STUDY ABOUT RADIOLOGICAL AND IMMUNOLOGICAL TREATMFNT FOR CANCER

(How did we establish our plan of the Cancer Therapy)

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癌の放射線並に免疫療法に関する研究

（吾々は如何に癌の治療計を樹てたか）

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私共は放射線照射によつて生じた癌細胞の崩壊産物（所謂カスパリー氏ネクロホルモン）が直接癌細胞を衝撃するのみならず，照射後或る時間を経過すればこの一部は自家抗原として働らき，之に対して抗癌抗体を生ずることによつて癌免疫が成立し，治療に大きな役割を演ずると言う仮説を立て，放射線照射による Biological Amplificationの説明を行つた．

この理論に従つて小照射野多門分割術式によつて術前術後に大変よい結果を得たことは既に本誌“癌の術前術後照射法に関する研究”と題して報告した通りである．この臨床上の事実に基いて過去槇殿の行つた悪性腫瘍の物質代謝に及ぼすレ線の影響に関する実験的研究や，網内系を代表する肝臓並に脾臓エネルギー代謝を勘案し，本誌22巻8号に掲載した術前照射並に摘出癌組織の治療的移植の担癌個体の血中抗体価に及ぼす影響に関する研究に発展して曩きに立てた仮説を実証したのである．

この理論に従つて吾々が立てた癌の治療計画を玆にまとめて報告する次第である．

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Chapter I. Foreword

Since December 1959, the authors began a study of the treatment of cancer by means of pre-operative and post-operative irradiation. This is one of the most important subject in the medical field today. We may be to blame for not having undertaken such a study earlier; on the other hand, some may wonder at our attempt to study this matter further. Until recently, however, radiotherapy for cancer has been employed with some degree of pessimism with a feeling that cancer is, after all, incurable and that Radiotherapy suffices only to afford some relief of pain and to prolong the patient's life. In the case of post-operative irradiation some years ago, there was no adequate power or capacity to kill any remaining cancer cells as there is today. It is quite doubtful how effective it was; it may not have been particularly effective. Furthermore, as we stated in our previous reports, the methods of irradiation varied widely among different practitioners, and there was little close contact between radiologists and surgeons.

When one realizes this situation, he will understand why we again began the study of this subject. Reviewing the present situation of cancer therapy in our country, it appears that surgery is regarded more highly than other forms of treatment, since it is effective in removing the primary tumor, the surrounding tissue and the associated lymph nodes. Energetic surgical methods, such as radical or wide excisions, were devised by our predecessors and these brought about many favorable results. However, the situation regarding cancer therapy at certain research institutes in foreign countries is that Radiotherapy ranks above all other methods, while surgery is employed only in those cases where irradiation fails to render the cancer cells extinct. Some scholars were surprised at our radical surgery in Japan, and they have had some doubts as to whether adequate cancer therapy is possible merely by surgery.

Some of our predecessors professed that cancer is 100 percent curable with early detection and early treatment, prescinding from the quality of the surgery. They further stated that the results of treatment depend entirely on whether there is early detection and early treatment. We must also agree with this type of thinking. There are many problems remaining today for surgery in its fight against cancer. We, as radiologists, must bear in mind that there is room for strong reflection on our part.

Chemotherapy in the field of cancer has, of course, strongly attracted our attention. We, as radiologists, strongly hope for effective chemotherapeutic agents in the cure of cancer, but to our regret this has not as yet, come about. Considering the occurrence and growth of neoplasms, there is some doubt as to how drugs which have no real affinity for tumor tissue can be effective.

Considering these points, we feel that most will agree that at the present time there is no more effective method in the treatment of cancer than the combined efforts in the fields of surgery and Radiotherapy.

Professor Nakayama of Chiba University, an authority in this field, has acquired much experience in the surgical treatment of esophageal and gastric neoplasms. He early recognized the importance of this approach, and strongly recommended that "application of pre-operative irradiation should positively be performed for cancerous surgery". (Ref #1 About pre-operative irradiation to cancer. Clinic and Study, Vol. 38, No. 11, Nov 1961). He has much experience in the treatment of esophageal cancer, regarded as one of the most difficult forms of cancer to treat. He has experienced the "evil nature" and "toughness" of cancer, to become the first man in this field in the world today. He feels the necessity of the use of pre-operative irradiation, knows of superiority of this form of treatment, and we have the greatest respect for his opinion. Reports concerning pre-operative irradiation have not been rare, even in past years. However, it is a joint research group of Chiba University, lead by Professor Nakayama, which has systematically combined pre-operative irradiation with surgery.

Those in other countries who believe in Radiotherapy above all other forms of treatment, find it difficult to accept pre-operative irradiation. However, it is well known that with the exception of early detected cancers, we cannot rely on X-ray alone, aside from 2 or 3 specific neoplasms. Although we have been pessimistic for more than 20 years in the application of Radiotherapy, many good results have been obtained in this field, such as with the use of radium in the treatment of gynecological cancer, intracavitary treatment, and in the use of irradiation with surgery. However, the methods of treating cancers of the esophagus, stomach and breast differed widely until the present time.

In order to use Radiotherapy most effectively and properly, we must understand the relationship of the individual with the neoplasm, the differences of the energies available and the rate of distribution of tissue dose. Some of the reasons there have not been more remarkable results in the field of Radiation Therapy until today are: Firstly, due to a lack of radiobiological studies, and secondly, an inadequacy of radiation energies to annihilate cancer cells, as stated, aside from lack of early detection. In a previous article (Ref #2. Study on the pre-operative and post-operative irradiation to cancer; 1. About the method of irradiation. Hiroshima Medical Journal, Vol. 14, No. 5, 1961) we explained that high energies are readily available today. Cytological studies which have been conducted concerning neoplasms are too numerous to mention, but the biological studies concerning the relationship of the individual and the neoplasm are extremely few and many subjects are still being omitted. We wonder why more consideration is not given this subject, despite the fact that in diseases such as tuberculosis, a key to the occurrence and development of the disease is the constitution of the individual who is affected. The case is similar in radiobiology, but research studies concerning the individual with cancer are few even though the neoplasm may have originated from cells which were originally normal.

Concerning the relationship of the host and the neoplasm, we have considered experimental studies since 1935. These have included the effect of irradiation on metabolic substances in malignant tumors, and an " abnormal change " was confirmed with the development of cancer. We have reported many new findings, including the fact that energy metabolism of vital visceral organs, such as liver and spleen, is depressed due to the cancer, and that Radiotherapy will also reverse such abnormal change. (Ref #3. Expeaimental study about the X-ray irradiation affecting to subtance metabolism of malignant tumor, Vol. 15, No. 9, 1939) We intend to add various important observations and experimental researches and intend to apply them clinically.

