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Studies on the treatment of malignant tumors with fibroblast-inhibiting agent III. Effects of chloroquine on human cancers

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Abstract

A fibroblast-inhibiting agent, chloroquine, used in the treatment of animal tumors led to a reasonably good result, and this approach was extended to the treatment of human cancers. Of histologically proven 54 cases, the drug was effective in 38, ineffective in 15, and unknown in one. It proved to be effective in all the patients who were treated for over 2 months with exception of terminal patients. Of the various malignant tumors treated, excellent therapeutic effects were obtained in patients with carcinoma of the lung and bladder. In the cases where the drug was effective there were a decrease of the size of tumors, fall of serum lactic dehydrogenase, increase of necrosis, inhibition of the stroma, as well as improvement of the symptoms and general condition. As to the mechanisms of the drug action, it would be necessary to consider of its anti-inflammatory and humoral effects upon the host in addition to its inhibitory action on the stromal connective tissue of cancers. The present chloroquine treatment appears to have its indication in inoperable cases, and pre- and post-operative cases, and for the prevention of reccurrence of tumors. Studies are currently in progress in our laboratory to discover more potent fibroblastinhibiting agents and on the combined chemotherapy of chloroquine and other anti-turnor agents. We are indebted to the Department of Urology of our University for the generosity to allow us to use the clinical data on patients with cancer of the urinary bladder.

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STUDIES ON THE TREATMENT OF MALIGNANT TUMORS WITH FIBROBLAST-INHIBITING AGENT

III. EFFECTS OF CHLOROQUINE ON HUMAN CANCERS

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The present day measures against malignant tumors includes early detection, surgical removal, irradiation therapy, and administration of anti-tumor agents, none of which, however, is far from being satisfactory. Of these, search for so-called anti-tumor agents has long been made, and many chemical agents and antibiotics have been tested for their possible carcinostatic activities. Chemotherapy of malignant tumors thus far has been directed to the attack of tumor cells themselves. Unfortunately, however, side effects of most of the anti-tumor agents made it impossible to continue the drugs. The same can be said of the irradiation therapy of cancer. With these approaches it would be a very difficult task to eliminate malignant tumors without doing any harm to normal tissues. It is conceivable that inhibition of the growth of the stromal connective tissue of cancer, which is apparently of a vital importance to the support of parenchymal cancer cells, will secondarily bring about deleterious effects on the latter.

Already several years ago, we observed a dramatic effect of chloroquine on Wakana-disease and bronchial asthma. Subsequently, it was shown that the agent has a potent fibroblast-inhibiting action[1,4], and clinically the drug proved of a considerable value inhibiting the progression of fibrosis of the liver. Accordingly, in view of the role of the stromal tissue of cancer, since 1960 we have come to use chloroquine in an attempt to suppress the growth of the young fibroblastic stroma intrinsic to malignant tumors[1,2,3,4,5]. As reported previously, the effects of the drug upon transplantable animal tumors were satisfactory, and the present paper deals with its clinical application.

MATERIALS AND METHODS

One hundred and three patients with various malignant tumors, the majority of which were inoperable, were treated with chloroquine. The treatment effects were evaluated on 54 of them, who were histologically proven to have carcinomas either by biopsy, operation, or autopsy. Of these 54 patients, 46 were admitted to our Department of Internal Medicine, and the remaining 8

were treated at the Department of Urology for carcinoma of the bladder.

All these patients received either 250 mg of chloroquine diphosphate or 200 mg of chloroquine diorotate usually once or twice daily by slow intravenous injection. The drug was injected slowly over five minutes. We made it a rule to give the drug as long as possible, and the longest duration of therapy ever attained was approximately one and a half years. Since the cancer is an irreversible disease, the criteria for the evaluation of treatment were as follows. Those obtaining subjective or objective improvement were classified as effective, those showing arrest of aggravation of symptoms and some relief of symptoms as slightly effective, and those running a downhill course as ineffective.

In the course of treatment, X-ray examination, gastrocamera, peritoneoscopy, and cystoscopy were performed as indicated. Histological studies, determination of serum lactic dehydrogenase, alkaline phosphatase, transaminase, cholinesterase, serum iron and copper were also done. Furthermore, organ concentrations of chloroquine on autopsied cases were measured by the method of BRODIE[6].

