Lymphnode reaction in cancer patient. The regional lymphnode and the mesenteric lymphnode, which is considered to react well at intraabdominal change, although this cannot be assumed to be regional ones in patients of stomach cancer, were studied histologically. Early death could be observed even in cases in which active lymphatic reaction was demonstrated in the non-metastasized regional lymphnodes (Fig. 4), leading us to the disapproval of the assertion of Black. On the other hand, prognosis seemed to be worse in the cases in which the reaction had spread as far as the mesenteric nodes any way (Tab. 6), while prognosis seemed to be favorable in the cases in which lymphatic structure was preserved relatively intact in the mesenteric nodes.

Case report.: Reduction of general resistance and tumor growth. A 54 year old man had a cancer of the size of child's head in lesser curvature of the stomach, at the same time having 2 small metastatic foci in the left lobe of the liver and metastasis in the mesocolon of the transverse colon. He received total gastrectomy, left lobectomy of the liver and resection of the transverse colon. Mitomycin C of 48 mg. in all was administered pre- and postoperatively. One week after the final injection of Mitomycin C (32th post-operative day), epistaxis was observed. Platelet count was 13700. Petechia appeared gradually all over the body (Fig. 5). Prednisolone was at once administered 20 mg. for 3 days, 10 mg. for 3 days and 5 mg. thereafter everyday. At the same time amino acid preparation and fresh blood was administered intravenously. Platelet count increased to 30000 after 1 week, 70000 after 2 weeks and petechia formation ceased. Then a tumor became palpable in the right hypochondric region, which was not observed at laparotomy, and enlarged progressively. Although more 1 week later platelet count became 100000, the tumor enlarged as large as child's head and the patient was driven to cachexy. He died 56 days after the operation.

Table 6 Lymphnode Reaction in Postoperative Early Death (Stomach Cancer)

Degree of cancer development*	Interval between opt. and death	Lymphnode reaction	
		Regional node	Mesenteric node
IV	2 month	Metastasis**	Metastasis**
IV	2 month	"	"
IV	5 month	Reticulosis Folliculosis	Fibrosis
IV	4 month	Metastasis**	"
III	2 month	"	Fibrosis
IV	2 month	Reticulosis	Reticulosis
IV	1 month	Reticulosis	Reticulosis Folliculosis
IV	7 month	Metastasis**	Reticulosis
II	14 month	Fibrosis	Reticulosis Folliculosis
IV	3 month	Reticulosis	Reticulosis Folliculosis

* Degree of cancer development is shown similarly to Tab. 4, 5.

** Metastasis means that meta-stasis was found in all the lymphnodes that could be studied.

Experiment 8.: An attempt to activate R. E. S. of tumor-bearing animals. The spleen was extirpated from tumor-bearing rats subcutaneously inoculated in the back with ascites hepatoma AH 130 at the period of reticuloendothelial hyperfunction. The spleen was homogenized and injected in the other tumor-bearing rats. Hereupon, regression of the tumor was observed in considerable frequency (Tab. 7). By the way, it was ascertained by cytotoxic activity test that the homogenate itself had no immediate effect upon tumor cells.

Table 7 Inhibitory Effect of Spleen Homogenate
(Subcutaneous Inoculation of Ascites Hepatoma AH 130)

Experimental group	No. of inoculation	No. of take	No. of no take	No. of death	No. of regression	Rate of regression
Control	54	44	10	34	10	22.7%
Injection of spleen homogenate from normal animals	54	44	10	35	9	20.4%
Injection of spleen homogenate from tumor-bearing animals	54	38	16	9	29	76.3%

DISCUSSION

Recently Old³⁷⁾ reported based on his studies on reticuloendothelial function of tumor-bearing animals that reticuloendothelial function is most activated at the time when the inoculum becomes slightly palpable and the same tendency was observed in artificially induced tumor as well as in spontaneous primary one. In our Experiment 1 and 2 also, reticuloendothelial function was most heightened 8 to 10 days after the inoculation when the early metastasis was observed in the regional lymphnodes, and the function declined gradually thereafter. When the primary tumor was, however, removed in the stadium of

utmost hyperfunction of the R. E. S., regression was observed in metastasized lymphnodes in considerable frequency, as was seen in Experiment 3.