With respect to the various energies, we accelerated our studies by installing a variety of equipment, such as the body cavity tube. Cobolt 60 apparatus, to add to the high voltage equipment we already had.

We have gained much confidence in Radiotherapy against cancer, owing a great deal to the various kinds of energies including ultra high voltage, which are available when needed. Our approach to the treatment of cancers has changed from pessimistic to an optimistic one because of advancements such as the pre-operative irradiation of esophageal cancer, improved methods utilizing high voltage apparatus such as Cobalt 60, and techniques such as rotation, pendulum and sieving.

In a previous article (Ref #4. Study on the pre-operative and post-operative irradiation to cancer, 12. About the depth-dose distribution of 60-Cobalt ray and consideration of its administration, Hiroshima Medical Journal, Vol. 14, No. 12, 1961) We have made it clear that we believe that proper treatment of cancer is not achieved by surgery alone nor Radiotherapy alone, but by the combination of the two. However, an exact treatment scheme should be established for each individual case.

In chapter 2 of this report we shall enumerate the results of our studies during the past year, establish a treatment scheme against cancers by utilizing the values in item 3, state how we can anticipate results in item 4, and state how we hope to advance in the combat of cancers.

In this study we have undertaken a new problem the " therapeutical transplantation of extirpated cancer tissue " and have developed an immuno-treatment of cancer practical in clinical use. However, this is in the form of a completed test for us, perhaps due to the fact that we have had no adequate research facilities. There were objections and admonitions which gave the impression that we had applied theory directly to clinical work, eliminating experimental studies. It is well known, however, that the previously reported studies of Makidono (Ref #5. Study on the preoperative and post-operative irradiation to cancer. 4. About the cancer therapy by therapeutical transplantation of cancer tissue. Hiroshima Medical Journal, Vol. 15, No. 5, 1961) formed the basis for the test of extirpation and transplantation of cancer tissue and retransplantation of irradiated and non-irradiated tumors, using transplantable Kato strain rabbit sarcoma.

We believe that the reader will now fully comprehend the reason why we have again selected this subject for study. One reason it was impossible for us to advance to this stage directly, despite the fact that we contemplated the radiobiological studies of the patient with cancer as early as 1935, was the interference by World War II. This also interfered with the study of the literature, and it seems to have caused much confusion in the system of our studies at present. For instance, the most unpleasant matter that we experience frequently now is that various problems which were deemed already solved by our predecessors long ago, are being proclaimed as new discoveries.

We wish to establish a most effective treatment plan based on the results of our studies. At the same time, we hope to gain much additional information by re-evaluating our methods frequently. We would like to have the comments, criticisms and suggestions of the reader.

Chapter II. Results of our Radiobiological Studies

Prior to establishing a treatment plan for cancer in the next chapter, we would like to enumerate the results of our studies as fundamentals. These may be divided as follows:

Item 1 Result of Studies Concerning Deep-dose Distribution of Various Energies
Item 2 Result of Radiobiological Studies Concerning Tumor Itself
Item 3 Result of Radiobiological Studies Concerning Individual with Cancer

Concerning the above, the reader is referred to our previous reports, as follows:

Item 1: Various Energies; Hiroshima Medical Journal, Vol. XIV, No. 9, 12, 1961

Item 2: Result of Radiobiological Studies in regard with the Histological Findings and Its Respiration and Glycolysis; Journal of Kumamoto Medical Society, Vol. XV, No.9

About the Destiny of Therapeutically Transplanted Tissues of Pre-operative Irradiated Tissues and Extirpated Cancer Tissues; Hiroshima Medical Journal, Vol. XIV, No. 10, 11, 1961.

Item 3: Experimental Studies on x-ray Affection exerting to Substance Metabolism of Malignant Tumor, Vol. XV, No. 9, 1939.

Considerations About the Irradiation Method; Hiroshima Medical Journal, Vol. XIV, No. 5, 1961.

Energies which are presently available are as follows:

a. Close irradiation (Body cavity tube)
b. Common high-voltage (200-250 KVP)
c. Cobalt 60 gamma ray
b. Radium ray

Their characteristics are as reported in our reports 9 and 12. Of course, Cobalt 60 tumor therapy is most effective when one considers the deep dose rate of these energies. Two-hundred KVP high voltage is next in effectiveness in this respect. The body cavity tube is localized to the body surface, and its application is limited.

We use these types of apparatus according to the site of the lesions, and by such selection expect them to be more efficacious in destroying the cancer cells. In their practical application we consider the advantage in terms of biological effect and in terms of the method of irradiation. Examples are the effect on depth dose by the size of the field, and time-dose relationship in terms of biological effect. In each individual case, one of a number of methods, such as fixed, rotation, pendulum and sieve is chosen, on the basis of its superior effectiveness.

The irradiation field is also selected according to the type of lesion. The depth dose varies markedly with the size of the irradiation field. Unnecessary irradiation of surrounding organs may cause toxic symptoms. We have obtained remarkable results in the use of the body cavity tube apparatus, using a short range. Clinically, we found that a small field (4×4 or 4×5 cm) caused the least reaction in the cancer patient. We are obtaining favorable results using "a simple divided method for multiple fields, with short irradiation range" and the practical aspects of this are described in a later chapter of this report.

We find that large fields and large doses are effective in the gynecological region, the extremities and the head, with comparatively less influence on the surrounding tissues. In selecting an irradiation field, we find it important to devise a method for irradiating the lesion, and at the same time avoiding side dispersion, according to the isodose curves of various energies.

The next important problem is to select a method of application, in terms of time. Large doses cannot be administered at a single treatment; divided application is the most effective method, either

a. Simple dividing method, or

b. Delayed dividing method

Accordingly, we are now using multiple fields with short range to apply a dose sufficient to kill cancer cells. Total destruction of cancer cells has become relatively easy today in the peripheral parts by using these methods. However, it must be borne in mind that it is necessary to deliver adequate dosage to the cancer cells, with a minimum of disorder to the surrounding tissues. The irradiation reaction is remarkably different in the peripheral parts, as compared to the sites of internal organs, the breast and the abdomen. A brilliant effect can be expected in treating cancerous tumors in the gynecological region, but large doses applied to a tumor in the upper abdomen, especially in the stomach, in 60-80% of the patients, there will be complaints of radiation sickness.

With Radiotherapy, we endeavor to improve the individual with cancer, symptomatically. Irradiation which aggravates the general condition and reduces the weight of the patient, as in some cases in the past, must be avoided. Therefore, each individual case must be carefully considered in order to secure the best result.