RESULTS

Of the 54 patients, 38 obtained drug effects interpreted as effective. These 38 patients comprised 11 cases of lung carcinoma, 11 cases of gastric carcinoma, 6 cases of bladder cancer, 4 cases of peritonitis carcinomatosa, two cases of recurrent colon carcinoma, and one case of advanced carcinoma of the liver, pancreas, breast, and uterus, respectively. On the other hand, the drug was ineffective in 15, and unknown in one. The patients we treated varied in the state of progression of the disease, and they were divided in two groups, to separate terminal cases, depending upon the duration of treatment. It was found that those 15 patients, in whom the drug was ineffective, received chloroquine for less than two months, while those placed on the drug for over 2 months obtained some sort of beneficial effect for a certain period of time except the one unknown case (Tables 1, 2).

In carcinoma of the lung, the therapeutic effects of the drug were more pronounced, providing improvement in 11 of 12 patients treated. Subjective complaints such as dyspnea, cough, chest pain and sense of pressure tended to improve within a day at the earliest and usually within a week after the start of treatment. This initial response was followed either by an asymptomatic phase of 10 months or in some patients by aggravation accompanied by the presence of pleural effusion. In those with mediastinal involvement, mitigation not only of dyspnea but of facial edema and venous dilatation was noted. An increase of the dosage of chloroquine induced gross hemoptysis in two patients with lung cancer. Improvement in the chest X-ray films was demonstrable in

Table 1 Therapeutic effect of chloroquine on patients with various kinds of cancers

Cases	Number of cases	Therapeutic effect			
		effective	moderately effective	failure	obscure
Lung cancer	12	11		1	
* Gastric cancer	19	7	4	7	1
Bladder cancer	8	6		2	
Peritonitis carcinomatosa	5	3	1	1	
** Intestinal cancer	2	1	1		
Liver cancer	5	1		4	
Pancreatic cancer	1	1			
*** Uterine cancer	1	1			
**** Breast cancer	1	1			
Total	54	32	6	15	1

* Include 1 case with postoperative liver metastasis
** Postoperative relapse
*** Intestinal invasion
**** Postoperative lung metastasis

Table 2 Period and effect of therapy with chloroquine in patients with various kinds of cancers

Period of therapy	Number of cases	Therapeutic effect			
		effective	moderately effective	failure	obscure
more than 2 months	22	19	2	0	1
less than 2 months	32	13	4	15	0

many cases in about a week after the start of therapy and became apparent in 3-4 weeks. There were a decrease of the size of tumors and tumor opacities, delineation of the tumor margin due to a decrease of the surrounding infiltrations, and a decrease of atelectatic changes. There were cases, however, in which no improvement was seen in the X-ray films (Table 3, Figs. 1, 2, 3, Photos. 1, 2).

In carcinoma of the stomach, about half of the patients were in the advanced stage of the disease, and in 11 of 19 cases the drug was effective. Improvement of the symptoms of abdominal distention, epigastric pain and vomiting followed as early as a week and at the latest a month after the initiation of therapy. Symptoms arising from stenosis of the cardia or pylorus often tended to be alleviated by the administration of the drug. In one patient an abscess formation in the abdominal wall ensued. Palpation of the abdomen, in some patients, revealed a slight decrease of the size of the tumor or sharpened edge of the tumor

Table 3 Therapeutic effect of chloroquine on lung cancer

Case number	Name	Age Sex	Chief complaint	Histology	Period of treatment	Improvement of subj. symp.	Improvement of obj. symp.
1	S. O.	56 ♀	Dyspnea	Undifferentiated carc.	11 months	+	+
2	K. D.	58 ♂	Cough	Squamous cell carc.	8 〃	+	±
3	K. M.	47 ♂	〃	〃	5/3 〃	+	+
4	F. M.	46 ♂	Dyspnea	〃	5 〃	+	+
5	S. I.	49 ♀	〃	〃	3/2 〃	+	−
6	M. Y.	73 ♂	Chest pain	〃	1/2 〃	−	−
7	H. A.	62 ♀	〃	〃	3 〃	+	±
8	S. S.	67 ♀	〃	Undifferentiated carc.	18 〃	+	−
9	K. O.	70 ♂	Cough	〃	8 〃	+	+
10	S. H.	57 ♂	Emaciation	〃	8 〃	/	+
11	F. N.	35 ♀	Cough	Adenocarc.	1 〃	+	−
12	S. W.	54 ♂	Facial edema	Undifferentiated carc.	2 〃	+	+
13	S. Y.	65 ♀	Dyspnea	Adenocarc.	4 〃	+	+