It has long been assumed that operative aggression enhances the development of residual tumor cells^{(9) (14) (40)} and this is frequently ascertained by clinical experiences that abrupt development of the tumor was seemingly caused by exploratory laparotomy. On the other hand, it is difficult to assume that microscopically viable tumor cells or small metastasis did not remain in all of more than 30% of 5 year survivors of gastrectomized cancer patients. In fact KALLENBACH⁽²⁹⁾ pointed out according to the findings of autopsy performed within 6 postoperative weeks that tumor cells were left in 1/2 to 1/3 of cases, which were radically operated on and died of some other causes. And there are also many investigators reporting spontaneous regression of human cancer^{(15) (24) (28)}. The findings of our Experiment 3 can be interpreted to be demonstrating a possibility of regression of metastatic tumors, which might be caused by excision of the primary tumor in the stadium of utmost hyperactivity of R. E. S., with resulting predominance of host resistances to residual tumor cells. This was also ascertained, as seen in Experiment 4, by higher and longer lasting serum cytotoxic activity in the group of regression compared with that of normal range in control group, suggesting a favorable influence of removal of the primary tumor on the host.

As has been discussed by SOUTHAM⁽⁴³⁾, among serological factors in cancer immunity, there exist some factors in the serum of cancer patients deemed to be non-specific, such as inhibitory effect upon tumor cells or lowering of properdin level^{(38) (42)}, as emphasized recently, which can be also seen in the serum of normal man. It is difficult to presume an establishment of immunity against malignant tumor from the concept of "antigen loss" of GREEN⁽²²⁾. However, it would be of utmost importance to take a concept of postnatal appearance of antigenicity into account, when one intends to interpret a series of autoimmune diseases, recently studied deliberately by WITEBSKY⁽⁴⁹⁾, by the aid of clonal selection theory of BURNET.⁽¹¹⁾ Hence, presence or absence of specific antibody against tumor is an important problem in association to that of antigenicity of tumor. In fact, there are not a few investigators who ascertained the existence of specific antigenicity and antibody in tumor^{(13) (7)}.

Hsu⁽²⁵⁾ reported that no particular effect could be observed in serum, even in cases in which the resistance could be improved by vaccination. GRACE⁽¹⁹⁾ studied intradermal allergic reaction, using an extract of autochthonous tumor. GRAHAM⁽²⁰⁾ found antibody in serum by means of complement fixation test against extract of autochthonous tumor.

FINNEY^{(16) (17)} successfully detected antibody against an extract of autochthonous tumor, using tanned cell hemagglutination. He put emphasis upon nuclear fraction in cancer and microsome fraction in sarcoma as the antigen⁽¹²⁾.

It is considered difficult to demonstrate antibodies against tumor, because of its extraordinarily small amount, if any. It is not, however, impossible to assume that demonstration of the antibodies becomes feasible, when the equilibrium is altered and the amount of antibodies comes to surpass that of the antigen by excision of the tumor.

Hereupon, antibodies were detected in serum of cancer patients before and after the removal of the tumor, using tanned cell hemagglutination, which has been employed fre-

quently to demonstrate antibodies in autoimmune diseases because of its subtle sensitivity. There were observed some cases which showed elevation of antibody titer after operation, among those cases of relatively favorable prognosis. In some cases, particularly, antibodies could be demonstrated in the dilution of more than 1000 times postoperatively. These findings roughly come to accordance with those in experiments in animals. Furthermore, the existence of incomplete antibodies against extract of autochthonous tumor in serum have been detected by the authors, using Coombs serum after the SINDO's method⁽¹⁾ as in tuberculosis. This has been impossible up to present.

Even though the time of operation can be decided according to the utmost hyperactivity of R. E. S. in experimental tumor, it is very difficult to expect much from operation in human cancer, when the development of cancer has come to impair reticuloendothelial function of the host. According to the findings of our reticuloendothelial function test in cancer patients (Experiment 6), in considerable number of cases reticuloendothelial function remained in normal range, although there were naturally some cases of hypofunction. It is a matter of fact that favorable prognosis cannot be expected merely from almost normal reticuloendothelial function. However, there is a considerable difference in host resistance regardless of the degree of tumor development revealed at surgery.

