Chemothrapy of Human Carcinoma with Citronellal and Citral and Their Action on Carcinoma Tissue in Its Histological Aspects up to Healing

By

Shungo Osato

Director of the Prefectural Central Hospital of Akita, Akita

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In the present paper I have reviewed results of our clinical investigations in chemothrapeutic treatment of carcinoma, and changes of the histological aspects of carcinoma tissue under treatment at different stages. As to the remedies, we used mostly citronellal per os and citral in the form of emulsion as intramuscular injection exclusively. In some other cases we combined anti-cancer remedies as Nitromin, Morphyrin and others. Both citronellal and citral are aldehydes of turpentine series with $C_{10}$. Of the 121 cases, which were observed from Oct., 1944 to March, 1959, 6 (≈5%) were permanently cured, having been followed up from 10 to 15 years.

Seven cases of removed stomach cancer in the course of treatment from 15 days to one year and four autopsy cases, of those who died suddenly or in rather short duration because of intercurrent occurrences during favorable course are our materials for histological investigation. They were thoroughly examined microscopically. It was revealed that under the action of remedies, first the degeneration of tumor cells followed by infiltration of plasma cells and other mesenchymal cells take place; then abundant proliferation of connective tissue throughout the carcinoma tissue occur. In this way carcinoma cells and carcinoma tissue get encapsulated, divided by connective tissue and completely annihilated. In rather advanced cases healing of carcinoma under cicatrization would be expected. But in early case of carcinoma, healing without leaving remarkable cicatrice is possible, as was verified in the case of stomach carcinoma, removed after 7 months' treatment.

Possibility of acceleration of healing process through antigen-autoantibody reaction between carcinoma cells and antibody produced in the host during the course of chemotherapy is surmised. In this case there will naturally be severe stress, so that it would be favorable only when the patient could overcome the reaction.

It is noted that here in Akita Prefectural Central Hospital we treated during 2 years and a half 25 cases of carcinoma, of which 3 are completely cured.
Chemotherapy of Human Carcinoma

Chemotherapy of malignant tumors has been an eager desire of mankind for ages. Relatively satisfactory results have been repeatedly reported by many ardent investigators in the case of cancer in the animal body. But, so far as I know, no one has ever claimed success in human cancer, especially in epithelial carcinoma.

I. Clinical observation

In 1950, I first reported several cases of gastric carcinoma, carcinoma of the colon sigmoideum, and pulmonary carcinoma with hemorrhagic exudation of the pleura treated with citronellal and citral with fairly good results. In 1954, Osato et al. reported on the same subject, describing a few cases of carcinoma under the histological investigation done with these medical substances and summarizing the results of the treatment up to that time.

Both citronellal and citral are unsatisfied aliphatic aldehyde of turpentine series with C_{10}:

\[
\text{Citrinal} \quad \begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \cdot \text{C} - \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C} = \text{CH} \cdot \text{CHO} \\
\text{CH}_3 \end{array} \\
\text{Citronellal} \quad \begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \cdot \text{C} - \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C} = \text{CH} \cdot \text{CHO} \\
\text{CH}_3 \cdot \text{C} - \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C} = \text{OH} \\
\text{CH}_3 \cdot \text{C} - \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CHO} \\
\end{array}
\]

So far as I know, Strong in the U.S.A. first reported on the anticancer action of heptylaldehyde in mammary carcinoma of mice. Boyland in England made a far reaching research in cancer chemotherapy applying aldehydes and ketones of aliphatic and aromatic series. Citral was one of the substances which Boyland found to have remarkable effect on animal cancer. These investigators seem to have applied none of those remedies to human cancer. I do not know of any instance where citronellal had ever been tried in cancer chemotherapy before I experimented with it. Even Dyer's "Index of Tumor Chemotherapeutic Studies" (1949) contains no such remedy.

As aldehydes are usually very irritating to the local tissue, the application of citronellal and citral to the human body has been subject to many difficulties. Citronellal can be administered per os and per anum, weakened by adding cod-liver oil (citronellal-cod-liver oil 3–5 cc per os a day). Citral is so irritating that it is preferable to apply it in emulsion (5–10 cc of 5% emulsion every day) to the gluteal muscle. As to the method of preparing the emulsion I have changed measures over and over again, and I am not yet thoroughly satisfied. The methods of preparing the emulsion given in our previous reports were, I
thought, the best on every particular occasion. This problem will be discussed later.

As to the side effect of the remedies, citronellal shows no remarkable side action with doses we are using in the patient. Lethal doses per os in mice is much higher calculated for man. Very few people complained about the odor of citronellal. The 5% emulsion of citral has no severe side action unless it would enter the blood vessels, what can be avoided if one is cautious enough on intramuscular injection. Lethal doses of the emulsion in mice on intra-abdominal injection are very much higher in comparison with body weight of man. Though we made many devices to make the fluid non-irritable at the loco of injection, we are not yet able to avoid the local tumefaction, pain and slight fever in sensible persons. It is good for avoiding such undesirable local side actions, that the patient practices local massage and poultice after injection. We are sure that

<table>
<thead>
<tr>
<th>Table I. Cancer Patients Treated with Citronellal and Citral (1944–1950)</th>
<th>Cases Treated for More than a Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>63</td>
</tr>
<tr>
<td>Cancer of the esophagus</td>
<td>4</td>
</tr>
<tr>
<td>Carcinoma of the liver</td>
<td>9</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>8</td>
</tr>
<tr>
<td>Rectum cancer</td>
<td>2</td>
</tr>
<tr>
<td>Cancer of the pancreas</td>
<td>4</td>
</tr>
<tr>
<td>Uterus carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Other carcinomas</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>99</td>
</tr>
</tbody>
</table>

† Tolerably improved: Appetite and body weight increased, anemia better, subjective and objective symptoms ameliorated, tumor becomes smaller, or X-ray findings improved.

* Much improved: Tumor disappeared or X-ray findings greatly improved. Tumor cells in the peritoneal fluid almost disappeared and complaints of the patient ceased.

‡ 4 of them were practically cured.

these remedies would not cause any side action as anemia, leucopenia, evidence of the damages of the bone marrow.
In 1959,\textsuperscript{19} I reviewed and summed up all the cases treated by this method since late 1944 (Tables I and II). Table I shows the cases observed 1944–1950 at my Internal Clinic at the Tohoku University Hospital, where I was, then, a professor. Table II shows the cases observed 1952–1959 at the Medical Clinic at the Fukushima Medical College Hospital, where I was professor and president. Almost all the cases treated under our medical care were inoperable, and the results of the treatment as a whole were not satisfactory. For instance, out of 99 cases of carcinoma treated within five and a half years (Nov., 1944–March, 1950), 35 died, nearly all in less than a month. The smaller number were operated upon in compliance with the strong wishes of their relatives. The 64 cases were under our care for more than a month. The details are summarized in Table I. Table II interprets the 57 cases treated within 7 years (March, 1952-April, 1959). In all we treated 121 cases of carcinoma in the advanced stage in 13 years. Of these cases 18 patients were much improved at least for some time. While manifesting general signs of recovery, with the tumor diminishing considerably in size, far going amelioration of Roentgen findings were noticed. They were followed up and 6 patients might be considered as permanently healed, – 5 stomach carcinomas and 1 pulmonary metastasis of an operated mammary carcinoma.