As previously reported (Ref #6. Same as Ref #1.), the fundamental mechanism in the radiobiological effect is the primary effect of destruction of the cancer cells, and a secondary biological effect exerted by cancer necrohormones. It was stressed that the proper dose should be selected after considering the effect of excessive cancer necrohormones on the entire body of the individual with cancer.

Item 2. Result of radiobiological studies concerning the tumor itself.

Here we shall consider the results of laboratory studies and clinical research. The laboratory studies involved research on the Kato strain of rabbit sarcoma; the clinical studies involved the use of pre-operative irradiation on cancer tissues.

When a piece of cancer tissue is minced and placed beneath the skin, the transplantation will be successful in 100% of the cases and the tumor will develop to the size of the tip of one's thumb in a period of 2 weeks following implantation, maintained in an active living state.

Tables 1 and 2 show the respiration and glycolysis effect, respectively, using the Warburg Manometric Method. The peculiarities of cancer cells are shown by active energy metabolism.

Table 1

Region	Atmung	Aerobe Glycolyse	Anaerobe Glycolyse	Hemmung der Glycolyse durch O_2	Meyerhof Quotient	Aerobe Glycolyse / Atmung
	QO_2	$Q_M^{O_2}$	$Q_M^{N_2}$	$\frac{III-II}{III}$	$\frac{III-II}{I}$	$\frac{II}{I}$
Active Development Region	−6.4	15.9	35.3	54.9	3.3	2.5
	−3.5	14.2	28.4	50.0	4.06	4.06
	−7.5	14.5	27.4	47.08	1.72	1.9
Average	−5.8	14.9	30.4	50.66	3.03	2.82

Table 2

Region	Atmung	Aerobe Glycolyse	Anaerobe Glycolyse	Hemmung der Glycolyse durch O_2	Meyerhof Quotient	Aerobe Glycolyse / Atmung
	QO_2	$Q_M^{O_2}$	$Q_M^{N_2}$	$\frac{III-II}{III}$	$\frac{III-II}{I}$	$\frac{II}{I}$
Active Development Region	−7.3	11.7	15.7	25.5	0.6	1.6
	−5.7	13.2	15.3	13.7	0.36	2.3
	−6.4	10.7	14.7	27.2	0.62	1.67
Average	−6.47	11.87	15.23	22.13	0.53	1.86

The histological picture to be expected is important in selecting the irradiation method. According to the effects on energy metabolism in the irradiation of rabbit sarcoma cells, we have investigated the following:

1. The irradiation method which is the most powerful to kill cancer cells
2. The histological picture of tumor which has been irradiated and the effects on

energy metabolism.

3. The remote effect on non-irradiated tumors when one tumor is irradiated.

1. In the past, the effect of x-ray on cancer cells has been determined by histological study. We find that there is a remarkable change in the energy metabolism of the cancer cells prior to the histological change. Accordingly, we conducted tests to determine a destruction dose of tumor cells, the irradiation method, and the selection of energies, according to the following:

a. The effect of x-ray irradiation on respiration and glycolysis of rabbit sarcomas.

b. The effects when irradiation factors have been changed.

i. When there is a change in dose.

ii. The effect of divided irradiation.

iii. The effect of difference in energies.

We have reported some of our results elsewhere. Our conclusions were as follows:

a. The x-ray irradiation has rendered marked defects on respiration and glycolysis of rabbit sarcoma.

b. Conclusions for subpara (b), above.

i. The tumor cells will be destroyed and resolved in direct proportion to the radiation dose. A full dose of more than 3600 r is required to kill tumor cells.

ii. A divided method is most effective. In our test, the sarcoma cells were completely resolved 20 days after the completion of irradiation, when a full dose of 3600r was applied, either 400r per dose for 9 consecutive days or 600r per dose for 6 consecutive days.

iii. No difference in effectiveness in destruction of tumor cells was noted using different energies.

2. The histological picture of post-irradiated tumor and the change of energy metabolism

The nuclei and cytoplasms were changed in the injured cells with lapse of time; those past 20 days following irradiation resulted in proliferation of connective tissue (fibrous reaction), and no healthy sarcoma cells were observed.

Table 3 shows that there is a marked depression of respiration and glycolysis in tumor cells.

Table 3 also shows that on the first day following irradiation in nearly 50%, there is a disorderly appearance as compared with that of healthy tumor cells. On the 5th day, respiration and glycolysis indicated that nearly all of the cells were dead. Those which were still living 20 days following irradiation were degenerating. We believe this proves that our irradiation method was adequate to kill tumor cells.

3. The remote influence upon non-irradiated tumors, when one tumor is irradiated: Non-irradiated tumors were shielded to check the remote effect of irradiation. Table 4 shows its result.

Table 3

Postirradiation	Atmung QO_2	Aerobe Glycolyse $Q_M^{O_2}$	Anaerobe Glycolyse $Q_M^{N_2}$	Hemmung der Glycolyse durch O_2 $\frac{III-II}{III}$	Meyerhof Quotient $\frac{III-II}{I}$	Aerobe Glycolyse / Atmung $\frac{II}{I}$
1st day	−3.4	8.9	16.4	45.7	2.2	2.6
	−4.8	9.8	15.3	35.9	1.14	2.04
	−3.7	10.2	14.7	30.6	1.2	2.8
Average	−3.9	9.63	15.47	37.4	1.51	2.48
5 th day	−0.3	0.7	4.2			
	−1.4	4.8	3.7			
	−1.2	3.7	3.2			
Average	−0.97	3.07	3.7			

Table 4

Region	Atmung QO_2	Aerobe Glycolyse $Q_M^{O_2}$	Anaerobe Glycolyse $Q_M^{N_2}$	Hemmung der Glycolyse durch O_2 $\frac{III-II}{III}$	Meyerhof Quotient $\frac{III-II}{I}$	Aerobe Glycolyse / Atmung $\frac{II}{I}$
Nonirrradiated tumor at 1st day	−3.6	10.2	16.9	39.9	1.9	2.8
	−5.8	13.3	22.7	41.4	1.6	2.3
	−4.2	12.3	19.8	37.8	1.8	2.9
Average	−4.53	11.93	19.73	39.6	1.77	2.67
Nonirradiated tumor at 5 th day	−5.7	14.2	29.7	52.2	2.7	2.5
	−6.3	15.7	32.4	51.5	2.6	2.5
	−8.5	16.4	30.6	46.4	1.7	1.9
Average	−6.83	15.4	30.9	50.03	2.33	2.3
Nonirrdiated tumor at 7 th day	−8.2	14.3	19.8			
	−2.7	15.5	22.21			
	−3.2	9.8	13.4			
Average	−4.7	13.2	15.17			
Nonirradiated tumor at 14 th day	−8.9	15.2	22.4			
	−4.0	17.8	13.8			
	−4.2	10.8	14.2			
Average	−5.7	14.6	16.8			

At first day following irradiation the living power declined, and this was probably in effect at the time of completion of irradiation. Restraint of respiration and glycolysis was distinct, but the pattern was of a malignant tumor.