Concerning the cases of breast cancer, BLACK⁽⁵⁾ reported that prognosis was favorable in those without metastasis in regional lymphnodes and at the same time revealing an appearance principally consisted of sinus histiocytosis, whereas prognosis was unfavorable in those showing degenerative picture. MOORE⁽²⁴⁾, BERG⁽³⁾ and others disapproved of this observation and BERG⁽³⁾, IMAI⁽²⁶⁾ and others attributed significance to stromal reaction of the tumor. Our study of regional lymphnodes in stomach cancer revealed that such reaction was markedly observed in non-metastasized lymphnodes adjoining to the nodes filled with tumor cells. Furthermore, among such cases early death was observed. These findings disagree with the opinion of BLACK⁽⁵⁾. On the other hand, prognosis was favorable in cases in which normal structure was maintained in further distant mesenteric nodes, while prognosis was unfavorable in cases in which metastasis or degenerative picture was observed in these nodes. From these findings, it might be said that prognosis is unfavorable when some changes are to be found in slightly distant nodes, suggesting some sort of invasion of the tumor to the nodes since cancer has become a disease of generalized nature. When the lymphnodes maintain their almost normal structure, there are many cases of favorable postoperative prognosis, which is presumably due to the fact that at this stage cancer remains to be a localized disease.

However, prognosis of cancer brought about by surgery is not favorable and chemotherapy or radiotherapy cannot be deemed to be effective. On the other hand, it has been said that removal of precancerous lesion does not always prevent the occurrence of cancer⁽²³⁾.

KONDO⁽³⁰⁾ pointed out a possibility of chemotherapy to decrease host resistance and gave a warning as "adverse effect". There are also many researchers who insist that cortisone or irradiation enhances the development of tumor, weakening the host resistance^(1) 2) 33) 45) 46) 50). As has already been shown in the case report, we have experienced some unpleasant cases which showed rapid growth of tumor presumably caused by disturbance of host resistance. From these considerations, it is strongly suggested that it must be ex-

tremely hazardous to treat cancer without the concept of host resistance.

BUINAUSKAS¹⁰⁾, MURRY³⁵⁾ and others observed effectiveness of immune serum in cancer treatment obtained from animals immunized with human cancer. GRAHAM²¹⁾ attempted vaccination. STONE⁴⁴⁾ reported that reimplantation of tumor cells treated in low temperature was effective, Ishibashi²⁷⁾ made studies to establish immunity by implantation of autochthonous tumor at a site distant from original site.

MIZUKAMI³²⁾ attributed significance to activation of R. E. S. by ligation of the splenic artery. In short, there have been many attempts to promote host resistance regardless of direct or indirect.

BORREL⁶⁾, BIACH⁴⁾ and others were, since early days, interested in anti-tumoral character of the spleen, and BRAUNSTEIN⁸⁾ made further studies systematically on this problem. From such a concept, we have also made Exp. 8, and ascertained that spleen homogenate prepared from tumor-bearing animal of the utmost hyperactivity of R. E. S. has an effect to hinder the growth of tumor, markedly activating reticuloendothelial function of other tumor-bearing animals. Participation of the spleen is not so large in the adults as in experimental animals³¹⁾. However, such a marked antitumoral effect of homogenate of the spleen which represents the R. E. S. of animals suggests a new approach to improve the results of cancer surgery at later stadium.

SUMMARY

In recent years, there is a tendency to investigate cancer under the concept of Host-tumor relationship. We have also made a series of experiments from a stand point of reticuloendothelial function of hosts, and have demonstrated that eventual regression can be observed in metastatic lesion in the residual lymphnodes when the primary tumor experimentally produced is removed at a certain stage of the tumor growth.

Moreover, in human cancer, even if the primary tumor is adequately removed, immediate recurrence can be seen, especially when the host resistance is weakened. The importance of host resistance and its activation in the treatment of cancer is emphasized in this paper.