The 5 cases of stomach cancer were followed up from 10 years to 14 years and 10 months. One died of acute pneumonia, not of relapsed carcinoma, three and

\begin{table}
\centering
\caption{Cases Treated for More than One Month during 1952–1958}
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
 & Number of cases treated & Much improved & Tolerably improved & Temporarily improved and then aggravated & Unchanged & Aggravated \\
\hline
Stomach cancer & 38 & 7\textsuperscript{*} & 5 & 4 & 7 & 15 \\
Carcinoma of the liver & 2 & 0 & 0 & 0 & 0 & 2 \\
Carcinoma of the esophagus & 3 & 0 & 0 & 1 & 0 & 2 \\
Lung cancer & 9 & 5\textsuperscript{†} & 0 & 1 & 4 & 1 \\
Rectum carcinoma & 1 & 0 & 0 & 1 & 0 & 0 \\
Other cancers & 4 & 0 & 0 & 1 & 0 & 3 \\
\hline
Total & 57 & 10 & 5 & 8 & 11 & 23 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} Two of them were operated later.
\textsuperscript{†} A case of metastatic lung carcinoma was cured after radical operation of mammary carcinoma.
<table>
<thead>
<tr>
<th>Cases</th>
<th>Treatment</th>
<th>X-ray finding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>before treatment</td>
</tr>
<tr>
<td>1. Y.M.</td>
<td>Jan., 1945–June, 1945 Citronellal per os et per anum</td>
<td>Jan., 1945</td>
</tr>
<tr>
<td>51-year-old Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56-year-old Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. E.S.</td>
<td>June, 1948–Oct., 1948 Citronellal per os et per anum with 1% citral, citral emulsion, intramuscular</td>
<td>June, 1948</td>
</tr>
<tr>
<td>55-year-old Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-year-old Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49-year-old Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53-year-old Female</td>
<td></td>
<td>Needle biopsy of the cavity fluid: tumor cells†</td>
</tr>
<tr>
<td>Followed up</td>
<td>N.B.</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>March, 1953: healthy after 7 years &amp; 9 months</td>
<td>April, 1959: healthy after 14 years &amp; 10 months</td>
<td>For about 5-6 years after the treatment occasional gastric pain in hunger. In 1955 medical care because of diarrhea in the morning. September 1958 retired from his post. After that time quite well.</td>
</tr>
<tr>
<td>March, 1953: healthy after 4 years &amp; 10 months</td>
<td>April, 1959: healthy after 10 years &amp; 11 months</td>
<td>February, 1952 was treated in Kurokawa Clinic of Tohoku University as chronic gastritis. Dec., 1955 gastrectomy in the Hospital Katta for stomach bleeding; microscopic examination, not cancerous. Hemorrhagic erosion?</td>
</tr>
<tr>
<td>March, 1953: healthy 4 years &amp; 5 months after treatment</td>
<td>April, 1959: healthy 10 years &amp; 6 months after treatment</td>
<td>In cold occasionally slight stomach pain, needed no medical treatment.</td>
</tr>
<tr>
<td>March, 1953: Feb., 1952 died of acute pneumonia 3 years &amp; 4 months after treatment</td>
<td>Oct., 1963: no complaints of stomach for 6 years &amp; 3 months after treatment</td>
<td>No relapse into the gastric cancer for 3 years &amp; 4 months, until his death.</td>
</tr>
<tr>
<td>April, 1959: No complaints of stomach for 6 years &amp; 3 months after treatment</td>
<td>Oct., 1963: (10 years &amp; 10 months) no complaints of the stomach</td>
<td>She was suffering from chronic rheumatism for many years.</td>
</tr>
<tr>
<td>March, 1958: (3 years &amp; 3 months) no complaint</td>
<td>Oct., 1963: (ca. 9 years) very good condition</td>
<td>Aug., 1952 Radical operation of mammary carcinoma of the right side. After that X-ray treatment 5,000 r. Aggravation of lung metastasis. In July, 1954 she was transferred to our medical clinic.</td>
</tr>
</tbody>
</table>
one-third years after leaving out direct care. Thus we included this case in the number of the completely healed. If I add one case of pulmonary metastasis of operated mammary carcinoma followed up 9 years till 1963 to those permanently healed, I count 6 cases out of the 121 cases treated between late 1944 and the end of 1959. I should like to show them in a table (Table III). The 5 cases of stomach cancer were diagnosed from palpated tumor, shadow defect in X-ray, examination of gastric juice and occult blood reaction in the feces as well as other general symptoms. They were observed in the period when the cytological diagnosis of gastric contents was not our routine clinical method of examination. As these cases had been described in detail on other occasions, I will not enter here further into their explanations, but I will give in this place X-ray photos of the stomach before and after treatment with short annotation in one plate for each case (Plats I-V for Cases I, 1-I, 5). The case of pulmonary metastasis of the operated right mammary carcinoma is worthy of description, as this case has not yet been described anywhere:

Case I, 6*: Y.S., 53-year-old female. (See Plate VI, Figs. 1-4 and Plate VII, Figs. 5-6). She was operated on in August, 1952: right mammary carcinoma and possible regional metastasis together with three ribs were removed. A month later a nut-sized lymph node in the right neck was extirpated. Then she was X-rayed from September, 1952 to March, 1954, 5,000 r. in two courses and got third grade burns on the right chest. As she became very emaciated and had a severe cough, she was transferred to the medical clinic with a dubious diagnosis of aggravated intrathoracic metastasis of carcinoma.

Status on admission to the hospital: She was extremely emaciated, coughing intensively, had no appetite; right thorax was covered by very thin glossy skin and excavated owing to rib-resection; she had dullness and gave no respiratory murmur in the lower two-thirds part of the right thorax; X-ray (Fig. 5) revealed a baby's head-sized intense shadow in this part and diffuse obscure shadow of the other part of the right lung; on needle biopsy in the IV intercostal space on the mamillary line ca. 1.5 cc yellowish, turbid fluid was obtained. Microscopically the sediments showed many irregular large cells, some with two nuclei, isolated or in groups: carcinoma cells (microphoto) (Figs 2-4). On further examination by X-ray we verified that there existed a lung cavity, containing fluid with a horizontal niveau.

Diagnosis: Aggravated lung metastasis after radical operation of the right mammary carcinoma.

Citronellal-cod-liver-oil aa, 6 capsules (ca. 1.5 g citronellal) per os and citral in emulsion (8%) 5.0 cc (0.4 g Citral) to the gluteal muscle, every day, from July 20

* For the sake of brevity the cases Y.M. and D.M. in Table III are numbered Case I, 1 and Case I, 2 respectively.

Similarly, the cases in Table IV are numbered Case II, 1, Case II, 2, etc.
Chemotherapy of Human Carcinoma to September 20, 1954 and afterwards citronellal per os only, until she left the clinic. In this case we administered Nitromin (nitrogen mustard N-oxide) 40 mg, 50 mg and 50 mg by intravenous injection in August, and in September 3 injections of 50 mg each. Because of its side action Nitromin could not be continued.

