Histopathological Studies on Autopsied Cases of Stomach Cancer Treated with Anticancerous Drugs

By Yoshiro Tachibana

From the Department of Pathology, Director: Prof. K. Akazaki and the Medical Clinic of Prof. T. Torikai, Director: Prof. T. Torikai, Tohoku University School of Medicine, Sendai; Japan

(Received for publication, August 8, 1961)

Researches on anticancerous drugs are advancing by leaps and bounds, innumerable drugs having been subjected to clinical trial already, but no ideal anticancerous drug has yet announced. For discovery of a better anticancerous drug, it seems indispensable to rescrutinize the effect of such agents in current use on the malignant neoplasms in human body more fundamentally, to grasp the demerits as well as the merits of the individual preparations advertized as anticancerous. From such a viewpoint, the present author made a histopathological investigation of the effect of administering of such drugs, using specimens obtained from autopsied cases of stomach cancer, the cancer most frequent among the Japanese, as materials. In the following, a summary report on the outstanding results is presented.

MATERIALS AND METHODS

The materials of this study were sampled from corpses autopsied within 12 hrs. after death, to minimize the effect of postmortem alterations, among the 123 cases of stomach cancer autopsied in 1954–60, at the Pathological Laboratory of this university; the specimens from 20 of stomach cancer cases that had received anticancerous drugs for more than a week and died within one month after discontinuance of the administration were examined as the treated cases, and 27 specimens from such cases that had no administration of anticancerous drug were taken up as controls. As shown in Tab. I, the treated cases are divided into groups by the varieties of the administered drugs: 4 cases of Nitromin group, 1 case of RC₄ group, 2 cases of Azan group, 3 cases of Mitomycin group, 8 cases of Carzinophilin group, 1 case of Predonin group and 1 case of X-ray deep-irradia-
**TABLE I**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Medication</th>
<th>Dose/day and method of administration</th>
<th>Total dose</th>
<th>Survival period after withdrawal of medication (day)</th>
<th>Operation</th>
<th>The other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>55</td>
<td></td>
<td>Nitromin</td>
<td>20-50mg i.v. 30mC i.p. 1000mg 2×</td>
<td></td>
<td>14</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>2 M</td>
<td>58</td>
<td></td>
<td>Nitromin</td>
<td>25-50mg i.v. 30mC i.p. 825mg 1×</td>
<td></td>
<td>10</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>3 M</td>
<td>57</td>
<td></td>
<td>Alatine-Nitrogen Mustard Etoxy-Nitromin</td>
<td>5-10mg i.v. 50mg 120mg 150mg 7</td>
<td></td>
<td>7</td>
<td>no0</td>
<td></td>
</tr>
<tr>
<td>4 F</td>
<td>25</td>
<td></td>
<td>Alatine-Nitrogen Mustard</td>
<td>5-10mg i.v. 90mg 0</td>
<td></td>
<td>0</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>5 F</td>
<td>70</td>
<td></td>
<td>RC₄</td>
<td>50mg i.v. 500mg 30</td>
<td></td>
<td>30</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>6 F</td>
<td>48</td>
<td></td>
<td>Alatine-Nitrogen Mustard Cyclohexyl Nitromin Carzinophilin</td>
<td>5-10mg i.v. &amp; i.p. 20mg i.v. 5000Unit i.v. &amp; i.p. 1655mg 120mg 330000U 4</td>
<td></td>
<td>4</td>
<td>no</td>
<td>ACTH 870mg</td>
</tr>
<tr>
<td>7 M</td>
<td>47</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. &amp; i.p. 215000U 15</td>
<td></td>
<td>15</td>
<td>op</td>
<td>ACTH 12.5mg</td>
</tr>
<tr>
<td>8 F</td>
<td>47</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. &amp; i.p. 200000U 30</td>
<td></td>
<td>30</td>
<td>op</td>
<td></td>
</tr>
<tr>
<td>9 M</td>
<td>65</td>
<td></td>
<td>Carzinophilin</td>
<td>50000 Unit i.v. 100000U 0</td>
<td></td>
<td>0</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>10 F</td>
<td>60</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. 100000U 5</td>
<td></td>
<td>5</td>
<td>op</td>
<td></td>
</tr>
<tr>
<td>11 M</td>
<td>48</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. 98000U 24</td>
<td></td>
<td>24</td>
<td>op</td>
<td>ACTH 220 I.U.</td>
</tr>
<tr>
<td>12 F</td>
<td>68</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. 85000U 0</td>
<td></td>
<td>0</td>
<td>op</td>
<td></td>
</tr>
<tr>
<td>13 M</td>
<td>54</td>
<td></td>
<td>Carzinophilin</td>
<td>5000 Unit i.v. 50000U 20</td>
<td></td>
<td>20</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>14 M</td>
<td>44</td>
<td></td>
<td>Mitomycin</td>
<td>2mg i.v. 30mC i.p. 84mg 3× 20</td>
<td></td>
<td>20</td>
<td>op</td>
<td></td>
</tr>
<tr>
<td>15 M</td>
<td>64</td>
<td></td>
<td>Mitomycin</td>
<td>2mg i.v. 68mg 1</td>
<td></td>
<td>1</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>16 M</td>
<td>55</td>
<td></td>
<td>Mitomycin</td>
<td>2mg i.v. 42mg 30</td>
<td></td>
<td>30</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>17 F</td>
<td>48</td>
<td></td>
<td>Azan</td>
<td>40-80mg i.m. 2000mg 1</td>
<td></td>
<td>1</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>18 M</td>
<td>62</td>
<td></td>
<td>Azan</td>
<td>80-160mg i.m. 1440mg 12</td>
<td></td>
<td>12</td>
<td>op</td>
<td></td>
</tr>
<tr>
<td>19 M</td>
<td>60</td>
<td></td>
<td>Röntogen</td>
<td>6500r 30</td>
<td></td>
<td>30</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>20 M</td>
<td>48</td>
<td></td>
<td>Predonine</td>
<td>10mg Per os 300mg 7</td>
<td></td>
<td>7</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

