CLINICAL TRIAL WITH A NEW ANTICANCER AGENT, SOEDOMYCIN

TETSUO KITAHARA, SHIZUO HOMMA and NORIHISA SATO
Tokyo Teishin Hospital, Surgical Division
MOMOE SOEDA
II nd Research Institute, Research and Development H. Q., J. D. A.
HIROSHI SUMIYAMA
Pharmaceutical Division, Hitachi Chemicals

(Received March 2, 1971)

Introduction

It has been shown that the host defence mechanism (immunity) plays an important role in the curative process of malignant tumors in man and animals. A close relationship between neoplastic changes and pre-existed deficiency of the immune response in the host[8,9], or between the oncologic actions of various carcinogens and their inhibitory effects upon the immune response of the host[10-12], or between the competence of the host to elicit immune response and tumor regression[14,17,19] has been demonstrated mainly by animal experiments. The improvement in therapeutic effect may be induced by addition of immunotherapy to surgery and postoperative chemotherapy[13,22], and an immunosuppressive agent, cortisone, is well known highly to reduce the chemotherapeutic effect of various anticancer agents[18,20,21]. It increases the incidence of metastases of malignant tumors[18,23]. On the other hand, immunosuppressive drugs are known to induce immunological tolerance[24-27] and to suppress rejection reaction in man and animals[28-32]. Immunological deficiency or induction of immunological tolerance may provide a favorable condition for neoplasia or progressive growth of neoplastic tumors[33-36].

Many types of anticancer agents such as alkylating agents, antipurines, antifolic acids, halogenated pyrimidines, vinca alkaloids, and steroids have been shown to be potent inhibitors of the immune response in animals[37-41] and in man[42-44,46].

For these reasons, it seems paradoxical to treat patients with malignant tumors with chemotherapeutical agents which induce significantly deleterious effects upon the immune response of the host essential for the defence against tumor growth.

A new anticancer agent, soedomycin, has a unique property to suppress the nuclear division of tumor cells and to induce the loss of viability of ascites tumor cells such as EHRLICH ascites carcinoma, Sarcoma-180, and YOSHIDA sarcoma, without causing any injurious effect upon the cells of organs and tissues, including the bone marrow, lymphatic, cardiovascular, urogenital systems, liver, gastrointestinal tract *etc.*

Clinical trials were initiated in September, 1965, mainly in order to evaluate its preventive effect upon the recurrence of gastric cancer after radical removal of the parent tumor. Total 83 patients were thus treated until September, 1970, of which 72 cases were patients with gastric cancer and 11 cases were those with cancers of the other organs.

In this paper we will report the therapeutic results obtained from patients treated for past 5 years.

I. Soedomycin

This agent was chemically extracted by SOEDA from culture media of *Streptomyces hachijoensis* in 1963, and then purified and named soedomycin in 1965[1,2,3]. It is now obtained in the form of white amorphous powder, highly soluble in water, but hardly soluble in ethanol or methanol. According to the data up to date, it seems to belong to polysaccharide having a molecular weight of about 1,000, and it shows a clear maximum absorption at 210 mμ on the absorption spectrum.

The LD_{50} of this agent for the mouse of dd-strain is more than 120 mg/kg by intraperitoneal route. It has neither myelotoxic nor lymphotoxic effect upon animals and man. It does not induce leukopenia, lymphopenia, anemia, thrombocytopenia, dysfunction of the liver, gastrointestinal toxic symptoms *etc.* The red blood cells, hemoglobin and hematocrit are

rather increased by administration of a daily dose of 5.0 mg/kg of this agent to the rabbit for 14 days. Histological examination of animals thus treated does not reveal any toxic changes in the bone marrow, lymphatic system, liver, kidney, cardiovascular system, lung, adrenal glands, gastrointestinal tract, and other organs.

For clinical purpose, a daily dose of 1.0 to 2.0 mg/kg is usually given i.v. for at least 3 weeks starting immediately after radical resection of the primary tumor. In cases wherein radical resection is incapable or in inoperable cases a longer course with a larger daily dose of soedomycin is usually required.

In spite of the complete absence of serious toxic side-effects, soedomycin is capable of inducing inhibition of nuclear division of ascites tumor cells of EHRLICH ascites cancer, Sarcoma-180 and YOSHIDA sarcoma. For instance, the nuclear division rate of YOSHIDA sarcoma cells drops, on average, to about a half 6 hours after i.p. injection of 0.2 mg/kg into the rat developing typical ascites tumor. This effect is usually maintained at least for 15 hours. With 1.0 mg/kg, it drops to about 30% and persists for 24 hours.