The patient was greatly relieved of the cough and developed appetite. Body weight increased as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 15, 1954</td>
<td>43.5 kg</td>
</tr>
<tr>
<td>December 23, 1954</td>
<td>44.5 kg</td>
</tr>
<tr>
<td>January 20, 1955</td>
<td>45.5 kg</td>
</tr>
</tbody>
</table>

The second needle biopsy on Sept. 11 at the same place as the first gave 1.0 cc light turbid fluid. Microscopically there were found no large cells except a few lymphocytes.

Fig. 6 shows the X-ray photo taken a year later: a streaky intense shadow at the lower part of the right lung was seen. Through contraction of the cicatrix the mediastinum deviated to the right side (Fig. 6).

The patient was followed up for 3 years and 4 months, while I was in charge of Fukushima Medical College, and was always in good condition. In November, 1963, she answered, on our inquiry, that she was enjoying good health. It is now about 10 years since she left the hospital.

Consequently 6 to 121, or 5% might not be a very large number. However, I do not know whether such data have been reported in the literature of chemotherapy of epithelial carcinoma, except for hormon therapy of prostata carcinoma. I think my data might be valuable as an encouragement in the hope of further chemotherapeutic development in this field, for I think a higher percentage of cure could have been expected, if we had had those cases under our treatment earlier.

For this reason we have been promoting our scheme in the Akita Prefectural Hospital now for two years. I should add a case here which we consider to have been clinically cured, and which has been under our control for one year and a half. Case I. 7: N.M., 56 years old. Male (see Plate VII, Figs. 7-8 and Plate VIII, Figs. 9-13). A civil engineer and building contractor, Diagnosis: Pulmonary carcinoma with pleural effusion. March 27, 1963, he had fever, cold, cough with sputa, pain in the chest, and then bloody sputa for three successive days. He was admitted to our hospital 7 days later. Dullness, weakened respiratory murmur and some friction-like wheeze, and X-ray shadow at the lower part of the right thorax were detected. The X-ray shadow reached the IV rib and filled the phrenicocostal sinus (Fig. 7). Exploratory puncture in the fifth intercostal space gave hemorrhagic fluid. Microscopic examination verified carcinoma cells in groups and isolated (Figs. 10-13). As is shown in Fig. 13, there was a formation as if it were part of a tubule of adenocarcinoma. We concluded that this case might be an adenocarcinoma. X-ray photo combined with pneumoperitoneum
gave no close relation between the diaphragma and liver (Fig. 8).

Citronellal-cod-liver oil per os and citral emulsion into the gluteal muscle were administered as usual. The patient had too sensitive a nature to remedies. With one or two injections of citral he had local tumefaction and fever, so that we could not give the injection every day alternatively into each of the gluteal muscles. We adopted a milder method of injection into each once a week. He could bear ingestion of 9 capsules of citronellal instead of 6.

In a fortnight dullness in the lower part of the right thorax diminished remarkably and exploratory puncture did not give further effusion. After treatment of one month and a half, the X-ray-shadow had practically disappeared. The two nut-sized shadows, which had been considered to be metastatic lymph nodes diminished in size. Sinus costo-phrenicus became light (Fig. 9). Although the patient had been quite well nourished, he added 6 kg in weight and left the hospital on the twelfth of August of the same year, after three months' sojourn in the hospital.

He continues to be well and is visiting us as an out-patient once a week. It is now a whole year and a half, and he is in a very good condition.

II. Change in the histological aspects of carcinoma tissue in the course of our chemotherapeutic treatment

Materials and method:

Our materials for this purpose are given in Table IV. a) Seven cases of stomach cancer resected at different stages of chemotherapy, from two weeks to one year. b) Four cases of autopsy of patients who died in relatively short time during good courses of chemotherapeutic treatment. c) Several cases, on whom biopsy was done after 26 days to 3 months of our chemotherapy of which 3 cases are given in Table IV. Cases of a) and b) are to be valued for our purpose. c) is not sufficient enough, but will give some information on this problem. Six cases from group (a) and three cases from (b) are described here. Numbers of those cases refer to consecutive numbers in Table IV. Blocks of tissue for preparing microscopic slides were taken from many places of the carcinomatous organ, so that we could get a perspective image of the tumor in the organ. The slides were stained not only with hematoxylin-eosin but also with elastica staining combined with Masson's or Mallory's method, for the purpose of better differentiation of mesenchymal tissue.

Case II, 1: S.N. In a 60-year-old woman with a large stomach tumor, who had received only two weeks of our chemotherapy before operation, changes were seen at the peripheral parts of the tumor: degeneration of carcinoma cells, such as vacuolar degeneration, obscure contour of cells, abnormally pale or dark stained nuclei, etc. More or less plasma cells were seen in connection with those tumor cells. Occasionally, reactive giant cells were noticed.
TABLE IV

a) 7 cases of gastric carcinoma, resected in the course of chemotherapy:

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Chemotherapy</th>
<th>Observed</th>
<th>Microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S.N. 60-yr-old</td>
<td>14 days</td>
<td>Sept. — Oct. 1960</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>2</td>
<td>T.A. 57-yr-old</td>
<td>1½ months</td>
<td>1960 — 1961</td>
<td>Gelatinous scirrhous</td>
</tr>
<tr>
<td>3</td>
<td>A.A. 75-yr-old</td>
<td>3 months</td>
<td>July — Oct. 1960</td>
<td>Carcinoma simplex, partly adenocarcinoma</td>
</tr>
<tr>
<td>4</td>
<td>J.K. 52-yr-old</td>
<td>3 months</td>
<td>Oct. 1962 — Feb. 1963</td>
<td>Carcinoma simplex, partly adenocarcinoma</td>
</tr>
<tr>
<td>5</td>
<td>T.K. 53-yr-old</td>
<td>5 months</td>
<td>March—Sept. 1959</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>6</td>
<td>T.H. 53-yr-old</td>
<td>7 months</td>
<td>April — Nov. 1963</td>
<td>? As carcinoma was cured when operated, we cannot give the diagnosis of the microscopic pattern</td>
</tr>
<tr>
<td>7</td>
<td>S.H. 42-yr-old</td>
<td>ca. 1 year</td>
<td>April, 1954 — July, 1955</td>
<td>Gelatinous scirrhous</td>
</tr>
</tbody>
</table>

b) 4 autopsy cases, Died accidentally in relatively short time in the course of chemotherapy with good results.