* i.v.: intravenous  
  i.p.: intraperitoneal  
  i.m.: intramural
tion group (control).

Of each specimen, the central and the peripheral part of the tumor were cut out, and besides, sections were sampled from the liver, the kidney, the spleen and the adrenal glands, regardless of presence or absence of metastasis, to prepare paraffin embedded sections. Staining was done with hematoxylin-eosin in most cases, but mucicarmine, PAS, Azan-Mallory's and Masson's trichrome stainings were also applied when necessity arose.

RESULTS

The materials in this study were all sampled from autopsied cases, as stated above. Since the administration of anticancerous drugs was began in the terminal stadium of stomach cancer in all the cases, and the administration had to be suspended on account of leucopenia and some such side-effects, the therapy was mostly discontinued within a month in most cases, the case with the therapy continued for 4 months being quite exceptional. In some cases, the anticancerous drug treatment proved temporarily effective, but the tumor was found reaggravated at death. Thus, the exact morphological effects of the drugs were not observable in all the cases, and minute caution was required in rightly evaluating the efficacy, but in studying the control specimens in collation, some findings suggestive of the efficacy of the anticancerous drugs could be morphologically noted. The results obtained are so variegated that generalization seems difficult enough, but the morphological characteristics suggestive effect of the efficacy of anticancerous drugs may be summarized as follows:

1) Atrophy, degeneration and necrosis of cancer cells: As is well known, such necrosis and disintegration of cells in the central part of cancerous tissues are often observable also in cases of cancer not treated with anticancerous drugs and always seen in particularly large cancerous focus and solid carcinoma, but in the specimens from the cases that received such drugs, these changes in cells were particularly notable. But after all, such differences are only quantitative, and not at all essential. These changes are probably histological occurrences due to circulatory disturbance. But in the peripheral zones of the cancerous tissues, namely, the outermost part of proliferating cancer cells in contact with the healthy surrounding tissue and the part in direct contiguity with the stroma, some changes apparently due to the direct effect of anticancerous drugs could be observed. Some of the cancer cells in these sites were found often atrophied, and also loosened in epithelial arrangement, sometimes necrotized and disintegrated. This finding was hardly observable in the control specimens and may be regarded as specifically due to the effect of anticancerous drugs. These changes were more apparent in the parts exposed to closer contact with the drugs carried by blood stream. Accordingly, such changes were usually more marked in the cases of scirrhous cancer, rich in granulation tissue, where the opportunity for
the cancer cells to come in contact of the drugs was more frequent, than in carcinoma simplex with scanty stroma. These changes are also more notable in the parts showing marked reaction of young granulation tissue and rich in blood vessels, than in the parts where the cancer cells were infiltrated into the dense connective tissue with poor capillaries; in the gastric wall, the most prominent changes were observed in the cancer infiltration foci of the submucosal and subserous tissues rich in blood capillaries and apt to show inflammatory reaction.

The differences of findings by the varieties of the administered drugs depend upon the differences of dosage and duration of the treatment but we may say that the Nitromine derivatives are strong in their effect of causing dissolution and degeneration of peripheral cancer cells and this effect may be deemed as characteristic to these drugs, together with the changes they cause in the stroma, as described below. In the cases treated with antibiotics, the accelerated necrosis of cancer cells, as observed also in the control cases, was notable. So, though differences in the degree of changes of cancerous foci following administration of different drugs may be inevitable, in the cases wherever the anticancerous effect was clinically discernible, changes of both the types above were usually equally notable, the cancer cells infiltrating the subserous tissue (and sometimes the submucosal tissue) being particularly subject to the effect of drugs, tending to lose their epithelial arrangement and to show the form of dissociated and scattered histiocyte-like cells.

2) Difference in effect of anticancerous drugs on different histological types of cancer: The above mentioned changes were observed in cancer cells of different types after drug-treatment, at least in restricted areas. On the other hand, the effects of drugs not sufficiently strong to cause disintegration or necrosis of cancerous tissues, that is, the milder effects, took more or less different forms according to the histological types of the cancer specimens. In adenocarcinoma cases, the disparity in size and form of the affected cancer cells were notable, and the frequency of appearance of cell forms as if suspended in the course of atypical mitosis and oversized nuclei seemed to multiply. On the other hand the degenerative changes such as vacuolation become more frequent and the mucus production usually tended to rise, so that in the cells of gelatinous cancer and the cancer type showing diffusive infiltration of signet cells inherently showing large mucus production, the tendency to gelatinous degeneration was amplified. Adenocarcinoma and scirrhous cancer partly mixed with gelatinous cancer are conspicuous. In the so-called carcinoma simplex or medullary carcinoma, the inequality of size and form of the nuclei and the cytoplasms show the tendency of intensifying, and in particular, in the case where medium- or large-sized cancer cells are in dense arrangement, the cells in the central part are enlarged and often take the form of squamous epithelia. It has been
stated above that scirrhous carcinoma is receptive to the influence of anticancerous
drugs; scirrhous cancer cells under the influence of such drugs show besides the
otherwise described changes also increase in size including giant cell formation.
The cell degeneration and atrophy here resemble the changes appearing in the
sites with dense stroma in the control specimens, but in the specimens of the
treated cases, in spite of the looseness of the stroma or the intense activity of
granulation tissue, the cells are often in the course of dissolution, atrophy and
destruction, and cells in atypical mitosis and giant cells are conspicuously
perceptible.
The above mentioned changes of cancer cells are not specific to the specimens
of drug-treated cases and are more or less observable in the control specimens
as well, but as these changes appear more frequently and in more multiple forms
in the former specimens, we may definitely attribute them to the effect of
anticancerous drugs.