On the 5th day, there was beginning recovery, and by the 7th day the values has declined to approximately the same as on the first day, where they remained for an additional seven days. At the 3rd and 5th week, there was abundant growth of tumor microscopically and the pattern of respiration and glycolysis indicated a normal growth pattern for the tumor. This indicated total resolution of the power of the cancer necrohormones. This indicates that the depression of energy metabolism following irradiation was due to cancer necrohormones produced at the time of irradiation of the primary cancer. However, we must be cautious in interpreting this as a true recovery. This may be caused by a temporary action by the necrohormones.

If observed over a period of time, the radiobiological effect will be manifested by an undulating or cyclic pattern. If there is a strong effect due to the necrohormone produced, the cyclic curve of the growth pattern is prolonged; whereas, if there is less effect due to necrohormones, the cycles of the growth pattern are more abrupt and short. The primary effect of of the radiation is the destruction of tumor cells and damage to the tumor cells due to restraint of energy metabolism, while the secondary effect is a general anti-cancer state on the part of the individual due to the action of necrohormones. The anti-cancer state established by the production of necrohormones result in improvement of the general condition of the patient, to facilitate surgery, and possible additional irradiation.

By our studies, pertaining to energy metabolism of tumor cells, we were able to learn the above, and in addition some interesting results concerning substance metabolism itself. For instance, salt metabolism which is so important to the existence of the individual and which reacts extremely promptly, was entirely changed with the alteration of substance metabolism. The kalium/calcium content within the tumor varied with individual rabbits, the number of days, with the period of time elapsed following implantation of tumor, and the size of the tumors. The growth and regression of tumor is in proportion to the kalium over calcium ratio, as the kalium content increases, the number of healthy tumor cells increases, whereas the calcium content increases, the number of denatured cells increases. When the cells, at the center of the zone of regression are transplanted into the rabbit, they will rereproduce at the usual rate. The kalium over calcium ration depends on the number of healthy versus denatured cells present.

At the first day, the kalium over calcium content conformed with the center regression zone; on the fifth day, the calcium content increased, while the kalium content decreased, and at that time the ratio was the opposite of that of the active development region. At the 20th day, there was a marked increase of calcium, with complete disappearance of the cancer cells and the calcium content remaining as a product of the dody defence.

The salt metabolism of the non-irradiated tumor caused a decrease of kalium and increase of calcium the first day after irradiation, but at the fifth day, kalium had regained its normal value, while the calcium remained increased. The kalium/calcium content is intimately related to the living power of tumor cells. We are now studying the extirpated human cancer tissues by means of Warburg's Monometering Method, hoping to solve some of the problems of human cancer, and to determine applicable dosage, solve the problem of cancer necrohormones, and to investigate further the problem of cancer immunity by clinical tests. By these means, we hope to solve the problem of human cancer.

In clinical research, we are observing the irradiation effect on extirpated cancer tissue, following pre-operative irradiation. We have observed similar results in our experimental studies, as the " irradiation-effectiveness-judging-criterion " originated by Professor Takizawa, (Ref #7. Study on the pre-operative and postoperative irradiation to cancer. 10. Consideration about the result of histological examination at pre-operative irradiated stomach cancer. Hiroshima Medical Journal, Vol 14, No. 11-12, 1961) and by means of these studies, we hope to determine proper dosage in cancer treatment. In the future, we intend to continue our study in this field by utilizing the above Manometric Method, and also by tissue culture methods.

Itsm 3. Result of radiobiological studies concerning individual with cancer :

We have reported in our first series on " Experimental studies on X-ray affection exerting substance metabolism of malignant tumor " (Ref #3) concerning the changes indicated in salt metabolism, especially kalium and calcium, according to the growth of tumor ; how it affects the individual ; how this abnormal change was influenced by reduction and resolution of tumor by X-ray irradiation ; and finally, what relation they have and with the metabolism of the individual with cancer, as a whole.

Elsewhere, in a part of this series of studies, we reported concerning pre-operative irradiation (Ref #8 & 9. Study on the preoperative and post-operative irradiation to cancer. 2. About the pre-operative irradiation for stomach cancer by close irradiation (body cavity tube) ; 3. Investigation on the second method of pre-operative irradiation. Hiroshima Medical, Journal Vol. 14, No. 5, 1961). The interaction between the metabolism of the tumor and the metabolism of the indiuidual with cancer is also described. Although this is a quite natural consideration in the study of the occurrence and development of cancer, we were the pioneer investigators to commence such a study.

From this study, we learned not only about the dhanges in salt metabolism, but also the fact that the salt metabolism in the individual can act as an indicator of a state during which there is stimulation of the development of cancer. Following therapeutic irradiation which results in the denaturing, destruction and resolution of cancer cells, the abnormal salt metabolism is restored to normal. We also found that in individuals with cancer who make such favorable progress there is a conversion which takes place in the salt metabolism in the so-called anti-cancer state. As a result, we became dissatisfied with the methods of pre-operative irradiation of others, and decided that a concrete scheme of cancer treatment is necessary, based on pre-operative and post-operative irradiation. when we speak of the " anti-cancer state " we do not refer only to changes resulting from the study of substance metabolism, but to changes which we have observed in the reticuloendothelial system in the liver and the spleen, which we have observed in the state of cancer immunity. The results which we observed in this regard have already been reported in the 2nd series of this study.

In the present study, we observed the influence of therapeutic irradiation of tumor in visceral organs, specifically, in terms of respiration and glycolysis studies in sarcoma in the rabbits and the relationship of kalium-calcium to respiration and glycolysis in sarooma in the rabbit. We observed a conversion from the so-called cancer-development-state to the anti-cancer-state.

Table 5.

Rabbit Number	Weight gram	Respiration & Glycolysis of Liver: Respiration QO_2	Respiration & Glycolysis of Liver: Glycolysis $Q_M^{N_2}$	Respiration & Glycolysis of Spleen: Respiration QO_2	Respiration & Glycolysis of Spleen: Glycolysis $Q_M^{N_2}$
263	1980	−7.55	2.56	−11.86	13.09
264	2030	−6.54	2.27	−8.15	12.39
265	2070	−7.93	1.86	−7.97	10.25
266	2120	−7.31	2.70	−10.07	10.59
267	1970	−8.89	3.22	−9.18	14.34
268	1950	−8.42	3.62	−9.07	9.89
269	2170	−8.07	2.01	−9.32	9.84
270	2200	−6.93	2.72	−10.16	12.17
271	2180	−6.19	2.57	−10.45	10.30
272	2930	−7.53	3.12	−9.54	9.35
Average		−7.54	2.57	−9.58	11.22

Table 6.