In vitro treatment of these ascites tumor cells with this agent easily results in the loss of viability of such cells, which become incapable of inducing ascites tumor if i.p. inoculated into susceptible animals.

It is of much interest that animals once received transplantation of ascites tumor cells treated, *in vitro*, with soedomycin acquire a certain degree of specific resistance within 10 days sufficient to tolerate i.p. inoculation of 10^5 to 10^6 intact tumor cells, which correspond to 10^3 to 10^4 times the minimal transplantable cell dose[1,2,3]. Inoculation of as few as 10 tumor cells is lethal to most WISTER rats.

Although its antitumor activity is not so potent, soedomycin may be a unique anticancer agent of much higher selective toxicity than any other anticancer agents commonly used at present for clinical purpose.

II. The object of clinical trial

A. Gastric cancer patients

The 5-year-survival rate of patients with gastric cancer whose primary cancerous lesions have been radically resected is around 30% according to the statistics of many authors[5~7]. The rate of patients wherein such radical resection can be performed ranges between 40 and 60%, and usually 50% of all cases of gastric cancer[4], so that the survivors of 5 years duration cannot exceed 20% of the total cases of gastric cancer.

Since it is paradoxical to expect a success in chemotherapy of more advanced cases wherein only subtotal resection of tumor is possible or inoperable at all with the same agents incapable of inducing complete cures in almost all radically operable cases, chemotherapy with soedomycin was applied mainly to the patient with gastric cancer whose primary tumor had been radically removed. (Group 1).

Postoperative chemotherapy should, of course, be started immediately after operation to eradicate the residual remnants of cancer cells within the period where the number of such cells is quite small. In our series, 67 cases were treated immediately after operation, but there were 5 other cases wherein chemotherapy was started several weeks or months after operation done in other hospitals (Group 2).

A-1. Patients in Group 1

The age and sex distributions of total 67 cases are shown in the following table (Table 1).

Table 1. Age and sex distributions

Sex	Age (in years)						
	20~29	30~39	40~49	50~59	60~69	70~79	Total
Male		6	4(1)	15(1)	14(1)	3	42(3)
Female	1	3	8	5	5(2)*	3	25(2)
Total	1	9	12(1)	20(1)	19(3)	6	67(5)

*(2) means that 2 patients died up to the end of December 1970.

The classification of total 67 cases due to the stage of gastric cancer is shown in the following table (Table 2).

Table 2. Stage distribution

Stage	1965	1966	1967	1968	1969	1970	Total
I		5	9	6	4	4	28
II	1	1	7(2)	6	1	2	18(2)
III			4(1)	8(2)	3	6	21(3)
Total	1	6	20(3)	20(2)	8	12	67(5)

The classification of 67 cases due to the postoperative course-lengths is shown in the following table (Table 3).

A-2. Patients in Group 2

Five cases included in this group did not receive immediate chemotherapy with soedomycin after

operation, because they had received radical operation in other hospitals. A period between 8 weeks and 10 months had passed after operation before they received chemotherapy with soedomycin in our hospital. According to the statistics of radically operated cases of gastric cancer, more than 20% of patients are known to develop recurrence and die within a year after operation. In view of this fact, the residual remnants of neoplastic cells may grow relatively rapidly after surgical enucleation of the parent gastric tumor. These cases in our series, therefore, have been followed up as a different category from that of the Group 1.

In this group, 35, 26, 15, 8 and 7 months have passed respectively since they received operation, and neither recurrence nor death has occurred until the end of December 1970.

B. Patients with other cancer

This group is consisted of total 11 cases of cancer of the various organs other than the stomach. There are 6 cases of colon cancer, 2 cases of rectal cancer, 2 cases of breast cancer, and one case of cancer of the thyroid gland. One of 2 cases of breast cancer was surgically treated in other hospital, so that chemotherapy with soedomycin was initiated about 2 months after operation. The other 10 cases were operated in our hospital and followed by immediate chemotherapy with soedomycin.

The classification of 11 cases due to their diagnosis and postoperative course length is seen in the following table (Table 4).

Neither recurrence nor death has occurred among these 11 cases until the end of December 1970.

III. Analysis of the therapeutic results

A. Patients with gastric cancer

A-1. Group 1 (67 cases)

In this group, 5 cases developed recurrence and died during the period between 16 and 26 months after operation. No death occurred within a year among total 55 cases wherein more than 12 months have passed since they received radical operation in our hospital. The 2 and 3-year-survival rates at the end of December 1970, in our series are 93.6% (44/47) and 88.9% (24/27) respectively which are by far better than those in any other previous series reported by many authors[4~7].