REFERENCES

- 1) Agosin, M. : Christen, R. : Badinez, O. : Gasic, G. : Neghme, A. : Pizarro, O. : and Jarpa, A. Cortisone-Induced Metastases of Adenocarcinoma in Mice. *Proc. Soc. Exp. Biol. & Med.*, **80** : 128-31, 1952.
- 2) Baserga, R. : and Shubik, P. The Action of Cortisone on Transplanted and Induced Tumors in Mice. *Cancer Research*, **14** : 12-6, 1954.
- 3) Berg, J. W. Inflammation and prognosis in Breast Cancer. : A Search for Host Resistance. *Cancer*, **12** : 714-20, 1959.
- 4) Biach, P. : und Wetmann, O. Ueber den Wachstum-hemmenden Einfluss der Milz auf das Rattensarcom. *Wien. Klin. Wochenschrift*, **26** : 1115-8, 1913.
- 5) Black, M. M. . and Speer, F. D. Lymphnode Reactivity in Cancer Patients. *S. G. O.*, **110** : 477-87, 1960.
- 6) Borrel : und Bridre. Cited from Biach's article (Reference No. 4).
- 7) Boyden, S. V. The Adsorption of Proteins on Erythrocytes Treated with Tannic Acid and Subsequent Hemagglutination by Antiprotein Sera. *J. Exp. Med.*, **93** : 107-20, 1951.
- 8) Braunstein, A. Zur Frage der Krebsmetastasen in der Milz. *Z. Krebsforsch.*, **32** : 119-25, 1930.
- 9) Buinauskas, P. : McDonald, G. O. : and Cole, W. H. Role of Operative Stress on the Resistance of the Experimental Animal to Inoculated Cancer Cells. *Ann. Surg.*, **148** : 642-8, 1958.
- 10) Buinauskas, P. : Ill, K. : Mc Credie, J. a. : Brown, E. R. : and Cole, W. H. Experimental Treatment of

- Tumors with Antibodies. Arch. Surg., **79** : 432-9, 1959.
- 11) Burnet, F. M. The New Approach to Immunology. New England J. Med., **264** : 24-31, 1961.
 - 12) Byers, E. H. : Finney, J. W. : Schram, A. C. : Mallams, J. T. : and Wilson, R. H. Isolation and Characterization of Reactive Autologous Tumor Fractions. Proc. Am. Assoc. Cancer Research, **3** : 309, 1962.
 - 13) Claude, A. : and Rothen, A. Properties of the Causative Agent of a Chicken Tumor : XIV Relation between a Tumor Nucleoprotein and the Active Principle. J. Exp. Med., **71** : 619-33, 1940.
 - 14) Druckrey, H. : Hamperl, H. : Hecken, H. : and Rarai, B. Chirurgische Behandlung von Tiergeschwuelste. Z. Krebsforsch., **48** : 451-67, 1939.
 - 15) Everson, T. C. : and Cole, W. H. Spontaneous Regression of Cancer. : Preliminary Report. Ann. Surg., **144** : 366-83, 1956.
 - 16) Finney, J. W. : Wilson, R. H. : Clark, D. A. : and Byers, E. E. A Study of the Immunologic Properties and Cytotoxic Activity of Antitumoral Autoantibodies in Patients with Malignant Tumors. Am. J. Med., **27** : 309, 1959.
 - 17) Finney, J. W. : Byers, E. H. : and Wilson, R. H. Studies in Tumor Autoimmunity. Cancer Research, **20** : 351-6, 1960.
 - 18) Freund, E. : und Kaminer, G. Ueber die Beziehungen zwischen Tumorzellen und Blutserum. Biochem. Z., **26** : 312-21, 1910.
 - 19) Grace, J. T. : and Kondo, T. Investigations of Host Resistance in Cancer Patients. Ann. Surg., **148** : 633-41, 1958.
 - 20) Graham, J. B. : and Graham, R. M. Antibodies Elicited by Cancer in Patients. Cancer, **8** : 409-16, 1955.
 - 21) Graham, J. B. : and Graham, R. M. The Effect of Vaccine on Cancer Patients. S. G. O., **109** : 131-8, 1959.
 - 22) Green, H. G. Immunological Aspects of Cancer. A Ciba Foundation Symposium on Carcinogenesis : Mechanism of Action. 131-64, 1959. J. & A. Churchill. Ltd., London.
 - 23) Grosse, H. Schuetzt die Operative Entfernung der Präkanzerose Tatsächlich vor Krebs ? Muench. Med. Wochenschrift., **98** : 1773-1, 1956.
 - 24) Gummel, H. : und Wittig, G. Ueber die Notwendigkeit einer Wertbestimmung maligner Tumoren. Chirurg., **31** : 448-51, 1960.
 - 25) Hsu, T. C. Reduction of Transplantability of Novikoff Hepatoma Cells Grown in vitro and the Consequent Protecting Effect to the Host against their Malignant Progenitor. J. Nat. Cancer Instit., **25** : 927-35, 1960.
 - 26) Imai, K. : and Otsuka, H. Host-reaction against Tumor. Saishin-igaku, **11** : 1808-19, 1956, in Japan.
 - 27) Ishibashi, Y. : Hattori, T. : Fujii, G. : Okada, K. : Sekiguchi, M. : Ashikawa, K. : and Motoya, K. Autoimmune Therapy of Cancer. Gekachiryo, **6** : 1-9, 1962, in Japan.
 - 28) Jenkins, G. D. Regression of Pulmonary Metastasis following Nephrectomy for Hypernephroma. : Eight Year Followup. J. Urology, **82** : 37-40, 1959.
 - 29) Kallenbach, H. Ueber Beziehungen zwischen Okkulten Metastasen und Dauerheilung beim Carcinom. Chirurg., **30** : 54-6, 1959.
 - 30) Kondo, T. : and Moore, G. E. Production of Metastases by Treatment with Carcinostatic Agents. Cancer Research, **21** : 1396-9, 1961.
 - 31) Lucas, R. V. : and Krivit, W. Overwhelming Infection in Children following Splenectomy. J. Ped., **57** : 185-91, 1960.
 - 32) Mizukami, T. : and Tsunamura, S. Some Contributions to Cancer Control by the Stimulation of the Physiological Protective Power of the Organism. Oncologia, **15** : 312-23, 1962.
 - 33) Molomut, N. : Spain, D. M. : Gault, S. D. : and Kreisler, L. The Induction of Metastases from Sarcoma 1 in C57B/6 Mice. Am. J. Path., **30** : 375-89, 1954.
 - 34) Moore, R. D. : Chapnick, R. : and Schoenberg, M. D. Lymphnodes Associated with Carcinoma of the Breast. Cancer, **13** : 545-9, 1960.
 - 35) Murray, G. Experiments in Immunity in Cancer. Canad. Med. Assoc. J., **79** : 249-59, 1958.
 - 36) O'Gorman, P. The in vitro Cytotoxic Activity of Murine Iso-antisera on Normal and Malignant Cells. Brit. J. Cancer, **14** : 335-45, 1960.
 - 37) Old, L. J. : Benacerraf, B. : Clarke, D. A. : Carswell, E. A. : and Stockert, E. The Role of the Reticuloendothelial System in the Host Reaction to Neoplasia. Cancer Research, **21** : 1281-300, 1961.
 - 38) Pillemer, L. : Blum, L. : Lepow, I. H. : Ross, O. A. : Todd, E. W. : and Wardlaw, A. C. The Properdin System and Immunity. : I. Demonstration and Isolation of a New Protein, Properdin, and its Role in Immune Phenomena. Science, **120** : 279-85, 1954.