Rabbit No.	Weight Gram	No. of days progressed after transplantation	Respiration & Glycolysis of Liver: Respiration QO_2	Respiration & Glycolysis of Liver: Glycolysis $Q_M^{N_2}$	Respiration & Glycolysis of Spleen: Respiration QO_2	Respiration & Glycolysis of Spleen: Glycolysis $Q_M^{N_2}$
273	2030	7	−7.21	2.18	−9.54	9.58
274	2120	7	−7.47	2.23	−8.09	10.62
275	2030	7	−5.91	1.62	−7.96	8.54
Average			−6.86	2.01	−8.53	9.58
276	2000	14	−7.78	1.37	−8.07	8.34
277	1970	14	−5.69	1.35	−9.67	10.95
278	1980	14	−5.02	1.43	−6.69	9.94
279	1900	14	−5.65	0.84	−7.35	7.36
280	1570	14	−4.84	1.31	−6.64	8.71
281	1830	14	−6.95	1.87	−8.17	8.43
Average			−5.99	1.36	−7.77	8.96
282	1890	21	−7.04	1.97	−5.33	8.59
283	1790	21	−5.43	1.37	−7.47	7.44
284	1930	21	−6.32	1.56	−8.24	9.80
285	1720	21	−8.22	1.50	−9.60	9.05
Average			−6.75	1.60	−7.66	8.72
286	1740	25	−6.34	1.37	−7.32	8.72
287	1830	25	−7.02	1.95	−6.47	7.34
288	1690	25	−5.43	2.01	−7.32	6.94
Average			−6.26	1.78	−7.04	7.66
289	1730	30	−3.81	1.45	−6.70	7.22
290	1530	30	−8.85	2.86	−7.47	7.88
291	1570	30	−8.97	2.30	−8.24	9.80
Average			−7.21	2.20	−7.47	8.27
292	1720	35	−4.73	2.00	−5.72	6.35
293	1530	35	−3.25	1.37	−6.32	7.24
294	1800	35	−3.84	1.86	−6.53	7.32
Average			−3.94	1.74	−6.19	6.97

Table 5 shows respiration and glycolysis values in the livers and spleens of normal rabbits. Table 6 shows respiration and glycolysis values in such livers and spleens into which sarcoma tissue was implanted. It is shown that these values in the sarcoma implanted organs were less than in those of the healthy animals ; in general, the degree of depression of these values was greater, the greater the development of the tumor. Approximately 30 days after the transplantation of the tumor, there was an acceleration of respiration and glycolysis values in the livers and spleens. which corresponds to the time of softening of the tumor.

Therefore, the growth of the tumor depressed the energy metabolism in the liver and spleen, with gradual development of a status susceptibility to tumor. It was also demonstrated that following X-ray irradiation of the tumor at the time when the energy metabolism in the visceral tissues was falling, there was a cessation of the depression of the respiration and glycolysis and a restoration of kalium-calcium content in the viscera, and the values were restored to normal for actually obtained values exceeding normal. This is shown in Table 7.

Table 7

Rabbit No.	Change of weight Gram	No. of days progressed after transplantation	No. of days progressed after irradiation	Respiration & Glycolysis of Liver: Respiration QO_2	Respiration & Glycolysis of Liver: Glycolysis $Q_M^{N_2}$	Respiration & Glycolysis of spleen: Respiration QO_2	Respiration & Glycolysis of spleen: Glycolysis $Q_M^{N_2}$
295	2130—1870	15	5	−11.16	1.32	−7.58	9.11
296	2050—1930	14	5	−11.06	1.42	−6.49	8.74
297	2120—1700	16	5	− 3.79	1.40	−6.83	9.83
298	2200—1790	14	5	− 9.64	2.12	−9.53	9.16
299	2050—1900	15	5	− 9.32	2.18	−7.35	9.23
Average				− 8.99	1.59	−7.56	9.01
300	2130—1670	15	10	− 7.78	3.12	−7.45	9.32
301	1980—1770	16	10	− 8.79	1.92	−7.97	8.45
302	1970—1730	16	10	−10.23	2.04	−8.58	8.27
Average				− 9.00	2.03	−8.00	8.65

However, the restored values of respiration and glycolysis in the liver and spleen do not always coincide, in terms of amount or in terms of time. This is a point for consideration in planning therapy. In the spleen, histological changes caused by tumor occur comparatively early; the shrinking of the Malthigian corpuscles and the depression of values of respiration and glycolysis show this. In general, the spleen is sensitive to various stimuli. If the cells of the spleen cannot be revived early and an irreversible change has occurred, no effect can be expected by cancer necrohormones produced by irradiation. The substance metabolism is not restored in such cases. The degree to which energy metabolism is depressed depends on irradiation dose. The spleen is strongly sensitive to cancer necrohormones. From this we see that the death of tumor cells is not the only effect of x-ray irradiation, there is also an influence against the factor which promotes occurrence and proliferation of tumor. This is important in the production of a therapeutic effect.

Elsewhere, we have emphasized the importance of mutual anticancer influence between primary and metastatic cancer (Ref #10. Study on the pre-operative and post-operative irradiation to cancer. 11. About the clinical condition of cancer patient transplanted with cancer tissue and the destiny of its therapeutical transplantation, Hiroshima Medical Journal, Vol. 14, No. 11-12, 1961).

An anti-cancer state is produced by many factors in the body of the individual affected, according to the Arndt-Schultz Law and a certain balance exists within the body. This is an important consideration in treatment planning. We believe that the opposite situation can also occur ; that is, that the cancer necrohormones may actually stimulate the growth of cancer.

Case Number 1 : A forty-three year old male underwent surgery for gastric cancer and the lesion in the stomach was removed, but the metastatic lesions in the head of the pancreas could not be removed. Two weeks following the surgery, 2000r skin dose was applied to the epigastrium. A Virchow's node was present, considered due to metastatic carcinoma, prior to the post-operative irradiation. The latter resolved with the irradiation, but on the 5th day, a tumor approximately 3cm. in size developed in the region of the right clavicle, which enlarged by the 5th day following the beginning of irradiation to approximately 5cm. We attribute this to over-production of cancer necrohormones by the irradiation of the Virchow's node-. We applied 3600r skin dose by means of superficial x-ray, over a period of 9 consecutive days, 400r per day. Anti-pyretics were administered to control fever. The tumor was was reduced within one week's time, and only a firm lymph node approximately 1.5cm. in size remained after completion of irradiation.