Five out of total 67 cases in this Group 1 expired due to recurrence, and the last death occurred 26 months after operation. Since then there has been neither recurrence nor death among total 42 cases who have survived more than 2 years without signs of recurrence since they received radical resection of the parent tumors.

In many other previous statistics, the number of survivors progressively decreases as time goes by during the course between 2 and 5 years after operation. For instance, the 2, 3, 4 and 5-year-survival rates in the URABE's series[5] are 57.2%, 44.4%, 35.5% and 32.2% respectively, while the 2, 3 and 4-year-survival rates in the KURU's series[7] are 50.6%, 42.5% and 31.9% respectively.

The survival rates in our series are shown in the following table (Table 5)

In our series, there are total 61 cases wherein

Table 3. Postoperative course-lengths

Total	Postoperative course (in months)									
	<6	6~11	12~17	18~23	24~29	30~35	36~41	42~47	48~53	54~62
67	6	6	6	2	8(1)	12(1)	10(2)	10(1)*	2	5

* 10(1) means that a period between 42 and 47 months has passed postoperatively in 10 cases and one of them died already.

Table 4. Classification of 11 cases

Diagnosis	Postoperative course (in months)							
	6~11	12~17	18~23	24~29	30~35	36~41	42~47	Total
Colon cancer	1	2	—	—	—	1	2	6
Rectal cancer	—	1	—	—	—	1	—	2
Breast cancer	—	—	—	—	—	1	1	2
C. of the thyroid gland	1	—	—	—	—	—	—	1
Total	2	3	0	0	0	3	3	11

Table 5. The survival rates in the Group 1 (in December 1970)

Stage	Postoperative course (in months)											Total
	<6M	6M	12M	18M	24M	30M	36M	42M	48M	54M	60M	
I	28/28	26/26	24/24	20/20	20/20	18/18	14/14	9/9	5/5	4/4	1/1	28/28
II	18/18	16/16	16/16	14/15	13/15	10/12	7/9	5/6	2/2	1/1	1/1	16/18
III	21/21	19/19	15/15	13/14	11/12	7/9	3/4	2/2	—	—	—	18/21
Total	67/67	61/61	55/55	47/49	44/47	35/39	24/27	16/17	7/7	5/5	2/2	62/67
%	100%	100%	100%	95.9%	93.6%	89.7%	88.9%	94.1%				
II+III	39/39	35/35	31/31	27/29	24/27	17/21	10/13	7/8	2/2	1/1	1/1	34/39
%	100%	100%	100%	93.8%	88.9%	81.0%	76.9%	87.5%				

more than 6 months have passed since they received operation. As shown in Table 2, the rate of patients surgically treated at the stage I in our series was over 40%. The rate of such patients is usually less than 20%[4]. Thus in the URABE's series, it was less than 3% (3/124), while in the KURU's series[7] it was 21.5% (165/768). In the YAMAGATA's series[6] and INOKUCHI's series[4] it was 10.6% (57/533) and 16.7% (62/371) respectively.

Consequently, this high rate of the stage I may have apparently contributed to an excellent result in our series, however, the 2 and 3-year-survival rates of the stages II and III in our series are 88.9% (24/27) and 76.9% (10/13) respectively. These figures are much higher than those in any other series mentioned above. For instance, the 2 and 3-year-survival rates in the KURU's series[7] were 40.0% (175/437) and 30.9% (81/262) respectively.

According to the previous statistics, the 5-year-survival rate of the patient surgically treated at the stage I is generally high and 22/22 or 100% in the INOKUCHI's series[4], 2/3 in the URABE's series[5], 30/33 or 90.9% in the YAMAGATA's series[6], or 66.0% in the TAGUCHI's series[16]. KURU[7] did not show the 5-year-survival rate in his series. (The 4-year-survival rate in his series was 23/27 or 85.2%).

The 2-year-survival rate of the patient surgically treated at the stages II and III was shown to be 69/121 or 57.0% (5), 253/496 or 51.0% (6), and 175/437 or 40.0% (7), while 3-year-survival rate of such cases was 53/121 or 43.8% (5), 165/461 or 35.8% (6), and 81/262 or 30.9% (7) respectively. Similarly, the 4-year-survival rate was 42/121 or 34.7% (5), and 23/117 or 19.6% (7), while the 5-year-survival rate was 38/121 or 31.4% (5), and 73/417 or 17.5% (6) respectively. For unknown reasons, NAKAZATO[15] and TAGUCHI[16] did not show the exact 3, 4 or 5-year-survival rate in their series.

In contrast, neither recurrence nor death has occurred among total 28 cases in our series wherein operation was performed at the stage I of gastric cancer. Thus the 3, 4 and 5-year-survival rates are 14/14, 5/5, and 1/1 respectively.