Fig. 1

Metastasis in Regional Lymphnode (Subcutaneous inoculation of ascites hepatoma AH 130 in the back of the foot). In animals showed regression after removal of primary tumor (1).

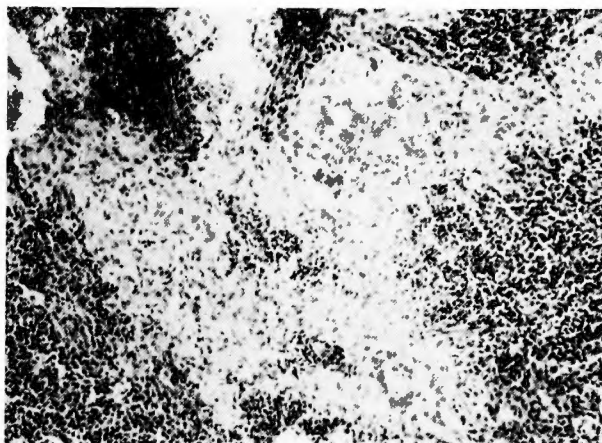
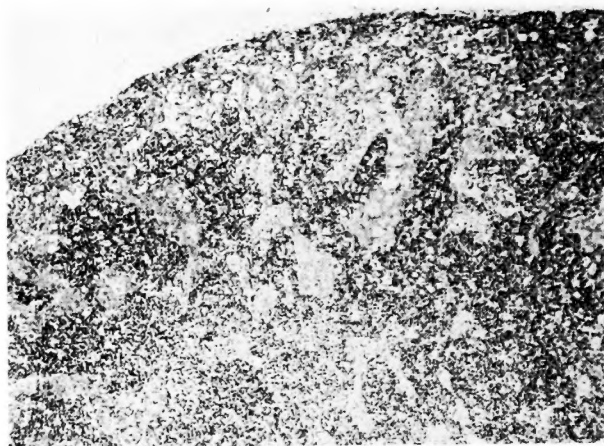
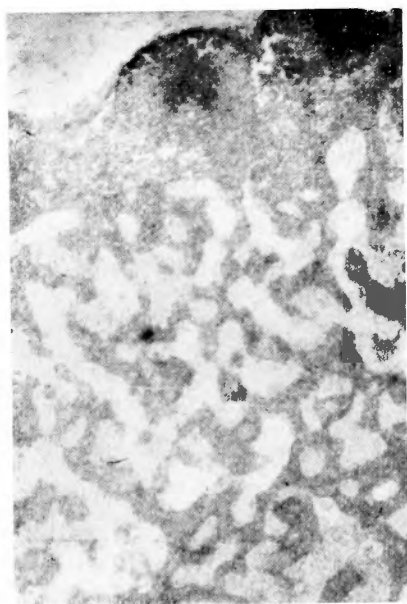