3) The effect of anticancerous drugs on the tumorous stroma: The cancer
may be classified by the criterion whether the histological structure consists
mainly of parenchyma or of stroma into carcinoma medullare, simplex and
scirrhosum. In any case, the stroma more or less distinctly shows the features
of granulation tissue and reveals more or less intense inflammatory reaction.1718 Such
findings are especially notable in stomach cancer. Now, administration of
anticancerous drugs affected the picture of carcinomatous stroma in the following
manner. After Predonine administration the inflammatory cells were reduced
in number, the stroma was turned into an edematous tissue and was furthermore
partly hyalinized. In the granulation tissue, the stroma after alkylating
substances and Azan administration were edemotaus and loss of cell reaction was
notable, so that inflammatory cell reaction was weakened even near the tip of
tumorous proliferation and only an edemotaus connective tissue surrounds the
tip. After rather long term administration of these drugs, such changes are
mixed with some hyalinization findings. After antibiotics administration, the
inflammatory cells are comparatively well preserved in the stroma, fibrosis
becomes perceptible and when obsolete hyalinization sets in. The highest
proliferation of the connective tissue was found in the cases subjected to X-ray
irradiation. Isotopic gold is usually applied intraperitoneally in combination
with systemic dosage of the other drugs, and its effect was apparent only inside
the peritoneum, probably acting in the characteristic manners of neoformation
of blood capillaries and proliferation of fibroblasts, besides causing atrophy,
degeneration and disappearance of cancer cells.19

4) Influence of anticancerous drugs on metastasized foci: The author's
specimens were classified into the types of peritoneal, hepatic and lymphnodal,
according to their mode of metastasis, as proposed by Enjoji20 and the effect of
the anticancerous drugs on the respective metastasized foci was examined. As
shown in Tab. II, in comparison with the untreated control cases, the rate of metastasis to the liver was lower in the treated peritoneal type cases, and cancerous peritonitis and metastasis to the adrenal glands were more frequent in the treated lymphnodal type cases. These findings were in good agreement with the results of histological examination.

### Table II.

<table>
<thead>
<tr>
<th>Type of metastasis</th>
<th>No. of operating group</th>
<th>Treated cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Peritoneal dissemination</td>
<td>Hematogenous metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Peritoneal type</td>
<td>Treated cases</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Hepatic type</td>
<td>Treated cases</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Lymphnodal type</td>
<td>Treated cases</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Peritoneal type</td>
<td>Treated cases</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphnodal type</td>
<td>Treated cases</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneal type</td>
<td>Treated cases</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

As detailed below administration of anticancerous drugs is often followed by formation of small necrobiotic or necrotic foci, reflecting the effectiveness of the agents against the foci in the liver as in the other organs. The tumor cells were particularly often found in atrophy, degeneration or necrobiosis near the periphery of the cancer where it touches the liver parenchyma, sometimes the hepatic cell cord being found in direct contact with the necrobiotic cancer cells in the metastatic focus. These findings are in good agreement with what may be expected from the characteristic courses of the portal vessels. It may be easy to understand that such changes appearing only as phenomena in the terminal stadium such as metastases to the liver should show low frequency in the treated cases. The anticancerous drugs tested seemed to have no marked effect on the metastatic foci in the lymph nodes and the lymphatic vessels.

Upon close examination, cancerous peritonitis is found caused by cancer cells from the stomach either reaching the focus in the serous membrane in a row through the tissue interstices and disseminating in the peritoneal cavity, or reaching the subserosal tissue in the form of emboli in the lymphatic vessels and thence spreading to the serosa. In these cases, even when the cancer cells
infiltrating the subserous tissue are under strong effect of the agents, the cancerous emboli in the lymphatic vessels are not much affected.

Among the 8 lymphnodal type cases treated with anticancerous drugs, metastases to the adrenal glands were observed in 6 cases. Of these, in 2 cases the metastasis came directly from the above mentioned cancerous peritonitis, and in the 4 others it was of hematogeneous nature. But metastasis to the adrenal gland was found in 2 of the 4 treated hepatic type cases, against none in the 6 non-treated cases of type, and in 4 of the 7 treated cases against 1 in 9 non-treated cases of peritoneal type, in both cases the frequency being higher in the treated cases. Such metastases have been perhaps facilitated by the congestion in the adrenal glands and excitation and exhaustion of their often observable after anticancerous drugs administration, as mentioned below. It is of some interest that while the frequency of hematogeneous metastasis is nearly uniform in all other organs, it is exceptionally high in the adrenal glands. The nearly entire absence of signs of the effect of anticancerous drugs in the histological picture of the metastatic cancer in the adrenal gland also suggests that the finding is not unconnected with the administration of the drugs.