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Chemotherapy</th>
<th>Observed</th>
<th>Microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>T.O. 60-yr-old</td>
<td>3½ months</td>
<td>Jan. 6, 1948 — May 3, 1948</td>
<td>Epithelioma basocellularare Carcinoma of the choledochus, severe epigastric colic following doudenal sounding</td>
</tr>
<tr>
<td>10</td>
<td>T.I. 73-yr-old</td>
<td>3 months</td>
<td>June 6, 1963 — Sept., 1963</td>
<td>Carcinoma simplex Pulmonary carcinoma, metastasis of the brain</td>
</tr>
</tbody>
</table>

c) 3 biopsy cases

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Chemotherapy</th>
<th>Observed</th>
<th>Microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>N.N. 55-yr-old</td>
<td>Twice, 26 days 2 months and a half</td>
<td>Esophagokopic Carcinoma simplex. See Reference (2)</td>
<td>Esophagian carcinoma</td>
</tr>
<tr>
<td>13</td>
<td>K.K. 72-yr-old</td>
<td>Before and 3 months</td>
<td>On the occasion of colon anastomosis</td>
<td>Adenocarcinoma Colon carcinoma. Liver metastasis</td>
</tr>
<tr>
<td>14</td>
<td>Y.H. 69-yr-old</td>
<td>Before and 3 months</td>
<td>Surgical uptake of neck lymph nodes</td>
<td>Undifferentiated carcinoma Metastasis of neck lymph nodes</td>
</tr>
</tbody>
</table>
Proliferation of collagen fibers demarcated tumor from the surrounding tissue quite well. This was microscopically an adenocarcinoma case.

Case II, 2: T.A. A 57-year-old male. The patient received citronellal and citral, in two courses, each course lasting about one and a half months with an interval of more than a month in between. As the tumor was situated at the pylorus, stenosis came early, though the tumor itself was diminished in size. So operation was persuaded. In this case groups of carcinoma cells showed degeneration and necrobiosis surrounded by quite noticeable proliferation of collagen fibers and infiltration of the mesenchymal cells. It is remarkable that the giant cells were often seen in the neighborhood of degenerated tumor cells. This case was histologically scirrhus and partly gelatiniform.

Case II, 3: A.A. 75 yrs, female. Diag.: Carcinoma ventriculi.

Observed from June 2, 1960 to Oct. 5. Her mother died from stomach cancer in 65 yrs. Since Feb. she had severe stomach pain, inappetance and got rapidly thin. A goose egg sized tumor was palpated in the epigastrium. X-ray revealed an extensive shadow defect extended from the horizontal part of the lesser curvature to antrum pylori, coincided with the tumor. Treatment from June 27 to Oct. 6 citronellal cod-liver oil per os. Because of local irritability, we could continue the injection of citral emulsion no longer than a week. Tumor got diminished in size, but on account of increasing stenosis of the pylorus, stomach resection was suggested.

There was quite a large carcinoma ulcer at the pylorus. Histological examination of the tumor verified adenocarcinoma. Extensive proliferation of fibrous tissue encapsulated the tumor as a whole and invaded into the tumor. In the inner part of the tumor the carcinoma tissue was rather well preserved. But in the peripheral part the tumor cells were so degenerated and destroyed that we saw almost network of stroma containing a few ruined rest of tumor cells on the connective fibers. Very many plasma cells and other histiocytic cells accompanied the collagen fibers. Here and there we met groups of small round cells like lymphocyte in between the remaining stroma.

Case II, 4: J.K. A case of a 52-year-old man. The patient was operated after 3 months of chemotherapy. This case was operated on, because of pyloric stenosis, while carcinoma itself had been reduced in size and well localized. This case, having been a tumor as large as a hen's egg at the beginning of the treatment, showed in the resected stomach a 3.5 cm diameter carcinomatous ulcer of the pylorus. Through microscopic examination, we verified the fact that almost all the parts of the tumor were invaded by stromal fibers. Only in a small portion amidst the ulcer, containing rather ordinary carcinoma tissue, there existed a few mitotic cells. The tumor was as a whole encapsulated by fibrous tissue. This was a case of carcinoma simplex mixed with adenomatous elements. We treated this patient with citronellal and citral combined with Merphyrin, an anti-cancer remedy con-
Chemotherapy of Human Carcinoma

Case II, 5: T.K. (See Plate IX, Figs. 14-17, Plate X, Figs. 18-21 and Plate XI, Figs. 22-25) The case of a 53-year-old man is very important, because he was treated for 5 months and then operated on. The patient gave evidence of a large ulcer in the upper region of the perpendicular part of the lesser curvature of the stomach (Fig. 14). Through our chemotherapy and repeated blood transfusions his blood had increased the number of red blood corpuscles from 950,000 to 3,500,000 per cmm, yet he had always appeared pale and continued to show strong blood reaction in the stool, so we decided to do operation. We found an ulcer of 5.0 cm × 3.0 cm with a rather smooth bottom, surrounded by a low bank of mucous membrane. Histological examination revealed that the bank-like elevation of mucosa contained no carcinomatous elements, only proliferated gastric gland.

Throughout the ulcerated part we noticed a high proliferation of the connective tissue infiltrated by plasma cells and other mesenchymal cells such as histiocyes (Figs. 16–25). The greater part of carcinoma tissue had changed into connective tissue (Fig. 16). Here and there we could find carcinoma cells remaining among the collagen fibers or surrounded by plasma cells and others. We often saw some formation of connective tissue growing abundantly around the carcinoma cells, as if they were tubercles (so-called “pseudotubercle cancéreuse” Babès) (Fig. 18). In other places alveoles of the adenocarcinoma were separated from each other by mesenchymal elements, attacked by plasma cells and other cells of mesenchymal elements and were becoming thinner and thinner. The whole tumor was thickly bounded by the wall of connective tissue. Moreover it was conspicuous that, in general, the tumors were inclined to be encapsulated by stromal tissue even at the earlier stage of our chemotherapy.

Case II, 6: T.H. (See Plate XII, Figs. 26–29 and Plate XIII, Figs. 30–35) I am going to add one more case of stomach cancer, which came under our treatment at a rather early stage of disease and was thoroughly treated. The patient was a man of 52 years.

He had a tumor as large as a pigeon egg, palpable at the epigastrium. X-ray examination revealed the shadow defect to coincide with the tumor (Fig. 27).

Among the gastric contents we found microscopically manifold carcinoma cells either separate or in groups (Figs. 33–35). After two months' treatment the tumor was no longer palpable, and after three months the mucosa relief in X-ray was practically normal (Fig. 28). We could speak of the tumor as having been healed, but chemotherapy was continued on the request of the patient for four more months. After seven months of chemotherapy we examined the patient through X-ray once more, intending to dismiss him. There was a small area of obvious disorder of the mucosa in the lesser curvature of antrum pylori. As we were afraid of the relapse, we thought it best for him to have himself operated.
We ascertained his willingness and consulted him on a convenient time. On opening the abdomen, the surgeon exclaimed, "There is nothing like a tumor", palpating the stomach from the outside. Opening the resected stomach, we found a small protuberance as large as a finger tip in the mucosa, where shadow irregularity in X-ray had been found. The microscopic examination of that part revealed proliferation of mucosa glands (Fig. 32) to coincide with the protuberance (Fig. 30). Defect of the muscularis mucosae and proliferation of collagen tissue were seen beneath it. As a whole there remained no more carcinomatous element in the stomach tissue that "chronic gastritis" as our pathologist diagnosed. So we could verify in this case that perfect healing of the carcinoma was proved histologically as well (Figs. 29–32).

It is noticed in this place, that Cases 3, 5 and 6 were treated with citronellal and citral only, what is important for evaluation of these remedies as cancer chemotherapeutics.

Case II, 7: S.H. Concerning case No. 7 we shall relate it later on.

*Four cases of autopsy are as follows:*

Case II, 8: T.O. As this case had been described in a previous report, I will not repeat it in this place.