Case Number 2 : A fifty-six year old male with diagnosis of lymphogranulomatosis presented with masses approximately 1.5cm. to 3cm. in size in the left cheek, adjacent to the left side of the mandible, both axillae and inguinal regions. The mass in the left cheek was irradiated by means of cobalt 60, with a skin dose of approximately 6000r, and the other regions were treated in the same manner. Four hundred r per day over 9 consecutive days was the schedule used in each case. An error was incurred when a technician administered 600r per day over a period of 6 days instead of the originally prescribed dose in the case of the cheek lesion. Although the symptoms subsided and all the tumors were reduced in size, the patient suddenly developed a fever of more than 40° centigrade on the 3rd day, and experienced weakness, nausea, and pain the treated area. These symptoms and the fever resolved in a period of 3 days and the involved nodes were subsiding satisfactorily.

These two casses are used to illustrate the concept that the balance existing between the amount of cancer necrohormones and anticancer state was destroyed and that a counter reaction in the form of development of a cancer stimulating state was caused by excessive necrohormones. We feel that this balance plays an important role in the treatment of the patient. By excessive irradiation, an over-production of necrohormones is produced. This state has been referred to by our predecessors as "karzinoreizdosis." We were surprised in case number 2 that sufficient dosage was delivered to produce such a strong reaction.

The important consideration of sensitivity of cancer cells arises in connection with therapy. There is a wide variation in the sensitivity of neoplasm; this depends upon the species of the cells, and degree of differentiation. The Bergonie-Tribondeau Law is recognized in the sensitivity of cells to radiation. The secondary biological effect is exerted in the form of sensitivity of the cancer cell to the cancer necrohormone. This has remained practically unnoticed regarding radiation sensitivity of cancer cell and should be a focal point in radiobiological study.

When the size of a tumor can be assessed by palpation, resolution following irradiation reflects the sensitivity. We do not see a disadvantage in adopting this method clinically. Though speed of resolution reflects sensitivity, we cannot always conclude that rapid resolution is a favorable reaction. One might expect that a given tumor would decrease to one half or one third of its original size in approximately 10 to 15 days following irradiation. However, wide variation exists so that one tumor may be reduced in size very suddenly with one or two small doses of irradiation, while little or no response is noted in others which receive an estimated 3000r skin dose. Obviously, the histology of the tumor is a prime factor. Sudden collapse may result from irradiation; we have treated a few cases where the patients were shocked to death by relatively low dosage and no more than two treamtents. We attribute this to sudden production of cancer necrohormone.

We must remember that the entire body of the individual establishes a complete cancer development stimulizing state; the cancer patient in the terminal stage is just about in this condition. We feel strongly that cancer cannot be treated only as a local disease, but as one which affects the entire body, affecting metabolism and immunity.

We measured the value of serum NPN in cancer patients on whom we conducted pre-operative irradiation, expecting abnormal changes as a result of the destruction of cancer cells by irradiation and the production of cancer necrohormone. Our results have already been reported (Ref 11. Study on the pre-operative and post-operative irradiation to cancer. 8. About the rise and fall of the rest stickstoff in blood after pre-operative irradiation to cancer, Hiroshima Medical Journal, Vol. 14, No. 11-12, 1961).

Production of excessive cancer necrohormone may produce a toxic effect with various symptoms. Individuals with a highly sensitive tumor respond quickly to irradiation and the symptoms subside, but this effect is not produced in those who have resistent tumors. This improvement of clinical symptom is also an important criteria in judging the sensitivity. On the basis of changes of NPN and improvement of clinical symptom, tumor response to pre-operative irradiation was classified as "increased", "decreased" and "unchanged."

In the later stages of cancer, NPN gradually rises, reflecting collapse of cancer cells; however, many factors relating to albuminous substances and kidney function make these values difficult to evaluate. At any rate, NPN values before and after irradiation do reflect irradiation sensitivity, and we feel that this is the most practical method of assessing sensitivity at the present time.

Chapth III. Establishment of Treatment Schedule for Cancer

Until recently, we feel that there was no consistency in the treatment of cancer. A treatment scheme combining the advantages of surgery and radiation should be established for the treatment of cancer. Until recently, surgeons operated and irradiated at their own discretion. The methods of postoperative irradiation were open to question, and much more so those employed in preoperative irradiation. There are many subjects remaining in the field of radiobiology which are not fully known, and some of our studies have been performed without complete comprehension. Therefore, it is natural that many ideas will not be put to practical use.

Surgery and radiation can now supplement one another more fully. Surgery should be performed when the patient is brought to the best condition by pre-operative irradiation; post-operative irradiation should be performed according to the findings at surgery. A treatment scheme for each individual case must be devised, combining all pertinent knowledge from the fields of surgery, radiology, pathology, biochemistry and physics.

We will use gastric cancer as an example; it is one of the types which we can expect to respond poorly to treatment. The treatment scheme includes pre-operative irradiation, surgery and post-operative irradiation, and the following general topics are observed.

Item 1 : Preoperative irradiation :

As shown in Table 8, there are two methods, based on the object of treatment. The first method is the fundamental one.

Table 8

Category	Object of Treatment	Object of Irradiation	Irradiation Range	Surgery
First method of pre-operative irradiation	To improve operation result	To devitalize and restrain the proliferation and metastasis of cancer cells	Primary cancer tumor	Radical surgery
Second method of pre-operative irradiation	To widen operation application	Destruction of cancer cells. To destroy and resolve as much cancer cells as possible.	Irradiation to primary cancer tumor and as wide of its surrounding region as possible	Remove the remaining cancer cells
Fundamental form of pre-operative irradiation is the first method, but a sufficient clinical experiences is required for its decision.				

Table 9 Selection of Applicable Dosage

1. The various clinical symptoms should be improved and the former comfortableness should be revived. 2. Tumors should favorably be reduced and resolved. 3. The various ahnormal changes, so-called the cancer-developing stimulize-state, caused by the growth of cancer should be restored. 4. Energy metabolism (QO_2, $Q_M^{N_2}$) of cancer cells should be lowered. 5. The effectiveness-judging-criterion by histoloigcal findings should be above XI. 6. NPN should show its sensitivity.
According to the result of clinical test, the applical test, the application dose shall be fixed between 600r and 1000r lesion dose, and between 2000r and 3000r skin dose. They should be conducted either by the simple divided method or delayed divided method.

(A) Decision for Applicable Dosage

The irradiation must be conducted to improve the clinical symptoms. Table 9 lists the important points determining applicable dosage.