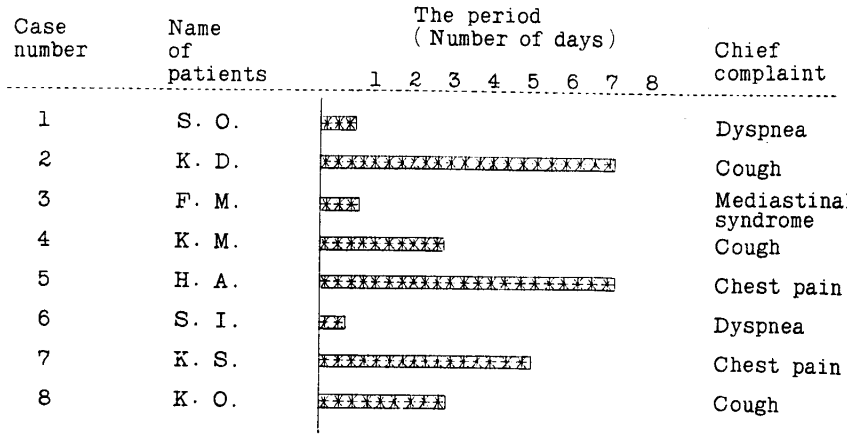

Fig. 1 Period required by chloroquine to exert its therapeutic effect on patients with lung cancer

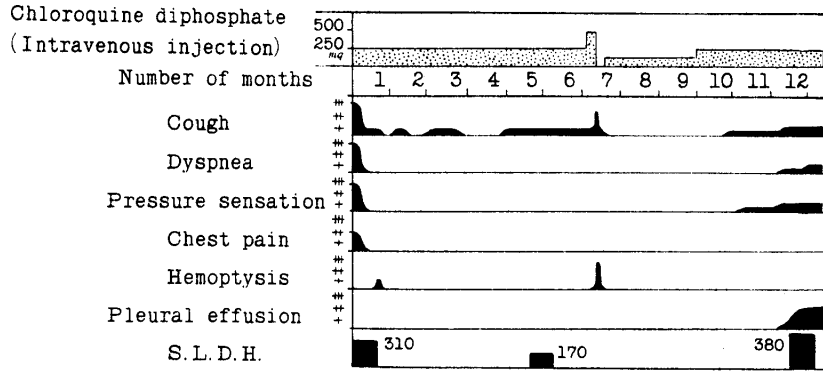

Fig. 2 Lung cancer (Undifferentiated carcinoma), S. O. 61y. ♀

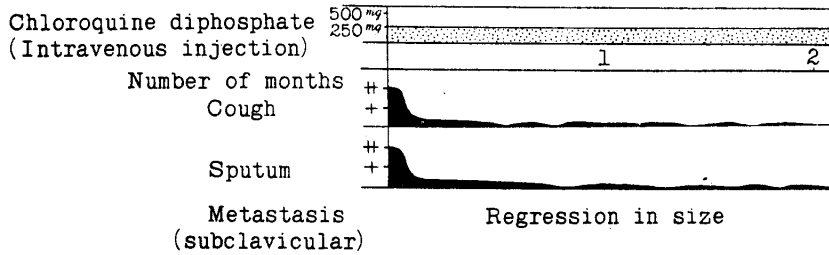

Fig. 3 Lung cancer (Undifferentiated carcinoma), K. O. 70y. ♂

following the treatment. On X-ray examination, a few patients with stenosis showed a marked improvement, but in general changes were not so impressive as in lung cancer. Gastrocamera examination disclosed clearing of the mucous membrane and a slight decrease of the size of the tumors in some cases. Two patients who obtained a marked relief of stenotic symptoms had scirrhous carcinoma (Figs. 4, 5, 6, Photo 3).

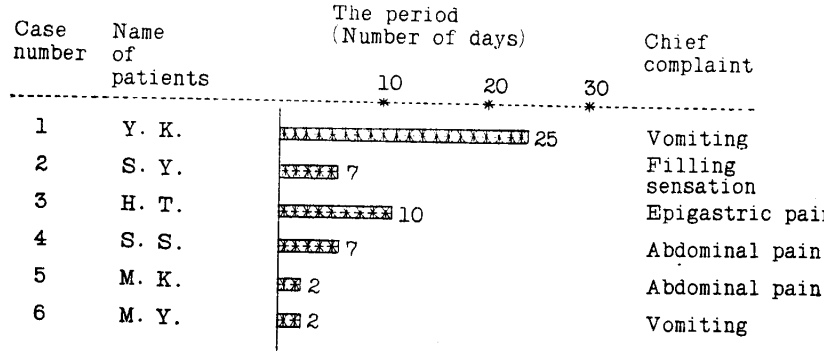

Fig. 4 Period required by chloroquine to exert its therapeutic effect on patients with gastric cancer