Case II, 9: M.S. A female of 72 years. (See Plate XIV, Figs. 36–39, Plate XV, Figs. 40–45 and Plate XVI, Figs. 46–49) She came on June 11, 1963 under our observation with complaints of general weakness, cough (without sputum), and poor appetite. Dullness at the lower part of the right thorax and X-ray shadow corresponding to it were revealed (Fig. 36). Exploratory puncture gave hemorrhagic effusion, in which many tumor cells were found microscopically, as are shown in Figs. 40–43. Some of the cells made a group as if they were exfoliated from a tubule of adenocarcinoma (Fig. 42). By bronchography it was revealed that the 4th and 5th bronchi of the right side were obstructed at 3–4 cm from the branching (Fig. 37). The tumor had most probably gone out of the right middle lobe.

Diagnosis: Primary lung carcinoma. 6 capsules 0.5 cc of citronellal-cod-liver oil aα per os and 5 cc of 5% citral emulsion into the gluteal muscle were continued for 4 months and a half.

Course: During the first month of the chemotherapy results were very favorable. Needle puncture of the pleural cavity, which was done every 8 days gave easily effusion for the first two rounds. For the third round only a few cc of the fluid were obtainable. The fluid given in the first two instances contained a great many carcinoma cells. But at the third time only a few cells were contained. The fourth puncture gave no fluid at all. After a favorable progress of one and a half months, the patient had cough and oppression in the thorax and subfebrile temperature. Some harsh rales were audible at the lower part of the right thorax,
which soon spread to the whole area of the same side. Her general condition became very bad. Then, however, she gradually recovered. The rough rales were gone. X-ray photos of the thorax, taken at the end of August and in September (Fig. 38), showed increased shadow of the mediastinum, which gradually decreased in October (Fig. 39). On November 1, when anticipation of her recovery seemed quite justifiable, she was suffocated to death abruptly while attempting to swallow a morsel of “mochi” which her family had brought to her.

Autopsy was held and the autopic diagnosis by the pathologist was as follows:

1) As to the macroscopic findings in the lungs, both the lungs were found elastic and soft, and the air contents almost normal. In the section plane some irregular strips of fibrous tissue were seen, which microscopically revealed obsolete carnificated pneumonitis with degenerated and exfoliated bronchial and alveolar cells. There was no sign of active pneumonic infiltration. The inner surface of the bronchi was soft and glassy. There was no sign of worsening effusion or tumor dissemination. There were a few fibrous bridges between pulmonary and costal pleurae. Nowhere in the lungs was there any finding suggestive of cancerous infiltration (Figs. 44–49).

2) Lymph nodes of the neck, mediastinum, peritoneum, retroperitoneum, liver hilus, stomach or pancreas were not involved in any metastasis of the tumor.

3) Furthermore, two dark brown stones in the gall bladder, concentric heart hypertrophy with many small cicatrices of the heart muscle, and arteriosclerosis of the aorta and coronary arteries were revealed.

Dr. K. Akazaki, Professor of Pathology at Tohoku University was kind enough to examine our microscopic preparations of this case thoroughly. He did not find any carcinomatous sign in the lungs and lymph nodes.

From all this we concluded that the lung carcinoma had been completely cured, when the patient met her abrupt death through suffocation.

Here we should add two cases ending with brain metastasis of carcinoma in the course of the chemotherapy.

Case II, 10: T.I., 73-year-old man. (See Plate XVII, Figs. 50–57), Admitted on October 8, 1963.

For more than a year the patient had had complaints of a respiratory disorder. In December, 1962, he was X-rayed and a shadow in the middle field of the left lung was found. On March 1, 1963 a round shadow of 1.8×1.8 cm in the left lung was discovered and X-rayed for a month under dubious diagnosis of pulmonary carcinoma. On admittance (October 8th) cough, ephemeral hemorrhagic sputum, general weakness without fever, poor appetite were the complaints. The patient was built tolerably well but quite thin. In the X-ray film a round dense shadow of 3.5×3.0 cm in size coincided with lingula pulmonis, where physical examination revealed a slight dullness and a weak respiratory wheeze and occasional
rales of a medium degree. Scattered carcinoma cells in sputum, were also observed.

Diagnosis: Primary lung carcinoma on the left side. Citronellal-cod-liver oil aa à 0.5 cc 6 capsules per os, and 5 cc citral emulsion of 5% into the gluteal muscle daily. In the course of two months the patient felt gradually better. He recovered from cough and sputum. His appetite improved. In X-ray finding the round shadow became somewhat larger, but less intense, especially in the central part, similar to the image in the case of tuberculoma, which had been reduced to softening. This status did not continue more than four months and a half, when he got a headache. On February 28, 1964 he suddenly complained of severe dizziness, and was unable to move at all. He took little food. Citronellal and citral could not be continued in this condition. He quickly became emaciated, and died in two months.

Autopsy revealed a tumor at the lower part (S₄) of the superior lobe of the left lung, partly necrotic and partly hemorrhagic, and as large as a hen’s egg. There was a metastasis of the tumor at the posterior part of the left lobe of the cerebellum, goose egg sized, which had also changed into a sack.

Microscopically the original tumor in the lung was encapsulated by a thick wall of connective tissue (Figs. 54 and 55). Pericapillary loss of carcinoma cells was noticeable in the original tumor, while the tumor at the cerebellum showed little glia reaction (Figs. 56 and 57) in the adjacent tissue.

The contrast between the original and the metastatic tumor, in their reactive attitude of the surrounding tissue was very keen. It might be remarked that the metastatasis of the cerebellum had not undergone the chemotherapeutic influence, because of the interruption as is explained above, while the original tumor had been under it for four months.

Microscopic diagnosis: Adenocarcinoma of the small cell pattern. Purulent bronchopneumonia of the right lower lobe and left upper lobe was also revealed. The right heart ventricle was dilatatory.

Case II, 11: S.M., 68-year-old male. (See Plate XVII, Fig. 58–69) S.M.'s younger brother died of stomach cancer at the age of 62. In the past 7 years he had been under medical treatment because of his hypertension (170–180 mm).

In January, 1962, he had general weariness. In May he had an X-ray taken, and his kidney and liver were examined. No functional disorder was detected. Erythrocytes sedimentation rate was 78 mm. There was a slight shadow in the right upper field of the chest in X-ray film, so PAS and INH were administered.

In April the general weariness was aggravated. In the afternoon the temperature was 37–38°C. Sedimentation rate 130 mm in an hour. Examination of the patient for malignant disease gave no confirmation. Steroid hormone used to detect rheumatic disease had no effect.

In the night of May 6, 1963, he twice passed 200 cc. hemorrhagic urine with
coagula. He was admitted to M.K. Hospital in Tokyo: X-ray photo of the lungs gave many shadows, which were interpreted as metastases of tumor. Tumor cells were detected in the sputa and urine (Figs. 62 and 63). Clear cells carcinoma was diagnosed. A tumor larger than a man's fist was palpated in the right flank. Being inoperable, the patient was discharged in a very serious and desperate state.

On June 6, citronellal and citral therapy was adopted and every few days 200 cc blood transfusion was resorted to.