The representative hematogeneous metastasis is that to the lung, and the anticancerous drug therapy seems to have no influence on the frequency of such metastasis; the effect appearing in the metastatic foci in the lung as examined histologically is seemingly weaker than that in the liver. This is perhaps not only due to the fact that such a metastasis is a terminal phenomenon, but also due to the low frequency of opportunities for the cancer cells to come in contact with the anticancerous drugs owing to the forms of emboli in lymphatic vessel or cancerous alveolitis characteristic to pulmonary metastases. In only 5 of the said 20 cases, bone marrow examination was performed; in them, nodular and hemorrhagic necroses were observable as signs of the effect of anticancerous drugs, not only in the parts affected by metastases, but also in any part of the bones including the marrow and the cortex, forming small nodules. Such changes, however, were sometimes present also in the non-treated controls, so that they may be attributable to the difference of distribution pattern of the arteries of the bone, but it was undeniable that the frequency and the scope of such changes were larger in the treated cases. Besides, signs of the effect of anticancerous drugs similar to those on the stomach wall were also observed in the cancer cells in the bone marrows.

5) Different effects on the cancer cells after different administrations: The anticancerous drugs are most frequently injected intravenously, but Azan is administered by intramuscular injection, and in some cases, intraperitoneal application is also used in combination. In my cases, 3 had been intraperitoneally injected with isotopic gold, 1 with Carzinophilin and 1 with Carzinophilin plus Alanin-nitrogen mustard. After such intraperitoneal administration,
decrease of ascites was clinically confirmed, but histologically a rather strong
effect to cancerous peritonitis was noted. The case with injected isotopic gold
has been discussed in the above. In the Carzinophilin-treated cases, not only
the tendency to degeneration and atrophy of cancer cells in the serous membrane
was enhanced, but besides a finding of nonspecific peritonitis slight inflammatory
cell infiltration and poor blood capillary formation was observed, and sometimes
fibrous incarassation of the serosa was often present. The effects of the agent on
the metastasized cancer in the liver was stronger following simultaneous in-
traperitoneal administration.

6) Changes in the other organs and tissues following administration of
anticancerous drugs: Of the clinical side-effects of anticancerous drugs, the
changes in the blood picture are most conspicuous (Wada et al.21)). In my cases,
the bone marrow examinations were made only in several cases of this study and
therefore the systematic investigations of the effect of the agents on the
hematopoietic organs were unfortunately not performed. In the lymphatic
system, the lymph organs including cortical nodules of the lymph nodes and the
spleen were found generally atrophied but not too highly impaired. The peripheral
vascular system was rather severely affected, in particular, the side-effect of
Azan on the system being already often noted (Yamamoto et al.,41 Morita et
al.22) and Iwai23), and in the one Azan-treated case of mine, too, hemorrhagic
necrosis was very obvious in the lungs, liver and kidneys, etc. In the cases
-treated with Nitromine derivatives, typical emboli were observed sometimes in
the spleen and kidney, etc., besides decrease of free cells in the spleen, edema of
the renal stroma, dilatation of the tubuli, edema, swelling and cylinder forma-
tion in the mesangium of the glomeruli in the kidney in some cases. In the
exceptional case (No. 6), who had suffered from severe thrombophlebitis from
the vena brachialis to the vena jugularis and died from advanced hemorrhagic
infarct in the bilateral lower lobes of the lung due to emboli in the pulmonary
artery, treatment with 1,655 mg of Alanin-nitrogen mustard and 330,000
units of Carzinophilin had been applied. Though we must be cautious in attribu-
ting all such vasculare lesions to the agency of anticancerous drugs, such findings
must be given due attention. In the liver of this case, besides edema, swelling
of the liver cells and such diffusive changes, necrobiotic or necrotic foci were found
in small nodular form, as mentioned already.