With regard to the stages II and III, the 2, 3, and 4-year-survival rates are 24/27 or 88.9%, 10/13 or 76.9%, and 2/2 respectively in our series, which are much higher than those in the other series cited above.

With regard to the overall survival rate, 33 out of 124 cases in the URABE's series (26.2%) and 244 out of 768 cases in the KURU's series (31.8%) died within a year after operation, while 243 out of 553 cases in the YAMAGATA's series (43.9%) died within one and a half years following operation. In our series, none of the total 55 cases died within a year following operation, and all survived more than one year, regardless of the stage of the disease. This may be an outstanding feature in our series.

Total 42 cases in our series have survived more than 2 years without any signs of recurrence. Neither recurrence nor death has occurred since then among these 42 cases, and 2, 5 and 17 cases have survived more than 5, 4 and 3 years respectively, all in good health. This long durable saving from recurrence of the disease may be another outstanding feature in our series.

Five cases developed recurrence and died during the course between 16 and 26 months following operation, 2 were surgically treated at the stage II and 3 at the stage III, however, 7 out of 8 cases operated at the stage II or III have survived more than 3 and a half years in good health since they received operation.

Although the number of cases in our series is not sufficient as yet, it may be evident that soedomycin chemotherapy given immediately after radical operation may have much contributed to inhibition

of postoperative recurrence of gastric cancer.

A-2. Gastric cancer in the Group 2

As mentioned above, 20 to 30% of radically operated cases of gastric cancer cannot survive one year following operation. This fact may mean that the residual remnants of cancer cells after surgical removal of the parent tumor may grow relatively rapidly within several months after operation and cause early death of the patient. Postoperative chemotherapy should, therefore, be started as early as possible after operation in order to eradicate such remnant neoplastic cells when they are quite small in number.

Five cases in this group were given soedomycin after the course of 8 weeks to 10 months since they had received operation in other hospitals. There were no signs of recurrence when chemotherapy with soedomycin was started, however, their further courses have been followed up included in a separate group from the Group 1, wherein chemotherapy with soedomycin was given immediately after operation, because the conditions under which they first received out chemotherapy might be substantially different from those of the Group 1.

In spite of delayed application of soedomycin chemotherapy, they have been quite well, and 35, 26, 15, 8 and 7 months have passed respectively since they received operation. No signs of recurrence have been observed in these cases up to the end of December 1970.

B. Patients with other cancer

As shown in Table 4, there are 6 cases of cancer of the colon, 2 cases of cancer of the rectum, 2 cases of cancer of the breast, and one case of cancer of the thyroid gland. Except for one breast cancer case, they received radical operation and immediate postoperative chemotherapy with soedomycin in our hospital. One patient with breast cancer received operation in other hospital and chemotherapy with soedomycin was started about 2 months later.

More than 3 years have passed in 6 out of 11 cases in this group without any signs of recurrence since operation was performed. Besides these, 2 cases of colon cancer and one case of rectal cancer have survived more than one year in good health. Although the number of cases in this group is too small, it still appears that chemotherapy with soedomycin may have contributed to inhibition of postoperative recurrence at least of colo-rectal cancer, considered in light of the data obtained from chemotherapy of gastric cancer.

Discussion

For many years, it has been a failure to induce complete relief even in most cases of cancer wherein radical resection of the primary tumor can be performed. In gastric cancer, more than 20% of such cases will develop recurrence and die within a year following radical removal of the parent tumor, whether they are given postoperative chemotherapy or not. In general, more than 50% of them cannot survive 3 years, and the survivors of 5-year-duration cannot exceed 30% of radically operable cases. The rate of such radically operable cases is, on average, 50% of all patients with gastric cancer, so that the rate of survivors of 5 years duration is less than 20% of the overall cases of this disease[4].

For this reason, much effort has been made for years effectively to suppress postoperative recurrence and thus substantially to improve the survival rate of the patient by means of chemotherapy with various anticancer drugs, but no significant success has been achieved up to the present time. Moreover, in some statistics it appears that the present chemotherapy routinely applied in our country may help rather than hinder the postoperative recurrence of gastric cancer.

It is, of course, far more difficult to attain complete relief of gastric cancer, wherein only subtotal resection of the parent tumor is possible or which is inoperable at all. It seems entirely impossible to achieve a success in inducing cures of long duration in such cases by means of chemotherapy with anticancer agents incapable of inducing complete cures in almost all cases of radically operable gastric cancer.