In several days his appetite came back and in a fortnight he had so recovered as to be able to take a walk in the garden.

Then at the beginning of August he complained of a headache. The headache got so severe, that at times he lost consciousness for a while. After 10 days he had quite recovered. At the end of August, X-ray photo of the thorax was taken, and this showed that there were no shadows remaining in the lungs. The tumor in the right flank was no more palpable.

Again he was admitted to the M.K. Hospital with the hope of being operated on for the right kidney. He was suggested stopping citronellal and citral, but a setback resulted from the discontinuation. About the 20th of November he lost his eyesight, headache became more severe, and had hemiplegy of the left side. He died on the 30th of November.

Autopsy was held on the same day, and the protocol of the Pathological Institute of Tokyo University gives the following report: Pathological diagnosis: Clear cell carcinoma of the right kidney (r. 430 g; 1.280 g)

1. The lobulated tumor occupying the upper half of the right kidney, measuring 8.0 × 7.5 × 7.5 cm in size with several daughter nodules, one at least as larger as a finger tip. Most tumor cells are regressed or degenerated. Proliferation of the stromal tissue and compression of the adjacent tissue were marked (Fig. 64).

2. Metastasis:

1) Hematogenous metastasis:

   a) Right upper lung lobe: two nodular, one finger-tip sized, and the other small-bean sized.

   b) Brain: the right temporal lobe and the right occipital lobe, one measuring 1 cm in diameter and the other 1.5 cm in diameter.

   c) Thyroid gland, microscopic.

2) No lymphogenous metastasis.

Other findings:

1) Swelling and centrolobular degeneration of liver (1,470 g).

2) Confluent bronchopneumonia, especially marked in the lower lobe of the right lung, and oedema of both lungs. Other findings omitted.
Microscopic examination of the metastatic nodules in the upper lobe of the right lung. The majority of the shadows, which were interpreted as metastases, have histologically disappeared, as they did in the film of August 30. The finger-tip-sized nodular metastasis in the upper lobe of the right lung, which seemed macroscopically old and fibrous, is microscopically encapsulated by a thick wall of fibrous tissue, and the carcinoma tissue itself is infiltrated by mesenchymal cells and invaded by fibrous stroma in a form of network. Another small metastatic focus gives quite a different aspect. A fresh group of tumor cells, accompanied by a hemorrhagic part, is surrounded by normal lung tissue.

Is it too wild and hasty a conclusion to say that because the old metastasis had been under the chemotherapeutic virtue for months, the stromal reaction must have resulted from it, but not from the new smaller metastasis?

As to the metastasis of the brain, the surrounding brain tissue of the metastasis showed remarkable sclerosis with glia reaction (Fig. 65). It is noticed that the metastatic tumor was also under the influence of citronellal and citral for some time.

What the biopsy cases signify: Since only a few cases were investigated in this way and it was not systematically performed, I will not enter into its details. I should only remark that in biopsy evidences were given that degeneration of carcinoma cells and proliferation of the stromal tissue in the cancer take place under our chemotherapy.

DISCUSSION

I. Since 1944 I have made inquiries about cancer chemotherapy with aldehydes of turpentine series, all with Citronellal and Citral. It is now just 20 years since I began this research. It would be of benefit if I now review all the cases treated by this method for a minimum period of more than one month. There are 121 cases in all, coming under our observation from October, 1944 to March, 1961. Of these case 6 (=5%) were permanently healed and followed up from 10 years to 14 years and 10 months. There are many other cases which were at least for a while almost healed, but were lost track of in course of time. Five of these six cases were observed, before cytological diagnosis was our routine method. But I am convinced of the correctness of the diagnosis. The last case, which was an aggravated lung metastasis after radical operation of mammary carcinoma, was diagnosed cytologically as well as roentgenologically. This patient was enjoying good health after having been followed up for 9 years, as of October, 1963.

I have been working here at Akita Prefectural Central Hospital for two years and a half. During this time we treated 25 cases of carcinoma, some of whom are still in the hospital. Three of them are healed: one, lung carcinoma, was clinically healed (Cases I, 7 N. M.). Two of them, one stomach carcinoma (Case II, 6)
and one lung cancer (Case II, 9) are microscopically verified to have been healed. I think the percentage of those cured would be far greater, had we been able to treat the cases at an earlier stage. The diagnoses of all these cases have been cytologically confirmed.

The problem is how the healing of carcinoma by this method takes place. II. Looking over all these data, I now come to the following conclusion, concerning the histological aspects under my method of chemotherapeutic treatment of carcinoma.

At an early stage we noticed, after relatively short duration of treatment, degeneration of carcinoma cells in the peripheral part of the tumor as is described in case II, 1. As if provoked by this degeneration of the tumor cells, there appeared wandering cells such as plasma cells, and others. We often saw eosinophilic cells increasing in the vicinity. In a somewhat advanced stage of treatment, we saw in all cases increased interstitial tissue surrounding and invading the carcinoma tissue. This, hand in hand with the defensive strength of the above mentioned cells such as plasma cells, proved efficacious in destroying and annihilating cancer cells. (Confer Case II, 3 A.A. and Case II, 6 T.H., especially).

We do not have a case healed with cicatrix of carcinoma tissue, that was histologically verified. But it is easily conceivable from the above described cases. Also Case I, 6 (Y.S.), whose aggravated pulmonary metastasis after radical operation of mammary carcinoma had been healed by our chemotherapy and followed up for 9 years after leaving the hospital, would prove this. In this case the shadow in the lung did not disappear but changed into an intensive shadow of cicatrice with retraction of mediastinum on its side.

But, when the tumor is not so large, the carcinoma tissue can be absorbed completely, as was seen in Case II, 6 (T.H.). Sometimes we saw in X-ray in other cases that the mucosa relief could be re-established afterwards, where shadow defect by tumor had been revealed.

Case II, 9 (M.S.) is very interesting because of the revelation of the healing process of carcinoma. As mentioned above, there was destruction of abundant carcinoma cells during the first step of our chemotherapy, which must have caused a rapid production of a sort of autoantibody in the host. When its accumulation reached the highest peak, there might have occurred an allergic reaction between the anti-cancer body and cancer cells in the host. This must have caused a severe stress to the host. In this reaction a great number of cancer cells must have been destroyed. And following that, further action of chemotherapeutic agents may have annihilated all the rest of carcinoma cells. So I think that the eventually occurring allergic reaction of this sort would accelerate healing of cancer. Euler discussed this problem suggestively in his newly published book "Chemotherapie und Prophylaxe des Krebses," in 1962.
It has been reported over and over again by such scholars as Becher\(^2\) (1899), Fischer\(^{10}\) (1913), Ribbert\(^{23}\) (1916), Babès\(^1\) (1926) Böhmig\(^8\) (1930), Innes\(^{13}\) (1934), Busch\(^7\) (1951–52), and in Japan also, by Imai\(^{11}\) (1951), Ota (1930), and Kojima\(^{14}\) (1959), that degeneration of carcinoma cells may appear at a small portion of the tumor without having undergone any therapeutic action, followed by mesenchymal cell infiltration and proliferation of collagen tissue; that such a granulation process, called “pseudotubercle” is occasionally seen in a natural process. Authors, such as Ribbert, and Kojima, argued that this is a phenomenon of a natural healing process against carcinoma. Ribbert believed it possible to accelerate this process in the carcinoma of the mouse by injecting extract of the lymph nodes into the host. It would be imaginable that adequate chemotherapeutic agents as citronellal and citral enforce this process and lead to complete healing. By the way it is to be noticed that Strong\(^{24}\) who first reported a telling effect of aldehyde on animal tumor, saw proliferation of connective tissue in the carcinoma of the mouse by application of heptylaldehyde. Nakauma\(^{16}\) in 1960 reviewed the morphology of carcinogenesis with regard to interstitial tissue of carcinoma. In his conclusion, he emphasized host-parasite relationship, quoting such authors as Yoshida,\(^{28}\) Okabayashi, and Butenandt. Takeda\(^{27}\) and his pupils made extensive studies on the problem of immunity and tumor.