There have been some reports on the adrenal cortex in patients with cancer
(Hamaguchi,24) Hahn,25) Setsuda26)). Generally speaking, in stomach cancer
cases, the adrenal cortex is atrophied, particularly thinned down in the fascicular
zone but remains somewhat thicker in the reticular zone. In the cases with large
retention of ascites, however, the adult glomerulosa was found thickened, but even
in such cases, the thickness of the cortex as whole in the control cases was not
found increased, while in the cases treated with Nitromin derivatives, the cortical
cells were often subject to swelling, cytolysis and such acute excitation lesions. After antibiotics administration, such lesions were milder and the cytoplasm of the cortical cells was densely granulated, and the lipoid was obviously diminished in all the cases.

Reports on the lesions in the solid organs have been published (Iijima et al.,²⁹) Kubota³⁰). In the author’s cases too, such lesions were always observed, but apparently more notable in the cases treated with alkylating substances than in those with antibiotics. But the severity of such lesions is more or less different according to the mode of drug administration, and it is particularly notable that in the cases pretreated with ACTH, exhaustion symptoms in the adrenal cortex are kept low and its change was limited to thickening. This finding is very interesting when it is considered in relation with problem of using anticancerous drugs and adrenocortical preparations in combination.²¹

The effect of anticancerous drugs was also found in secondary inflammation foci, and also in the histological nature of terminal bronchopneumonia. For example, after the administration of alkylating substances, mobilization of polynuclear leucocytes and formation of granulation tissue in the inflammatory foci were limited and exudation of such foci was often observed, but after antibiotics administration the original antibacterial effect seemed apparent³²).

DISCUSSION

Evaluation of the effect of anticancerous drugs on cancer, using autopsy specimens, ²¹³⁰³¹³²³³³⁴³⁵³⁶³⁷³⁸³⁹⁴⁰ is a very difficult task, since the cells of malignant tumors are naturally very apt to degeneration and disintegration and strict precaution is called for in such a study. In the present study, the cases were not seldom where the clinical effect of decrease of ascites and improvement of subjective symptoms had been apparent, but the picture of such improvements were hidden at the autopsy beneath the pictures of exacerbated tumor that had caused the death of the patient or under the aftermaths of side-effects of the agent. In the 20 cases cited in this study, clinical efficacy had been noted in 6 cases. In these cases, where should we seek the morphological substrata of the apparent improvement of clinical symptoms before death (the cause of which we will not touch upon here)? Upon studying specimens from autopsy cases after Sarcomycin treatment, Hirafuki¹¹ stated that the morphological foundation of the clinical improvement, especially, contraction and extinction of the cancer can be sought in nothing but the nonspecific changes consisting in necrosis, degeneration and hemorrhage in the tumorous tissue, and finding in the surrounding tissue. He also asserted that only when the action mechanism of the anticancerous drugs has been elucidated, by help of biopsy of spontaneously cured cases of malignant neoplasms, such morphological changes can be rightly interpreted. Among the 27 control cases in the present study, no one was cured.
spontaneously, but in all these cases, upon closer examination, various degeneration processes including necrosis in the cancer tissue were always observed as well as the process of active proliferation. But such degenerative processes were limited in scope, and in the stomach wall as well as the metastasized foci, at the tip part of proliferation between the tumor and the surrounding tissue, active cancer cells were always observed.

The stroma of stomach cancer is found in different conditions from case to case, but always showed the features of granulation tissue more or less notably, and usually accompanied inflammatory cell reaction. The cells of cancerous parenchyma showed findings of many types by cases, but in one individual case, the proliferating cancer cells are usually found in rather uniform shape and size. Sometimes, giant cells are sporadically in existence, but in no case could be seen the picture of large-cellular or polymorphcellular carcinomas as often observed in carcinomas of the thyroid and pancreas.