It is well known that all or most anticancer agents clinically used at present are potent inhibitors of the immune response in man[27,42~44,46] and animals[37~41,45]. It has been demonstrated that inhibitors of the immune response of the host may induce immunological toleranse to various antigens including allografts in adult animals[24~26,41,47] and in man[27~30,47]. In human transplantation surgery, immunosuppressive drugs such as azathioprine (Imuran), 6-mercaptopurine, prednisone, and dactinomycin have been used to suppress rejection reaction of the recipient[28~30]. Clinically, carcinoma metastatic to the kidney was transferred to the recipient when he received a kidney transplant from a cadaveric

source[28~30]. The tumor persisted and grew while the recipient received immunosuppressive therapy, but underwent immunologic rejection when the administration of immunosuppressive drugs was discontinued and the major portion of the tumor was removed[30]. Transplantation of human cell lines from man to man usually does not occur and cells are rejected promptly in healthy recipients[28,48,49], but it was demonstrated that human tumors can be serially maintained in cortisone-treated laboratory animals such as hamsters, rats, and mice[50,51]. These studies have emphasized the importance of the host's immune response in determining the behavior of allogeneic transplanted tumor in man, and these findings may suggest that the immune mechanism may be operating in spontaneous neoplastic growth in man, at least in those tumors that may have specific antigenic components.

According to the opinions of RUBIN[35] and BURNE[36], it appears that the induction of immunologic tolerance or the existence of immunologic deficiency may always provide a favorable condition for neoplasia or progressive growth of neoplastic tumors.

In experimental studies with S-180, FERRER and MIHICH[14] found that the therapeutic treatment alone or the host immunologic reaction alone was unable to cause complete regression of tumors. In contrast, the combination of these 2 factors led to cures in a significant number of animals. Based upon these findings they suggested that the effective therapy would depend upon the availability of agents sufficiently selective to inhibit the growth of the tumor without impairing the immunologic response of the host.

GLYNN *et al.* treated CDBA F_1 hybrid male mice bearing advanced leukemia L1210 with halogenated derivatives of methotrexate and obtained an extensive increase in survival time and appreciable number of survivors of indefinite duration. However, many of these survivors were shown refractory to reinoculation with either antifolic-sensitive or resistant sublines of leukemia L 1210[52,53]. Thus, increased cures of animals by halogenated methotrexate was attributed to the elicitation in the host of an immune response which contributed to the inhibition of growth of leukemia L 1210.

REINER *et al.* observed that immunosuppressive anticancer drugs such as cyclophosphamide (endoxan), methotrexate, and 5-fluoro-2-deoxyuridine increase the incidence of chemically induced tumors in mice[33,34], while the enhancement of metastases was induced by antilymphocytic serum[54] or cortisone treatment[23] in murine tumor systems.

In view of these facts, it seems resonable to consider that 2 types of actions are responsible for the overall effects of anticancer chemotherapy seen in animal experiments. One is the therapeutically induced inhibition of the growth of the tumor and another is the immunologically dependent regression of the impaired tumor.

Thus, the difficulty in chemotherapy of human cancer may be attributed to hitherto known anticancer drugs inevitably associated with deleterious side effects to induce potent suppression of the immune response of the host, which may result in the inhibition of the immunologically dependent regression of the impaired tumor.

Soedomycin was found out according to the fundamental principle to obtain an agent sufficiently selective to inhibit the growth of neoplastic cells without impairing the immunological response of the host. It induces no harmful effect upon normal organs and tissues of the host. It is neither myelotoxic nor lymphotoxic. It does not induce leukopenia, anemia, thrombocytopenia, impairement of the liver, gastrointestinal disturbance, and alopecia not infrequently seen among patients treated with other anticancer drugs routinely used for clinical ipractice. Despite these, it therapeutically induces nhibitio n of the growth of experimental tumors such as EHRLICH'S ascites or solid tumor, S-180, or YOSHIDA'S ascites or solid sarcoma.

Since the effect of anticancer chemotherapy is inversely proportional to the size of tumor mass[18,55~57], the first step of success in chemotherapy of human cancer should be the discovery of chemotherapeutic measures completely to suppress the postoperative recurrence in the radically operable cases of cancer. It seems quite paradoxical to expect a therapeutic success in obtaining cures of indefinite duration in an appreciable number of the patient, wherein the cancer lesion has been partially removed or inoperable at all, with an anticancer agent ineffective in inducing complete cures in all or most cases in which the cancer lesions have been radically removed.

For these reasons, total 83 cases consisting of 72 cases of gastric cancer and 11 cases of other cancer were treated with soedomycin as early as possible after they had received radical resection of the

parent tumors. The results obtained in our series have been significantly better than those in any other series reported by many authors, wherein no postoperative chemotherapy was given[5] or similar postoperative chemotherapy was given with mitomycin C, endoxan, toyomycin, and 5-FU[7,15,16].