We first arrived at dosage values according to the changes in respiration and glycolysis of tumor cell and by judging the histological effect. Then we gained clinical experience by applying these dosages in the treatment of many patients. We arrived at figures of 600 to 1000 r to lesions, with 2000 to 3000 r air dose. Doses were adjusted according to sensitivity of tumors. There was variation with type of apparatus and irradiation methods. More than 3000 r is required for the second method.

(B) Terms and Methods of Irradiation

Table 10 Terms and Methods of Irradiation

10 X-ray apparatus (200 KVP) Secondary voltage: 160-2000KVP Secondary amp. 2mA-20mA One dose for one irradiation field: 200-300r skin dose, Full dose for one irradiation field: 2000-3000r skin dose, Area of one irradiation field: To be based on the small irradiation field about 4×4 cm. dia. or by the sieve method. Irradiation method: Simple divided method for multiple fields, with short irradiation range 2. Close irradiation (Body cavity tube) Secondary voltage: 60-75 KVP Secondary amp: 4 mA One dose for one irradiation field: 400-600r skin dose, Full dose for one irradiation field: 3000-6000r skin dose, Area of one irradiation field: 3-5 cm. dia. tube, Irradiation method: Simple divided method for multiple fields, with short irradiation range 3. Cobalt-60 gamma ray apparatus One dose for one irradiation field: 200-300r skin dose, Full dose for one irradiation field: 2000-3000r skin dose, Irradiation method: Simple divided method for multiple fields, with short irradiation range
For Post-operative Irradiation: In case of cobalt 60 gamma ray, one time irradiation is sufficient, if a full dose between 600r and 8000r skin dose is applied for one field. In case of using other kind of apparatus, the maximum dose should be applied and an additional irradiation-4 to 5 courses a year should be conducted for first three years, if necessary.

Item 2. Decision of Surgery:

Surgery should be performed when the individual patient is brought to his best condition with pre-operative irradiation, when "an anti-cancer state" is established. One week following completion of pre-operative irradiation, clinical symptoms of the patient are evaluated and the first or the second method is selected. If the first method is appropriate, the patient is operated immediately. If the second method is considered more suitable, additional irradiation is administered.

Table 11 lists important factors in determining the time of surgery, and these are based on our radiobiological studies, described in Chapter II.

Table 11 Decision for Surgery

1.	Most suitable period for the improvement of clinical symptoms (period of appetite, weight, and comfortableness are regained).
2.	When the biological abnormal changes of iudividnal with cancer is fully restored.
3.	When the energy metabolism of visceral organs, such as liver and spleen, of individual with cancer is restored or raised.
4.	When the energy metabolism of cancer cells is lowered to the minimum degree. (Period of the energy metabolism had lost as the healthy cancer cells)
5.	When the entire body remote-effect of cancer necrohormone is inmost powerful state.
	In consequence with the result of above clinical tests, the most suitable period for surgery is to be fixed between 10 and 15 days after the completion of pre-operative irradiation.

Item 3. Therapeutic Transplantation of Extirpated Cancer Tissue:

Pre-operative irradiation resulted in accomplishment of the anti-cancer state due to the production of cancer necrohormones, which in turn resulted from the destroyed products of the cancer cell. The anti-cancer state is brought about by the direct effect of cancer necrohormones, the indirect effect of cancer immunity, and the adjustment of the environment due to changes in substance metabolism.

We must consider that extirpation of the primary cancer at surgery may deprive the body of a site for the production of cancer necrohormones. We observed some clinical cases in which the secondary method of pre-operative irradiation was used, in which this seemed to take place. That is, there were sudden wide spread metastases following surgery and extirpation of cancer, with a worsening of the condition of the patient. The cases received pre-operative irradiation. Probably, their lives would have been prolonged and their pain relieved, had they been treated as inoperable patients, using radiation therapy.

The purpose of our therapeutic transplantation of extirpated cancer tissus is to maintain the proper quantity of cancer necrohormones in the patient following surgery. A small amount of extirpated cancer tissus is transplanted subcutaneously. It is enveloped in fibrous tissue immediately after transplantation, and the transplantation can be performed without any risk. If this transplanted tissue is left without any further procedure, it will proliferate and there will be reason for metastasis with passage of time.

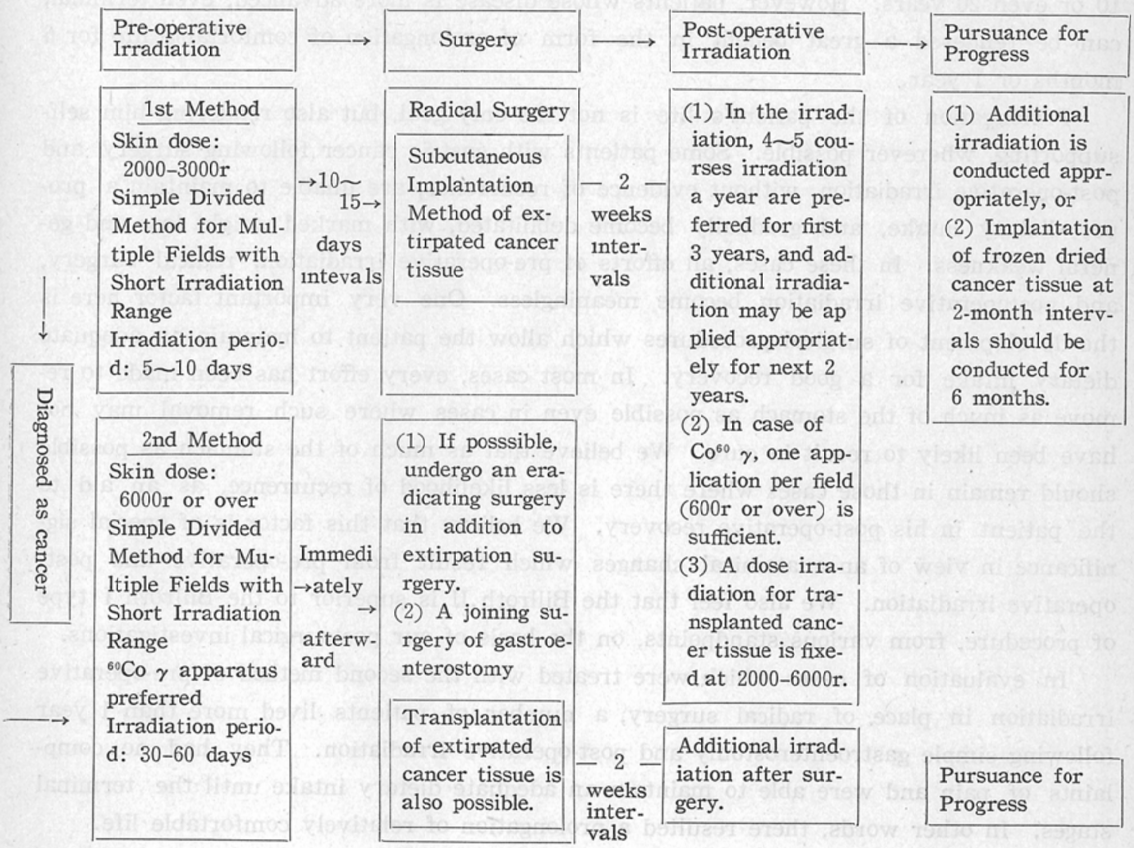
Accordingly, we apply a dose of 2000 to 6000 r postoperative irradiation according to growth and absorption of the transplanted tissue. The cancer cells can be completely annihilated by irradiation with 6000 r, especially those which actively proliferate. The amount of transplanted tissue is 5 to 10 grams, and this will be absorbed in approximately 2 months. In the case of second and third transplantations, a method will be developed to implant dried frozen tissue subcutaneously. This effect can be proved experimentally. We believe that anything based on reasonable theory and effective in combating a highly malignant cancer should be so applied. We feel that these criteria are satisfactory, and experimental and clinical evidence supports this method.