Fig. 2

Metastasis in Regional Lymphnode (Subcutaneous inoculation of ascites hepatoma AH 130 in the back of the foot). In animals showed regression after removal of primary tumor (2).

**Fig. 3**

Metastasis in Regional Lymphnode (Subcutaneous inoculation of ascites hepatoma AH 130 in the back of the foot). Non-treated group.

**Fig. 4**

Case of Active Regional Lymphnode Reaction: 63 year old man, having a symptom in the upper abdomen since 1 month. Operated on as stomach cancer. Although active lymphnode reaction was seen in non-metastasized lymphnodes in excised material, prognosis was unfavorable and died within 5 month after surgery.

**Fig. 5**

Case Report: 54 year old man, revealing hemorrhagic tendency 1 week after pre- and postoperative administration of Mitomycin-C of 48 mg. for stomach cancer in greater curvature.

- 39) Stavitsky, A. B. Micromethods for the Study of Proteins and Antibodies. : I. Procedure and General Applications of Hemagglutination and Hemagglutination-Inhibition Reactions with Tannic Acid and Protein-treated Red Blood Cells. *J. Immunol.*, **72** : 360, 1951.
- 40) Schatten, W. E. An Experimental Study of Postoperative Tumor Metastasis following Total Removal of Primary Leg Tumor. *Cancer*, **11** : 455-9, 1958.
- 41) Sindo, T. : Utahashi, T. : Hiyama, A. : Haga, K. : Ito, M. : and Ichikawa, Y. Studies on a New Method for the Incomplete Antibody in Tuberculosis. *Jap. J. of Bact.*, **12** : 389-95, 1957.
- 42) Southam, C. M. : and Pillemer, L. Serum Properdin Levels and Cancer Cell Homografts in Man. *Proc. Soc. Exp. Biol. & Med.*, **96** : 596-601, 1957.
- 43) Southam, C. M. Relationships of Immunology to Cancer. : A Review. *Cancer Research*, **20** : 271-91, 1960.
- 44) Stone, H. B. : Curtis, R. M. : and Brewer, J. H. Can Resistance to Cancer be Induced? *Ann. Surg.*, **134** : 519-28, 1951.
- 45) Toolan, H. W. Transplantable Human Neoplasms Maintained in Cortisone-treated Laboratory Animals. : H. S. no. 1 ; H. Ep. no. 2 ; H. Ep. no. 3 ; and H. Emb. Rh. no.1. *Cancer Research*, **14** : 660-6, 1954.
- 46) Toolan, H. W. The Potentialities of Normal Cells Implanted in Cortisonized and/or X-radiated Hosts. *Cancer Research*, **17** : 248-50, 1957.
- 47) Vygodchikov, V. Pathogenesis and Immunology of Tumors. 1959, Pergmon Press, London.
- 48) Witebsky, E. : Rose, N. R. : Terplan, K. : Paine, J. R. : and Egan, R. W. Chronic Thyroiditis and Autoimmunization. *J. A. M. A.*, **164** : 1439-47, 1957.
- 49) Witebsky, E. The Question of Self-Recognition by the Host and Problems of Autoantibodies and their Specificity. *Cancer Research*, **21** : 1216-22, 1961.
- 50) Wood, J. S. : Holyoke, E. D. : Clason, W. P. C. : Sommers, S. C. : and Warren, S. An Experimental Study of the Relationship between Tumor Size and Number of Lung Metastases. *Cancer*, **7** : 437-43, 1954.