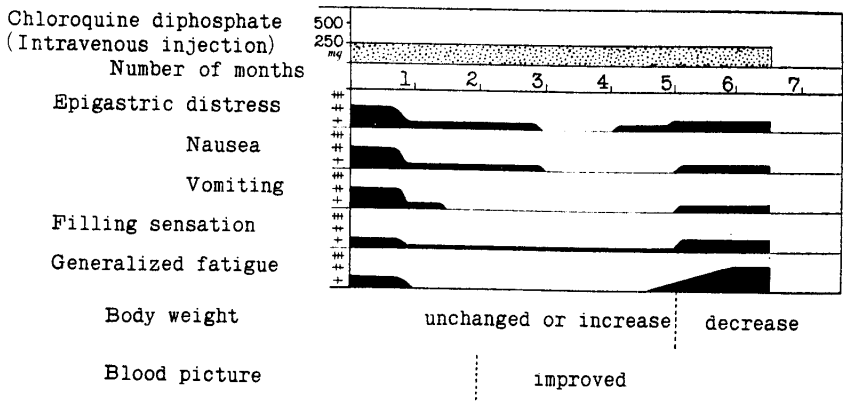

Fig. 5 Gastric cancer (Carcinoma simplex), Y. K. 61y. ♀

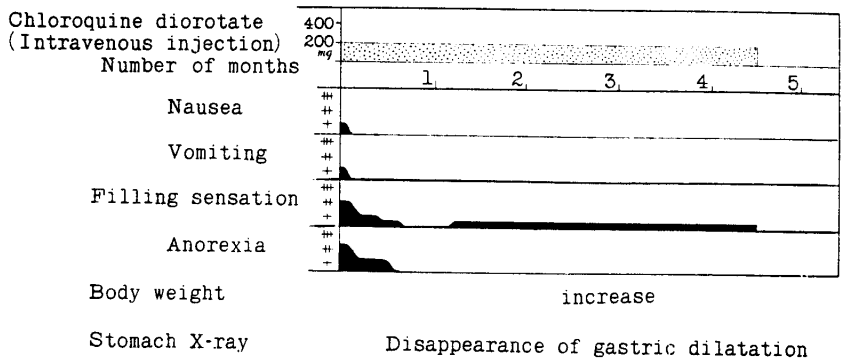

Fig. 6 Gastric cancer (Adenocarcinoma), M. Y. 48y. ♂

In four of the five patients with peritonitis carcinomatosa, the drug was effective, and there was a decrease or disappearance of the sense of abdominal distention and ascites (Figs. 7, 8).

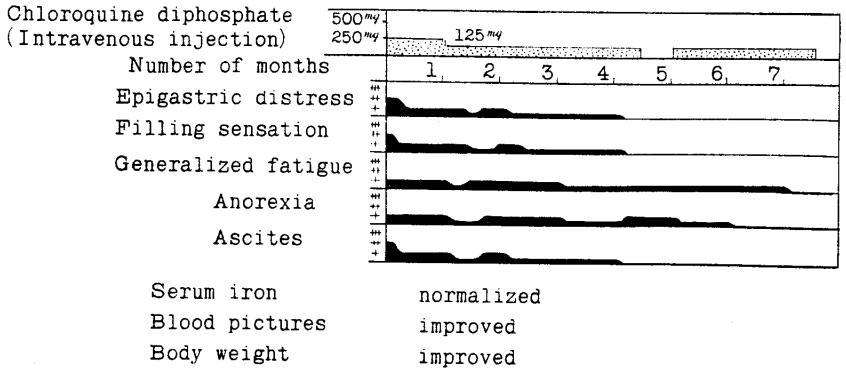

Fig. 7 Peritonitis carcinomatosa (Adenocarcinoma) M. K. 48y. ♀

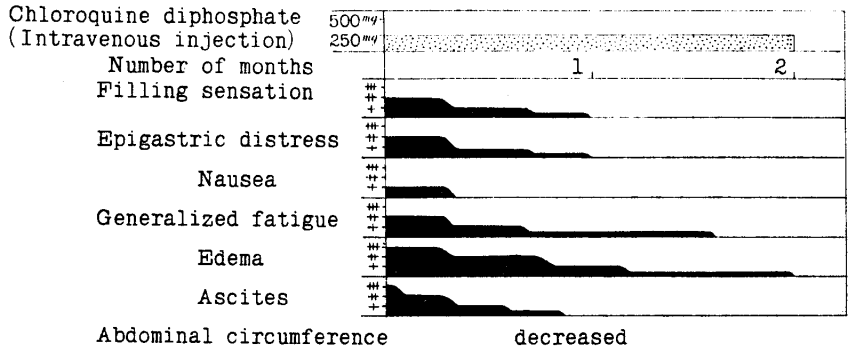

Fig. 8 Peritonitis carcinomatosa (Adenocarcinoma), Y. N. 67y. ♂

One patient with hepatoma showed a decrease of the tumor size and improvement of the genereal condition, but four other hepatoma cases barely responded to the therapy because of the rapidly progressing late stage of the disease. Chloroquine was fairly effective in advanced cases of carcinoma of the pancreas, intestine, breast, and uterus.