In general, more than 20% of radically operable cases of gastric cancer developed recurrence and expired within a year after operation[5~7], while none of the total 58 cases in our series expired during the course of one year following operation. This is one of the outstanding features in our series. It may be extremely difficult to expect an extensive increase of survivors of 5-year-duration by means of chemotherapy with anticancer agents incapable of suppressing postoperative recurrence in all or most radically operable cases for as short as a year following operation.

Even in the cases operated at the stage I, the 5-year-survival rate was reported as low as 63% in the series given no chemotherapy or 66% in the series postoperatively treated with mitomycin C[16]. In our series neither recurrence nor death has occurred among total 28 cases operated at the stage I for post 62 months since September 1965.

Five cases of gastric cancer operated at the stage II (2 cases) and III (3 cases) in our series expired due to recurrence during the course of 16 to 26 months since they had received operation in our hospital, but the remaining 67 cases have been quite well without any signs or symptoms of recurrence.

The 2-or 3-year-survival rate of the cases of gastric cancer in our series operated at the stage II and III is 24/27 (88.9%) or 10/13 (76.9%), at the end of December 1970. These figures are much higher than those in the statistics cited above. For instance, URABE *et al*[5] reported that these were 57.0% (69/121) and 43.8% (53/121) respectively, and KURU[7] showed that these were 40.0% (175/437) and 30.9% (81/262) respectively. NAKAZATO[15] reported that the 2-year-survival rate in his series postoperatively treated with a full course of 40 mg of mitomycin C was 73.7% (84/114), but he did not show the 3-year-survival rate of that series.

There are total 42 cases of gastric cancer operated at various stages in our hospital, who have survived more than 2 years without any signs or symptoms of recurrence. It is much noteworthy that among these cases recurrence has never developed thereafter, and 17, 5 and 2 cases have been in good health for more than 3, 4 and 5 years respectively. The remaining 18 cases have been also well for 25 to 35 months quite free from any signs of recurrence. This long durable saving from recurrence seen in these cases is another outstanding feature in our series.

Total 11 cases of cancer in the organs other than the stomach were similarly treated with soedomycin. In 6 out of these cases, more than 3 years have passed without recurrence since radical operations were performed. The remaining 5 cases have been also well with no signs of recurrence.

Thus, although the number of patients in our series is not so sufficient at present, it may be clear that the postoperative treatment with soedomycin, a new anticancer agent, has much contributed to effective suppression of recurrence and thus significantly improved the postoperative prognosis of the patient with either gastric or other cancer whose parent tumor had been radically operated.

The data of the similar cases of gastric cancer are growing progressively now, on which we will report in the near future. On the details of the patient with cancer, wherein the tumor was only partially removed or inoperable at all, we will report later on separately from radically operated cases of gastric or other cancer.

Acknowledgement

The authors are much indebted to Dr. K. KAMIKO, Director of IInd Research Institute, J. D. A., for his deep interest and heplful advice in this work.

References

1. SOEDA, M.: Studies on anticancer activity of soedomycin, a new anti-tumor agent. Nippon Acta Radiol. 26 : 1483~1491, 1967.
2. SOEDA, M.: Studies on anticancer activity of soedomycin, a new anti-tumor agent. Nippon Acta Radiol. 26 : 1492~1501, 1967.
3. SOEDA, M.: Studies on antitumor immunity : Report No. 4. Natl. Defense Med. J. 14 : 1~6, 1965.
4. INOKUCHI, K. & FURUSAWA, M.: Jap. Med. J. No. 2211, 3~9, 1965.
5. URABE, M., YAMAMOTO, K., TAKANO, R., TAKEMORI, S. & MIURA, S.: Jap. J. Cancer Clin. 10 : 791~799, 1964
6. YAMAGATA, S.: Jap. J. Cancer Clin. 10 : 370~374, 1964.
7. KURU, M.: Jap. Med. J., No. 2262, 3~6, 1967.
8. BERENBAUM, M. C.: Effects of carcinogens on immune process. Brit. Med. Bull. 20 : 159~164, 1964.
9. PREHN, R. T.: Function of depressed immu-