和文抄録

主病巣切除後の担癌宿主の抵抗性

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臨床的に早期手術が施行出来たと思われる症例に、予想外の早期の再発転移を認めたり、末期症例で姑息的手術に止まつた症例にかなりの長期生存や、時には自然治癒を思わせる症例が経験されて、臨床家に奇異の感を抱かしめることがある。

或る個体に発生した癌の発育や経過に動揺があることはその癌自体の悪性度が変化したと考えるよりも宿主たる生体側の抵抗性に変動があつたためと考えざるを得ない。最近かかる見地からHost-tumor relationshipなる立場で癌を検討しなおす傾向があり、われわれも2～3の実験や臨床成績から検討を加えてみた。

1) 先づ腹水肝癌 AH 130 及び吉田肉腫を用いて、初期転移の起つたと思われる時期に主腫瘍のみを切除して、以後の転移巣の動向につき検索した。即ち腹水肝癌 AH130 をラットの足背又は皮下に移植すると、腫瘍は局所に発育するのみならず、移植後10日目には、全例、領域リンパ節にも転移を形成して結局腫瘍死する。この担癌動物の網内系機能を新コンゴロート係数及び ^{198}Au 脾摂取率にて逐次検索してみると、移植後8～10日目以最も亢進し、以後次第に減弱する。かかる初期転移を形成し、しかも網内系機能の最も亢進している時期に領域リンパ節の転移巣を残し、主腫瘍のみを切除すると、30/40では転移巣が発育して結局腫瘍死するが、残りの25% (10/40)では転移巣の自然退縮がみられた。吉田肉腫でのかかる時期は移植後4日目で、この時に主腫瘍を切除すると18.8% (10/53)に転移巣の自然退縮がみられた。腹水肝癌 AH130及び吉田肉腫共に主腫瘍切除の時期が遅れると効果が少ないか、又は全く効果がみられなかつた。これらの変化を組織学的に逐次追求してみると、転移リンパ節の退縮は、細網細胞が主体となつているのが観察された。

2) 上記の実験例につき、血清の腫瘍細胞に対するCytotoxic effectをしらべてみると、腫瘍死するものでは正常範囲内の変動であつたが至然退縮を示した群ではCytotoxic effectの上昇が認められ、且つその上昇は血清中の γ -グロブリンの変動に従つて変動している如く思われた。

3) 臨床的な癌が実験癌にみられたような早期のものであれば、例え最近述べられている如く流血中癌細胞の存在や手術野における癌細胞の遺残が存在しても手術に対する予後に期待が持てよう。しかし例えば胃癌患者の網内系機能を新コンゴロート係数でしらべてみても必ずしも一定の傾向がみられないことが多く、臨床的癌の時期を予測することは困難である。そこで胃癌につき腸間膜リンパ節の反応態度につき検索した。術後2年間の予後との関係を見ると、腸間膜リンパ節の反応がrichであつたものに予後不良のものが多く、このことは、領域外と考えられる腸間膜リンパ節に迄変化の及んでいる場合には癌が既に全身的であつて、手術後の予後も不良であつたものと考えられた。

4) 臨床例の胃癌切除後に血清中タンニン酸処理血球凝集反応の抗体価の変動を追求してみると症例によつては1000倍以上の抗体価のみとめられたものがあり、かかる例では予後も良好であつた様に思われた。

反対に術後抗癌剤の投与によつて、かえつて全身抵抗性の減弱を来し、癌の発育を促進せしめた症例がしばしば経験され、生体の抵抗性を考慮せずに癌の治療に当ることは甚だ危険であると考えられる。

5) 古来癌患者の抵抗性を刺激して癌治療に利用せんとする試みが行なわれて来たが、われわれも網内系機能の亢進している時期の担癌動物の脾乳剤が、他の同様な担癌動物の網内系を著明に刺激して、癌の発育に抑制的に作用することを明らかにした。