It is of note that alleviation of pain was observed in all the cases treated. Metastatic nodules also became smaller in a few instances. In a large number of cases, there was improvement of anemia, erythrocyte sedimentation rate, serum protein and body weight. The serum lactic dehydrogenase was decreased in all the drug-responsive cases in which it was determined. The serum iron occa-

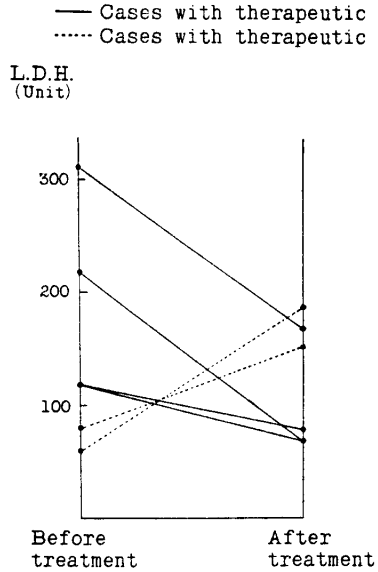

Fig. 9 Changes of S. L. D. H. with chloroquine treatment of cancer

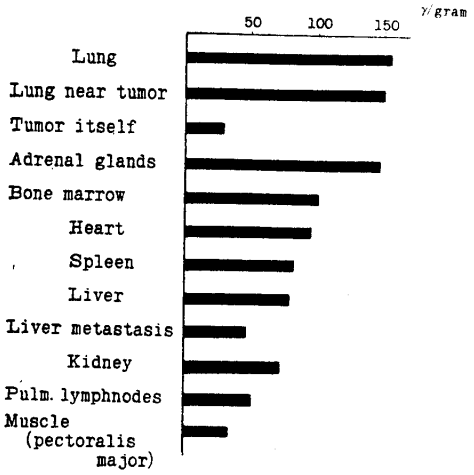

Fig. 10 Organ distribution of chloroquine in autopsied cases of lung cancer

sionally showed a slight elevation. There was no significant alteration in the values of alkaline phosphatase, transaminase, cholinesterase and serum copper. At autopsy softening and an increase of necrosis of the tumors were observed macroscopically or microscopically, although these changes were not solely attributable to the action of the drug. The concentration of chloroquine in the tumor tissue was found to be relatively small (Figs. 9, 10).

Chloroquine was effective in 6 of 8 patients with carcinoma of the bladder treated at the Department of Urology, and in two of the six there was a marked improvement. Improvement or disappearance of the subjective complaints such as hematuria, pollakisuria and dysuria was frequently followed by the cystoscopic findings of a decrease of the tumor size, flattening of the tumor, disappearance of the daughter tumors or clearing of the mucous membrane. Histological changes due to chloroquine were inhibition of the growth of the stromal connective tissue, reduction of inflammatory cell infiltration and replacement of polymorphonuclear cells with round inflammatory cells, while parenchymal tumor cells showed little morphological changes (Table 4, Figs. 11, 12).