Among many hypotheses, carcinogenesis by somatic cell mutation seems to be becoming prevalent.\(^6\),\(^9\) Whatever carcinogenesis may prove, the tumor existing is nothing but a foreign body in a particular system as are parasites to the host, depending on the other body for their growth and nutrition. My standpoint as to the chemotherapy of carcinoma generally is to regard carcinoma as if it were a chronic infectious disease surmizing a host-parasite relationship between carcinoma and the system.

As I mentioned elsewhere,\(^{17}\) adenocarcinoma seems most sensitive to our chemotherapy, while other patterns are also quite sensitive, but not exhaustively so. It seems to me scirrhous is quite resistant; for example, Case II, 7, S.H., had been operated three years before with diagnosis of stomach ulcer, which was later microscopically revealed as scirrhous. Then the patient was thoroughly X-rayed. But he got tumefaction in the abdominal wall and visited our clinic. We diagnosed relapse of carcinoma, and administered citronellal and citral for about one year. After that he was operated once more in compliance with his wish. A finger-tip-sized mass was revealed as remaining carcinoma at the place of old gastro-enterostomy. Some pattern of carcinoma seems to offer resistance to our remedies.

In any case citronellal and citral are not so strong as to have a high curing effect in the case of advanced carcinoma. Combined use of some other remedies with citronellal and citral will be very advisable. In 1961 Osato \textit{et al.}\(^{20–23}\) reported
that citronellal or citral combined with small doses of PCMB (parachloro-mercuribenzoic acid) had shown additional action of the two agents on MH 134 carcinoma of C3H dd mouse, while the use of Nitromin (Nitrogenmustard N-oxide), Chromomycin, Carcinophylin or Sarkomycin combined with citronellal had not given better effect than when each was used singly. We are now trying it in human cancer cases to see whether it also holds good in clinical as it did in animal experiments.

It would be very desirable, if there be any, who would testify citronellal and citral for cancer chemotherapy. I should like to give some information about preparing the remedies I think now the best:

I. Citronellal per os:
   Chocolate black 50 g grind well in a mortar mix well
   Glucose (anhydrous, extra pure 500 g)
   pour
   Citronellal-cod-liver oil aa 1,000 cc
   distribute in gelation capsules a. 0.5 cc

II. Citral for intramuscular injection:
   Citral 24.0 cc 10' in homogenizer with
   Benzyalcohol 4.0 cc 4,000 turns, cooling in
   Olive oil 48.0 cc ice water
   *5% Na. taurocholate 8.0 cc
   Aq. ad 360 cc 5 in homogenizer
   †6% Gummi arabici 40 cc

Reserve in cool (not in refrigerator) and dark place. Good for injection even after years, if it is shaken slightly.
Quantities are shown for 400 cc, fitted to the homogenizer I am using now.

CONCLUSION

1. In the present paper I reviewed the results of chemotherapy of carcinoma with citronellal and citral during the past 20 years. 6 (=5%) cases out of 121 advanced carcinoma proved to have been permanently healed, followed up from 10 years to 14 years and 10 months.

2. Here in Akita Prefectural Central Hospital 25 cases of carcinoma were treated, of whom 3 cases are completely healed, one clinically, two microscopically.

3. Thus I think we are able to affirm that some carcinoma patients can be cured by our chemotherapeutic treatment.

* Solve in water and boil for short time.
† Solve in hot water. Filtrate twice with cotton and boil for 10'.
4. As to the process of healing, first degeneration and annihilation of carcinoma cells by the action of the remedy; second infiltration of plasma cells, histiocytes and other cells into the carcinoma tissue hand in hand with proliferation of connective tissue, surrounding and invading the tumor.

5. a) Through annihilation of tumor cells, healing occurs without leaving cicatrix, when the tumor is not big.

b) Through changing into cicatrix, if tumors are bigger.

c) Eventually, through allergic reaction of the autoanticancer body against carcinoma cells, healing can be accelerated.

6. My experiences of tumor chemotherapy with good results are confined to epithelial carcinoma.

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EXPLANATION OF ILLUSTRATIONS

Plate I. (Case I, 1, Y.M.) a-g
6 years ago hyperacidity. Since last Spring belching and pain in the stomach.
Status on admission: very thin, anemic, somewhat cachectic. A hen’s egg sized tumor was palpable in the left epigastrium, hard, uneven not movable.
X-ray examination: a disk-like niche of about 5.5 cm in length diameter at the upper part of the lesser curvature was revealed coincided with palpable tumor.
Treatment: Feb. 2, 1945 to July 2. Citronellal-cod-liver oil 3.0 cc. per os and 8.0 cc. per anum. Body weight increased by 4.5 kg. Followed up 14 years and 10 months. Good health.

Plate II. (Case I, 2, D.M.) a-e
Diag.: Carcinoma ventriculi. 7 months ago dull pain in the stomach after meal for several weeks. Since before two weeks the same complaint and heartburn. He lost rapidly in weight. A hen’s egg sized tumor was palpated in the epigastrium. Occult blood in feces positive. X-ray: In a shadow defect on the horizontal part of the lesser curvature, which was verified coincided with a hen’s egg sized tumor, a niche as large as a sparrow’s egg was situated.
Treatment: Citronellal-cod-liver oil + 1% citral 3 cc per os and 8 cc per anum. The tumor as well as shadow defect disappeared.
Followed up for 10 years and 11 months, no relapse.

Plate III. (Case I, 3, E.S.) a-d
No heredity of cancer. At 17 yrs chronic bronchitis.
Since the end of the last year heaviness and dull pain in the stomach. Became rapidly thin. Status on admission; A tumor as large as a hen’s egg in the epigastrium, moderately movable. Occult blood in the feces positive. X-ray: Shadow defect in the lesser curvature of the stomach coincided with the tumor.
Treatment: Citronellal-cod-liver oil + 2% citral 3 cc per os and 8 cc per anum. Later combined with injection of emulsified citral (5%) 5 cc in gluteal muscle. Tumor decreased-rapidly no more palpable after one month. He gained 3.5 kg in 3 months. Followed up for 10 years and 8 months after discharge, always well.