nological reactivity during carcinogenesis. J. Natl. Cancer Inst. 31 : 791～805, 1963.
10. STJERNSWARD, J.: Age-dependent tumor-host barrier and effect of carcinogen induced immunodepression on rejection of isografted MC-induced sarcoma cells. J. Natl. Cancer Inst. 37 : 505～512, 1966.
11. WEISS, D. W., BONHAG, R. S. & LESLIIE, P.: Studies on the reterologous immunogenecity of a methanol-insoluble fraction of attenuated tubercle bacilli. II. Protection against tumor isografts. J. Exptl. Med. 124 : 1039～1065, 1966.
12. STEINKULLER, C.B., KRIEGBAUM, L.G. & WEISS, D. W.: Studies on the mode of action of the heterologous immunogenecity of a methanol-insoluble fraction of attenuated tubercle bacilli. Immunology 16 : 255～275, 1969.
13. MARTIN, D. S., HAYWORTH, P., FUGMANN, R. A., ENGLISH, R. & MCNEILL, H. W.: Combination therapy with cyclophosphamide and zymosan on a spontaneous mammary cancer in mice. Cancer Res. 24 : 652～654, 1964.
14. FERRER, J. F. & MIHICH, E.: Dependence of the regression of sarcoma 180 in vitamin B_6-deficient mice upon the immunologic competence of the host. Cancer Res. 27 : 456～461, 1967.
15. NAKAZATO, H.: J. J. S. S. 70 : 602～603, 1969.
16. TAGUCHI, T.: J. J. S. S. 70 : 600～602, 1969.
17. MIHICH, E.: Host defense mechanisms in the regression of sarcoma 180 in pyridoxine-deficient mice. Cancer Res. 22 : 218～227, 1962.
18. MARTIN, D. S., FUGMANN, R. A. & HAYWORTH, P.: Surgery, cancer chemotherapy, host defense, and tumor size. J. Natl. Cancer Inst. 29 : 817～834, 1962.
19. MIHICH, E.: Combined effects of chemotherapy and immunity against leukemia L 1210 in DBA/2 mice. Cancer Res. 29 : 848～854, 1969.
20. STOERK, H. C.: Cortisone and immunity to homogenous tissue-loss of "Individuality differentials" from tissues of cortisone-treated rats. Ann. N. Y. Acad. Sci. 56 : 742～747, 1953.
21. TOOLAN, H. W.: The possible role of cortisone in overcoming resistance to the growth of human tissues in heterologous hosts. Ann. N. Y. Acad. Sci. 59 : 394～400, 1955.
22. MARTIN, D. S., HAYWORTH, P. E. & FUGMANN, R. A.: Enhanced cures of spontaneous murine mammarry tumors with surgery, combination chemotherapy, and immunotherapy. Cancer Res. 70 : 709～716, 1970.
23. AGOSIN, M., CHRISTEN, R., BADNEZ, O., GASIC, G., NEGHEME, A., PIZARRO, O. & JARPA, A.: Cortisone induced metastases of adenocarcinoma in mice. Proc. Soc. Exptl. Med. 80 : 128～131, 1952.
24. SELA, M., FRICHS, S. & FELDMAN, M.: Specific immunologic unresponsiveness to synthetic polypeptide antigens. Science 139 : 342～343, 1963.
25. HOEHN, R. J.: Induction of tolerance to mouse tail skin homografts by combining paired immunosuppressive agents and cellular antigens. Transplantation 3 : 131～139, 1965.
26. SCHWARTZ, R. & DAMESHEK, W.: Drug induced immunological tolerance. Nature 183 : 1682～1683, 1959.
27. LEVIN, R. H., LANDY, M. & FEI, E.: The effect of 6-mercaptopurine on immune response in man. New Engl. J. Med. 271 : 16～22, 1964.
28. MARTIN, D. C., RUBINI, M. & ROSEN, V.: Inadvertent transplantation of carcinoma. J. Am. Med. Assoc. 102 : 752～754, 1965.
29. MCINTOSH, D. A., MCPHAUL, J. J.. PETERSON, E. W., HARVIN, J. S., SMITH, J. R., COOK, F. E. & HUMPHREYS, J. W.: Homotransplantaiton of a cadaver neoplasm and a renal homograft. J. Am. Med. Assoc. 192 : 1171～1173, 1965.
30. WILSON, R. E.: HAGER, E. B., HAMPERS, C. L., CORSON, J. M., MERILL, J. P. & MURRAY, J. E.: Immunologic rejection of human cancer transplanted with renal allograft. New Engl. J. Med. 278 : 479～483, 1968.
31. SANTOS, G. W., OWENS, A. H. & SENSENBRENNER, L. I.: Effects of selected cytotoxic agents on antibody production in man. Ann. N. Y. Acad. Sci. 114 : 404～423, 1964.
32. HERSH, F. M., CARBONE, P. P., WONG, V. G. & FREIREICH, E. J.: Inhibition of primary immune response in man by antimetabolites. Cancer Res. 25 : 997～1001, 1965.
33. REINER, J. & SOUTHAM, C. M.: Effect of immunosuppression on first generation isotransplantation of chemically induced tumors in mice. Nature 210 : 429～430, 1966.
34. REINER, J. & SOUTHAM, C. M.: Increased growth of tumor isotransplants after immunosuppression of the recipient mice by methotrexate or 5-fluoro-2-deoxy-uridine. J. Natl. Cancer Inst. 38 : 753～759, 1967.
35. RUBIN, H.: The immunological basis for non-infection rous sarcoma. Cold Spring Harbor Stump. Quant. Biol. 27 : 441～452, 1962.
36. BURNET, F. M.: Immunologic aspects of malignant disease. Lancet 1 : 1171～1174, 1967.
37. GABRIELSON, A. & GOOD, R.: Chemical suppression of adaptive immunity. Advan. Immunol. 6 : 91～229, 1967.
38. SANTOS, G. W. & OWENS, A. H.: 19 S and 7 S antibody production in the cyclophosphamide or methotrexate treated rat. Nature 209 : 622