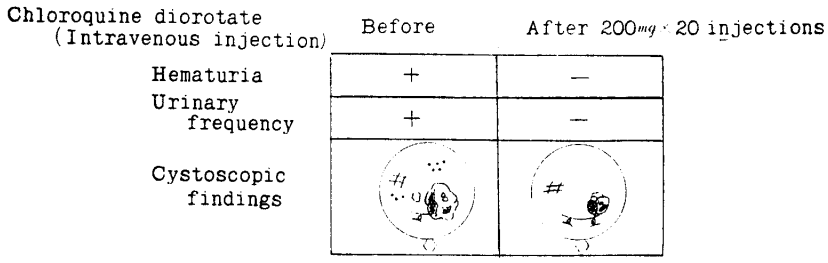

Fig. 11 Urinary bladder cancer (Transitional cell carcinoma) M. S. 62y. ♂

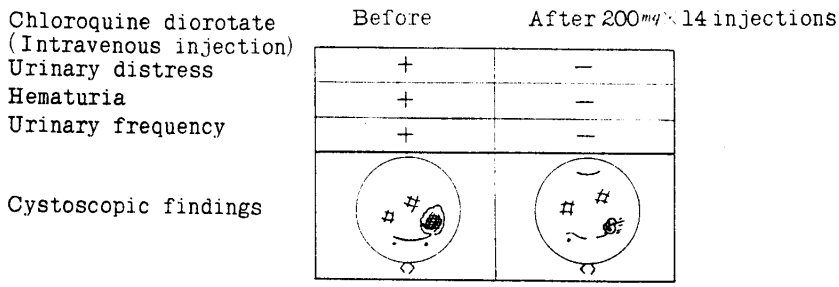

Fig. 12 Urinary bladder cancer (Transitional cell carcinoma) E. O. 67y. ♂

Table 4 Therapeutic effect of chloroquine diorotate on urinary bladder cancer

Case number	Name	Age Sex	Chief complaints	Histology	Period of treatment	Improvement of subj. symp.	Change observed with cystoscope
1	K. S.	66 ♂	Hematuria	Transitional cell carcinoma	26 days	improved	Tumor--no change Mucosa--clear
2	M. S.	62 ♂	Hematuria Urinary frequency	〃	20 〃	disappeared	Tumor--regression in size Daughter tumor--disappeared Hyperemia--disappeared
3	E. O.	67 ♂	Urinary distress Hematuria Urinary frequency	〃	14 〃	〃	Tumor--prominent regression in size Hyperemia--disappeared
4	S. I.	43 ♂	Urinary distress Hematuria	Undifferentiated carcinoma	26 〃	improved	Tumor--flattening volcano type
5	E. F.	65 ♂	Hematuria	Transitional cell carcinoma	13 〃	no evident change	Tumor--some regression in size Surrounding invasion--disappeared Border of neck--clear
6	C. T.	38 ♀	Hematuria	Adenocarcinoma	8 〃	〃	no evident change
7	Y. M.	64 ♂	Hematuria Urinary frequency	Transitional cell carcinoma	15 〃	disappeared	〃
8	S. T.	62 ♂	Hematuria Urinary frequency Urinary distress	〃	20 〃	no evident change	〃

Side effects of the drug were slight, and 8 of the 54 patients had nausea, anorexia, dizziness or blurred vision but no leukopenia. Gastrointestinal complaints were most frequently observed but even in these cases prolonged administration of the drug could be maintained by decreasing the drug dosage or

by combining ATP preparation. Transient vertigo or diplopia that was occasionally seen immediately after injection of the drug could be minimized by giving the drug very slowly with patients in the recumbent position (Table 5).

Table 5 Side effect of chloroquine (in 54 carcinoma cases)

Side effect		No. cases
Gastrointestinal symptoms	Nausea	2
	Anorexia	2
	Sense of fullness	2
Neurological symptoms	Dizziness	1
	Drowsiness	1
Ophthalmic symptom	Blurred vision	1

DISCUSSION

Chloroquine was effective in patients with various cancers except far advanced cases, and the drug was of particular benefit in carcinoma of the lung and bladder. Improvement of the subjective complaints occurred early and could be dramatic. It is to be noted that even the intractable pain commonly seen in almost all the cancer patients could be alleviated. The fact that some of the human tumors became smaller after treatment while the drug merely inhibited the growth of animal tumors is suggestive of its superior drug effects in human cancers.

The periods from the start of treatment to the time when patients obtained beneficial effects differed among various tumors. That patients with lung cancer were usually benefited shortly after the initiation of therapy could be explained by the probable higher concentration of the intravenously injected drug in the lesser circulation. In gastric cancer many patients are asymptomatic and it is difficult to accurately pursue the effects of the drug, but those with stenotic symptoms, particularly two patients with scirrhus, were greatly relieved. A necrosis-inducing action of chloroquine as stated earlier, might have been responsible for gross hemorrhage in two cases of pulmonary cancer following an increase of the drug dosage and formation of an abdominal abscess in one case of gastric cancer. The cancer patients treated with the drug did not complain much of the intractable pain which we commonly encounter in cancer clinic. The excellent effects of the drug in peritonitis carcinomatosa reconcile with some of the *in vivo* experiments[1,2,3,5]. The *in vitro* experiments[1,2,3,5] have excluded a possibility of the direct drug action on cancer cells in the peritoneal cavity, and its effects upon the host should be considered important. This humoral effects

as well as its anti-inflammatory action[3,4,7] should be taken into account to explain the early relief of symptoms in some of the cancer patients. These and other multiple drug actions of chloroquine are now under investigation.