The above-mentioned changes in the cancer cells were confirmed as the results of examination of specimens of the treated cases, always with such histological features and other findings observed in non-treated controls in mind. As retrogressive changes, degeneration and necrosis of cells were observed not only in the central part of the cancer foci but also in the marginal parts adjacent to the stroma and the surrounding tissue. In the cells of stomach cancer themselves, polymorphcellular formation, gelatinous degeneration and squamous cell metaplasia were notable, inflammatory cell reaction in the stroma was deficient and histological changes from formation of edematous connective tissue to hyaline fibers were observed; the frequency and the extensiveness of such changes may be taken to betray the effect of anticancerous drugs.

In animal experiments on the effect of anticancerous drugs, the problems of the difference of effect by variety of the drugs and the site subject to its action have been chiefly taken up (Ishidate, Umezawa, Hata et al.). But with such postmortem specimens as examined in the present study, the evaluation of any difference in efficacy must be done with utmost caution and a discussion on the difference of efficacy by the variety of drugs on the basis of histological findings is made even more difficult. It could be ascertained, however, that after administration of Nitromine derivatives, the tendency for the cancerous tissue to lose the epithelial character and to fall into dissolution and degeneration was more in evidence, while after antibiotics administration advance of degeneration and necrosis in spontaneous manner was more marked. In the stroma, inflammatory cell reaction was maintained intact after antibiotics administration, but after Nitromine derivatives administration this reaction was inhibited and the tendency to edematous degeneration was intensified.

Such a difference in efficacy is more apparent upon intraperitoneal administration of anticancerous drugs in the cancerous peritonitis cases, for here the serous
membrane is thickened after antibiotics administration, while it is hyalinized and thinned down after Nitromine derivatives administration, and after administration of isotopic gold the capillary endothelium and the fibroblasts are proliferated and swollen. Upon systemic administration, the effect of anticancerous drugs comes out differently by sites according to the quantity of the drug reaching the site in blood flow. For example, in the stomach wall, the cancer cells infiltrating the submucosal and the subserous tissues rich in blood vessels and granulation tissue are readily exposed to the effect of anticancerous drugs, and in the very cancer tissues, scirrhous cancer rich in stroma is more apt to show the effect of drugs than medullary carcinoma, while in carcinoma simplex the peripheral parts are particularly affected. Next, in the cases of gastric carcinoma the effect of anticancerous drugs was far more notable in the case of metastasis to the liver than that to the lymphnodes, but the infiltration foci around the latter was found subject to the effect. Degeneration and necrosis of cancer cells were often found in metastatic foci in the bone-marrows. These findings suggest that more lymph-affinitive drugs should be selected or the mode of administration should be reconsidered, to assure efficacy of anticancerous drugs against the lymphnode metastases of cancer.

As described above, the author's examinations have led to findings substantiating the effects of reduction of tumor in size and decrease of ascites clinically observed in general as effects of anticancerous drugs, though it cannot be denied that some inequality in the efficacy in causing changes in the cancerous tissues was manifest according to the difference in cancer types and in the variety of drugs applied. On the other hand, in the author's specimens of cancer cases mostly treated with drugs in the terminal stadium of disease where operation was too late or postoperative recurrence was apparent, no effect of the prolongation of life was noted. The side-effects of the drugs cannot be neglected in a discussion on this point.

The liver, as stated above, is comparatively affected by the effect of anticancerous drugs, owing to its free blood flow, but this condition also makes it liable to lesions in the parenchyma due to the drugs. In my specimens, small necrotic foci were often found in the liver.

Leucopenia is often clinically recognized as a disturbance of the hematopoietic organs but sometimes the lymph apparatus in the spleen is atrophied and the free cells in its medulla are decreased. Next, we must specially mention the excitation lesions of the adrenal cortex; on the one hand, metastases to the adrenal glands become more frequent in the terminal stadium, while on the other, the exhaustion of the adrenocortex results in earlier death.