Item 4. Post-operative Irradiation Schedule:

Apparently the radiologist should not fail to be present at surgery, since cooperation with the surgeon is necessary and the radiologist must have a knowledge of findings at surgery. The postoperative irradiation should be conducted under the direction of the surgeon and it is natural that the radiologist should ask for the surgeon's direction prior to conducting radiation therapy, in case the radiogists is unable to be present at surgery.

A single course of post-operative irradiation will usually suffice in treatment of more

Fig. 1.



favorable cases in which radical surgery is performed and no metastases are evident. When all of the cancer tissue cannot be removed, 4 or 5 courses of radiation therapy per year may be required during the first three years, with any additional irradiation as occasion demands.

The above remarks apply to x-ray irradiation; in the case of cobalt 60 gamma ray, the dose of 6000 to 8000 r per field can be used. With this dosage, any remaining cancer cell in the field can be considered killed during the first course. Accordingly, the post-operative irradiation course at present is 6000 r air dose, and 3000 r to the lesion, by ultra-high voltage such as cobalt 60 gamma ray. Close irradiation or tangent irradiation is suitable. Figure 1 illustrates the above.

Chapter IV. Anticipation for Pursuance of Remote Result

A five year survival period is considered basic now, rather than three year survival, following surgery. On the basis of the above treatment planning, we have attempted to assess the result on a 5-year survival basis.

Prolongation of comfortable, useful life is of course the goal in the treatment of all patients. Those cases detected and treated at an early stage of development, especially with certain histological patterns of differentiation, can be expected to remain alive for 10 or even 20 years. However, patients whose disease is more advanced, even terminal, can be rendered a great benefit in the form of prolongation of comfortable life for 6 months or 1 year.

Prolongation of the patient's life is not the only goal, but also rendering him self-supporting, wherever possible. Some patients with gastric cancer following surgery and post-operative irradiation, without evidence of recurrence, are unable to maintain a proper dietary intake, and gradually become debilitated, with marked weight loss and general weakness. In these cases, all efforts of pre-operative irradiation, radical surgery, and postoperative irradiation become meaningless. One very important factor here is the development of surgical procedures which allow the patient to maintain an adequate dietary intake for a good recovery. In most cases, every effort has been made to remove as much of the stomach as possible even in cases where such removal may not have been likely to result in cure. We believe that as much of the stomach as possible should remain in those cases where there is less likelihood of recurrence, as an aid to the patient in his post-operative recovery. We believe that this factor is of special significance in view of an anatomical changes which result from pre-operative and post-operative irradiation. We also feel that the Billroth II is superior to the Billroth I type of procedure, from various standpoints, on the basis of our postsurgical investigations.

In evaluation of cases which were treated with the second method of pre-operative irradiation in place of radical surgery, a number of patients lived more than 1 year following simple gastroenterostomy and post-operative irradiation. They had no complaints of pain and were able to maintain an adequate dietary intake until the terminal stages. In other words, there resulted a prolongation of relatively comfortable life.

In those cases, in which the disease is not detected early, there will be rapid development of terminal stages, despite extensive removal of tissue and resection of other organs. Treatment planning will vary in each individual case.

We have been able to progress to the clinical application, from knowledge obtained from animal tests, radiobiological studies, and confirmation in the pathological field. We have divided preoperative irradiation into two major categoriesy a first and second method of pre-operative irradiation. Under the first method, a prolongation of life at least 5 years is hoped for. In the case of the second method a better result should be obtainable if: the former clinical symptoms are improved; if it is possible for the patient to maintain an adequate dietary intake as long as possible; if an effort is made to prolong the life even by days or hours; if the patient can be made relatively comfortable until death.

Chapter V. Summary

With the improvement of equipment and the facilities for Radiotherapy, we employ as wide a variety of energies as possible. We feel that we can be more confident of the result of therapy by including the use of cobalt 60 gamma ray. However, we believe that the cancer is not curable by the use of irradiation alone, regardless of methods, nor is it curable merely by resecting the lesion. All means of treatment must be utilized.

Anyone who observes the histologic findings in lymph nodes and vessels of extirpated cancer tissue will be very aware of the danger of the cancer cells and of the essential need for pre-operative irradiation. Also, on observing the marked effects of pre-operative irradiation will agree with this treatment scheme for cancer.

At present, we are evaluating the results of our treatment planning and will pursue the evaluation into the future in the search for important facts to aid in future treatment. One year has elapsed since we commenced our present treatment scheme and we now will publish the results of our analyses during the past year.

Although, the fine effect of this treatment cannot be determined unless we see the future progress for next five or ten years, our latest study of cancer immunity "Effect of the pre-operative irradiation and subcutaneously implantation of extirpated cancer tissue on the antitumor antibody levels," Vol. 22, No. 8 of this journal, will prove the correctness of our scheme.

We have now solved the problem of biological amplification and applied it clinically, which had never been cleared in the past, by the auto-immunity-antigen antibody reaction caused by irradiation. That is, we had adopted the following method to practice our scheme: Firstly, keep the individual with cancer in anti-cancer state by the pre-operative irradiation; remove the cancer tissue by a surgery; subcutaneously implant the cancer tissue as antigen; and measure the antibody production.

As already noted in my paper concerning the cancer immunity, the antibody titer in individual with cancer has indicated the rise and duration, which proves that all our method such as the method of pre-operative irradiation, determination of surgical intervention period, and the method of therapeutical transplantation are logically correspond with my theory.

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- Authors -

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