Plate IV. (Case I, 4, K.Y.) a-e
He stayed in the hospital from July 9, 1948 to Oct. 2.
No cancer in his family. Since last July heaviness in the epigastrium and occasional diarrhea. Since March gastric pain, lassitude and rapid loss of body weight.
On admission: anemic and somewhat thin. Tumor larger than hen’s egg was palpable in the epigastrium, hard and uneven.
Occult blood in the feces positive. Achylia.
X-ray: Shadow defect near pyloric port, coincided with tumor, was revealed.
Treatment: Citronellal-cod-liver oil + 2% citral 3 cc per os and 8 cc per anum. Intramuscular injection of 5% emulsion of citral 3-8 cc. After 3 months tumor was no more palpable.
Followed up: He was for 3 years and 4 months always well and then died from acute pneumonia not relapse of cancer.

Plate V. (Case 1, 5., T.S.) a-c
T.S. 49 yrs. Female.
Diag.: Chronic rheumatic arthritis + stomach carcinoma.
While she was in the hospital for treatment of chronic rheumatic arthritis she complained of dysphagia. X-ray revealed shadow defect in the fornix of the stomach and stenosis of the cardia. Two tumor-like resistances were palpated deep in the epigastrium. Stomach carcinoma was diagnosed.
From Oct., 1952 to Jan., 1956 treated every day with citronellal-cod-liver oil as 3 cc per os and intramuscular injection of 5% emulsion of citral 5 cc. After that citronellal-cod-liver oil was given per os:
Besides intravenous injection of 40 mg. Nitromin 3 times a month, 12 injections in all.
She gained in weight and dysphagia disappeared.
Followed up for 10 years and 10 months. No complaints of the stomach. Chronic rheumatic arthritis not healed.
Plate I. Y.M. 51 yrs. Male. 
Diagnosis: Carcinoma ventriculi.

At the admission to the hospital.

b) June 1, 1945. 
At the discharge.

c) A large carcinoma niche. 
Plate I Continued.


e) Feb. 1, 1945 (the same as d).

f) April 26, 1945.


a) Dec. 9, 1947. At the admission.
b) April 30, 1948. At the discharge.
e) March 9, 1948.

a) July 5, 1948. At the admission.
b) Oct. 2, 1948. At the discharge.
d) Sept. 21, 1948. The shadow defect disappeared.

a) July 9, 1948. At the admission.
b) Sept. 3, 1948. At the discharge.
   Shadow defect at the pylorus.
e) Sept. 23, 1948.
   No more shadow defect.
Plate V. T.S. 49 yrs. Female.

Shadow defect in the fornix of the stomach.

b) June, 1952. Stenosis of the cardia and dilatation of the esophagus

c) Nov. 11, 1952. The shadow defect disappeared.
Plate VI (Case I, 6).

Fig. 1. The portrait of the patient a year after leaving hospital.

Figs. 2-4. Microphotos of Ca. cells in the punctata of the pulmonary cavity. Oil
Plate VII. Fig. 5. X-ray photo. of the chest on admission to our hospital.
Fig. 6. X-ray photo. of the chest a year after discharge.

Plate VIII. (Case I, 7).
Fig. 7. X-ray photo. of the thorax on admission.
Fig. 8. X-ray photo. taken under pneumoperitoneum. Arrows show diaphragm.
Plate VIII.

Fig. 9. X-ray photo. of the thorax after 2 months' treatment.
Fig. 10-13. Microphotos of Carcinoma cells in pleural effusion. Oil immersion.
Plate IX  (Case II, 5).

Fig. 14. X-ray photo. of the stomach on admission.  Shadow defect, shown with arrows, in the upper part of the lesser curvature.

Fig. 15. X-ray photo. after 2 months' treatment.
Plate X.

Fig. 18. Pseudotubercle — low magnification.

Fig. 19. Same image — middle enlargement.
Plate XI.

Fig. 22. Carcinoma tissue — low magnification.
Fig. 23. Middle enlargement of the same image.
Fig. 24. Tumor-like tumefaction of lymph node at the serosa side of the stomach —
Plate XII (Case II, 6).

Fig. 26. X-ray photo. of the stomach, taken one and a half months before admission on Feb. 28, 1963.

Fig. 27. X-ray photo. of the stomach on admission in the hospital on April 5, 1963.

Fig. 28. X-ray photo. of the stomach after 6 months' treatment, Sep. 25, 1963.

Fig. 29. Microphoto. of the submucosa tissue of the removed stomach, where carci-
Plate XIII.

Fig. 30. General view of the slice of the stomach, where carcinoma had been palpated, enlarged 3 times the original size. The finger tip sized eminence of the mucosa is shown with arrows.

Figs. 29, 31 and 32. Microphotos of the stomach mucosa and submucosa. Fig. 32 shows proliferation of the stomach glands; middle enlargement.

Figs. 33-35. Carcinoma cells in the gastric contents taken under the action of chymotrypsin.

Fig. 33. Middle magnification.
Plate XIV (Case II, 9).

Fig. 36. Taken on admission on June 12, 1963.
Fig. 37. Taken with bronchography on July 16, 1963.
Fig. 38. Taken on Aug. 30, 1963, when aggravated by allergic reaction.
Fig. 39. Taken on Oct. 31, 1963, the day before the abrupt suffocation of the patient.
Plate XV.

Figs. 40–43. Carcinoma cells in the pleural effusion — oil immersion.

Fig. 44. Lung tissue in the subpleural part at the sinus costo-phrenicus. Lymphocytic cells in group are seen.

Fig. 45. Right lung tissue at the lower part of the inferior lobe. Cicatization same as Fig. 44. An arteria with thickened adventitia at middle lower part and abundant mucous secretion at the right part of the image.
Plate XVI.

Figs. 46-49. Microscopic images from different parts of the lung.
Fig. 47. Desquamation and proliferation of alveolar cells.
Figs. 48 and 49. Desquamation and proliferation of bronchial epithel cells.
Plate XVII (Case II, 10). Figs. 50–57.
Figs. 54–55. Parts of the lung carcinoma, with abundantly proliferated connective tissue.
Carcinoma cells are degenerated and Carcinoma tissue is infiltrated by histiocyctic cells.
Figs. 56–57. Brain metastasis of the tumor — little glia-reaction.

Fig. 50. Jan. 6, 1964.

Fig. 51. Metastasis in the cerebellum.

Fig. 52. Tumor cells in sputum. 40 × 10.

Fig. 53. 100 × 10
Fig. 54. Original tumor in the left lung. Proliferation of connective tissue in the tumor. 10×10

Fig. 55. Original tumor in the lung. 10×10. Carcinoma tissue is separated by columns of connective tissue.

Fig. 56. 10×10

Fig. 57. 10×10
Fig. 58. June, 1963.
Metastasis in the lung.

Fig. 59. Tomography

Fig. 60. August, 1963.
Metastatic shadow disappeared.

Fig. 61. Pyelography, June, 1963.
Fig. 62. Tumor cells in the sputum.

Fig. 63. Tumor cells in the urine.

Fig. 64. Original tumor in the kidney.

Fig. 65. Brain metastasis. Proliferation of glia cells in the adjacent tissue of brain metastasis.
Fig. 66. Old metastasis. 4×10

Fig. 67. 10×10

Fig. 68. Fresh metastasis. 10×10

Fig. 69. 40×10