Our previous experiences with chloroquine in the treatment of several hundred cases of bronchial asthma have indicated that the drug has no serious side effects incapacitating its prolonged administration[8]. The drug, under the dosage employed, could be used without any harm such as leukopenia as is often seen with other anti-tumor agents.

The majority of the cases of carcinoma of the lung, bladder and stomach responding to the present therapy were those in the non-terminal stage of the diseases of the slowly progressing type. This indicates that the drug, when used in the early stage, may considerably prolong the life-span of cancer patients. We believe from the present studies that chloroquine is indicated as a drug of choice for those who are not yet cachectic but enough advanced to be inoperable, and for postoperative cases to prevent the reccurrence of tumors. Search is being made for a more potent fibroblast-inhibiting agent, and clinical and basic studies are in progress on the use of chloroquine in conjunctin with other so-called anti-tumor agents and for prophylaxis of the development of tumors.

SUMMARY

A fibroblast-inhibiting agent, chloroquine, used in the treatment of animal tumors led to a reasonably good result, and this approach was extended to the treatment of human cancers.

Of histologically proven 54 cases, the drug was effective in 38, ineffective in 15, and unknown in one. It proved to be effective in all the patients who were treated for over 2 months with exception of terminal patients. Of the various malignant tumors treated, excellent therapeutic effects were obtained in patients with carcinoma of the lung and bladder. In the cases where the drug was effective there were a decrease of the size of tumors, fall of serum lactic dehydrogenase, increase of necrosis, inhibition of the stroma, as well as improvement of the symptoms and general condition.

As to the mechanisms of the drug action, it would be necessary to consider of its anti-inflammatory and humoral effects upon the host in addition to its inhibitory action on the stromal connective tissue of cancers. The present chloroquine treatment appears to have its indication in inoperable cases, and pre- and post-operative cases, and for the prevention of reccurrence of tumors. Studies are currently in progress in our laboratory to discover more potent fibroblast-inhibiting agents and on the combined chemotherapy of chloroquine and other anti-tumor agents.

We are indebted to the Department of Urology of our University for the generosity to allow us to use the clinical data on patients with cancer of the urinary bladder.