~624, 1966.

39. SAHIAR, K. & SCHWARTZ, R.: The immunoglobulin sequence. I. Arrest by 6-mercaptopurine and restitution by antibody, antigen, or splenectomy. J. Immunol. 95 : 345~354, 1965.
40. BLINKOFF, R. C.: γM and γG antibodies in mice. Dissociation of the normal immunoglobulin sequence. J. Immunol. 97 : 736~746, 1966.
41. BOREL, Y. & SCHWARTZ, R.: Inhibition of immediate and delayed hypersensitivity by 6-mercaptopurine. J. Immunol. 92 : 754~761, 1964.
42. SWANSON, M. & SCHWARTZ, R.: Immunosuppresive therapy. The relation between clinical response and immunologic competence. New Engl. J. Med. 277 : 163~170, 1967.
43. MAIBACH, H.I. & EPSTEIN, W. L.: Immunologic responses of healthy volunteers receiving azathiopurine. Intern. Arch. Allergy 27 : 102~109, 1965.
44. HERSH, E. M., CARBONE, P. P., WONG. V. G. & FREIREICH, E. M., CARBONE, P. P., WONG, V. G. & FREIREICH, E. J.: Recovery of immune responsiveness after drug suppression in man. J. Lab. Clin. Med. 67 : 566~572, 1966.
45. NATHAN, H. C., BIEBER, S., ELION, G. B. & HITCHING, G. H.: Detection of agents which interfere with the immune response. Proc. Soc. Exptl. Biol. Med. 107 : 796~799, 1961.
46. MITCHELL, M., WADE, M., BERTINO, J. & CALABRESI, P.: Effects of cytosine arabinoside and methotrexate upon antibody synthesis and delayed hypersensitivity in man. Proc. Am. Assoc. Cancer Res. 9 : 50, 1968.
47. SCHWARTZ, R. S.: Are immunosuppressive anticancer drugs self-defeating ? Cancer Res. 28 : 1452~1454, 1968.
48. SOUTHAM, C. M.: Homotransplantation of human cell lines. Bull. N. Y. Acad. Med. 34 : 416~423, 1958.
49. THIERSCH, J. B.: Attempted transmission of acte leukemia from man to man by the sternal marrow route. Cancer Res. 6 : 695~698, 1946.
50. TOOLAN, H. W.: Growth of human tumors in cortisone treated laboratory animals. Cancer Res. 13 : 389~394, 1953.
51. TOOLAN, H. W. : Transplantable human neoplasms maintained in cortisone-treated laboratory animals. Cancer Res. 14 : 660~666, 1954.
52. GLYNN, S. R., HUMPHREYS, S. R., TRIVERS, G., BIANCO, A. R. & GOLDIN, A.: Studies on immunity to leukemia L 1210 in mice., Cancer Res. 23 : 1008~1015, 1963.
53. GOLDIN, A. & HUPHREYS, S. R.: Studies of immunity in mice surviving systemic leukemia L 1210. J. Natl. Cancer Inst. 24 : 283~300, 1960.
54. DEODHAR, S. D., CRILE, G., Jr. & SCHOFIELD, P.F.: Immunosuppression in allogeneic murine tumour system. Lancet 1 : 168~170, 1968.
55. MARTIN, D. S.: Cancer chemotherapy : Immunologic and chemotherapeutic interrelationships. J. Am. Med. Assoc. 128 : 723~726, 1961.
56. MARTIN, D. S. & FUGMANN, R. A.: Clinical implications of the interrelationships of tumor size and chemotherapeutic response. Ann. Surg. 151 : 97~100, 1960.
57. MOLKOV, Y. N.: Prevention by aurantin of recurrence and metastases after surgical removal of transplantable tumors. Vop. Onkol. 6 : 19~25, 1960.