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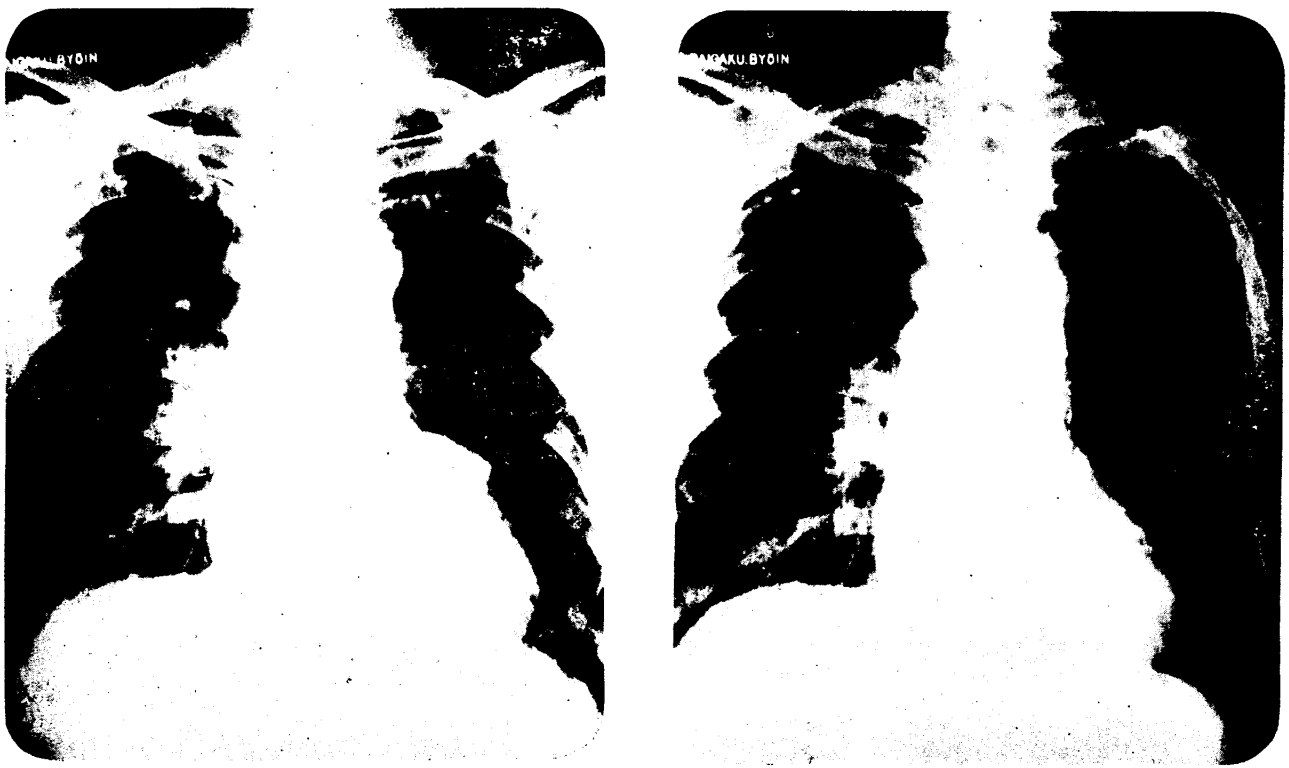
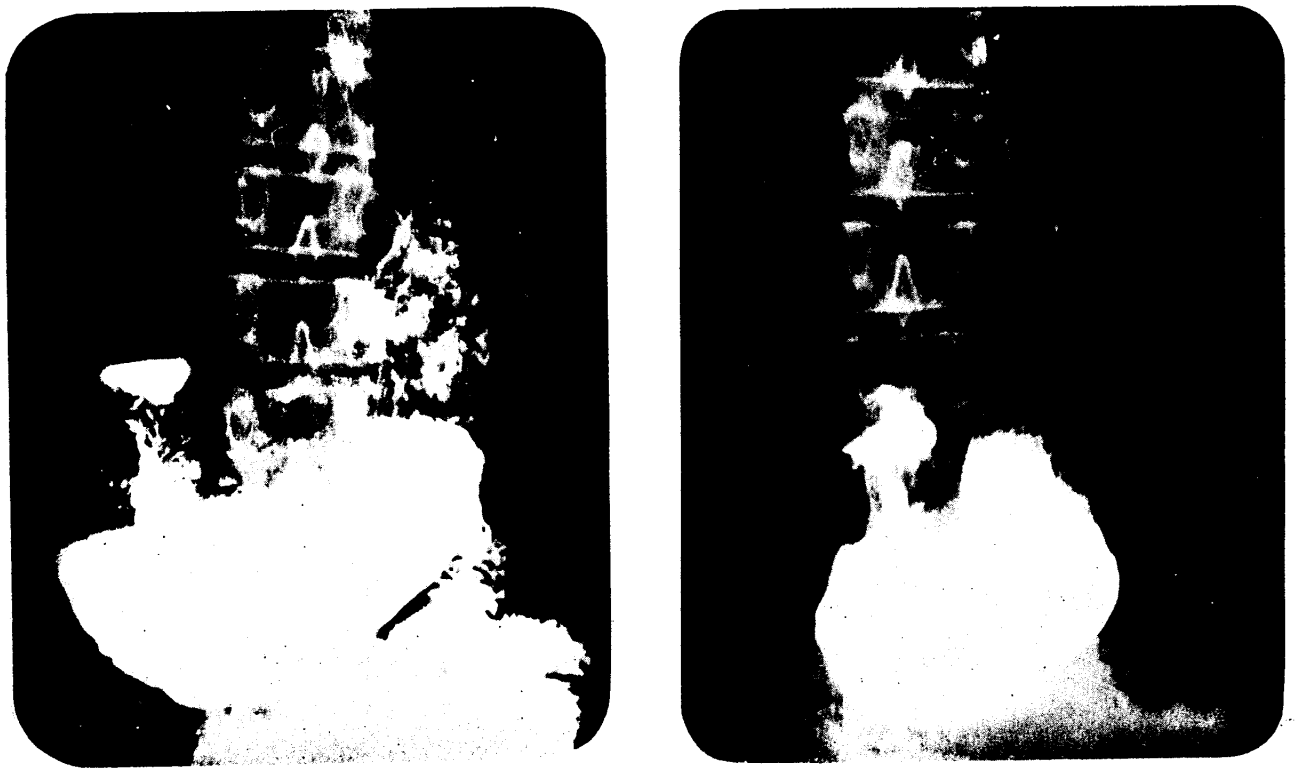
Before treatment　　3 weeks after treatment

Photo. 1　S. O. Lung cancer (Undifferentiated carcinoma)



Before treatment 2 months after treatment

Photo. 2 K. O. Lung cancer (Undifferentiated carcinoma)



Before treatment

3 weeks after treatment

Photo. 3 M. Y. Gastric cancer (Adenocarcinoma)