These side-effect lesions are apparently worse after Nitromin derivatives administration than after antibiotics. It seems, however, that such side-effects may be at least partly excluded by pretreatment with ACTH and such adreno-
cortical preparations. In fact, in the cases of my specimens pretreated with ACTH, nearly no exhaustion of the adrenocortex could be confirmed.

As the patients of stomach cancer treated with anticancerous drugs had all died during the therapy or within a rather short period after the therapy, these may be called cases of no effect of such drugs. But when we recall that in every case of them, some histopathological signs, more or less manifest, of the effect were observed, we may be justified in expecting successful progress in the future of the chemotherapy for carcinoma just recently introduced in clinical practice.

CONCLUSION

20 specimens sampled at autopsy of stomach cancer cases treated with anticancerous drugs were histopathologically studied, with similar specimens from 27 cases not treated with such drugs as controls. The results obtained were in summary as follows:

1. In the drug-treated cases, atrophy, dissolution, necrosis and such non-specific retrogressive degeneration of cancer cells were quantitatively more advanced than in the control specimens. Such changes were particularly observable in the tip of cancerous proliferation, and more notable in scirrhous cancer than in medullary carcinoma or carcinoma simplex.

2. As more mild changes attributable to the effect of anticancerous drugs, disparity in size and form, atypical mitosis, mucous degeneration, giant cell formation and squamous cell metaplasia were more frequently found, but these changes were not essentially different from similar changes found also in the controls.

3. In the tumor stroma of the drug-treated cases, generally speaking, the inflammatory cell reaction was reduced and edematous swelling was advanced, in somewhat different manner and degree according to the variety of the anticancerous drugs, as follows:
   a) After administration of alkylating substances and Azan, the stroma was highly edematous, the cell reaction was mild, and the degeneration and dissolution of contiguous cancerous tissue was notable.
   b) After antibiotics administration the stromatic reaction remained rather well preserved, but coagulative necrosis and variegation of the cancer tissue in original form were advanced.
   c) After intraperitoneal application of isotopic gold, characteristic findings were observed in the granulation foci of non-specific peritonitis.

4. All the cases examined were classified into the types of peritoneal, hepatic and lymphnodal, according to their mode of metastasis, and the effect of anticancerous drugs on the metastasized cancer was found generally similar to that on the primary focus, but seemingly subject to the influence of the conditions of blood flow and the mode of drug administration.
5. In the drug-treated cases, the liver showed the changes of edema, cell swelling and small necrotic foci, and the adrenal glands revealed swelling of the cortex and in most cases after Nitromin derivatives administration the acute excitation lesions of swelling and dissolution of adrenocortical cells; after administration of antibiotics such lesions were milder and the cytoplasm was found amplified. In the cases pretreated with ACTH, such lesions were always kept mild, swelling of the cortical cells alone being marked.

6. Findings of embolic necrosis and thrombi probably secondary to vascular lesions were notable in some cases after Azan and alkylating agents.

7. As discussed above, the anticancerous drugs studied in the present work had some effect, sometimes powerful enough, against cancer tissues, but we may expect for further study on the questions of improving the permeability, the mode of administration, preventing the side-effects of the drugs and prolonging the life of the treated patients.

References

   Umezawa, H., ibid., p. 64.
   Hata, T. et al., ibid., p. 78.
   Hirafuku, I., ibid., p. 400.
9) Sato, H., Field of Surgery (Jap.), 1959, 7, 1101.
13) Akazaki, K., Gann, 1958, 47, 464.
20) Enjoji, M., Gann, 1958, 48, 23.
23) Iwai, Y. et al., Gann, 1956, 46, 208.
33) Oboshi, S., Gann, 1955, 46, 200.
34) Kuroyanagi, S. et al., Gann, 1956, 47, 62.
35) Ishii, R., Gann, 1956, 47, 63.
37) Suzue, K. et al., Gann, 1957, 48, 491.
Fig. 1. Specimen after 10 day's treatment with 5–10 mg of Alanin-nitrogen-mustrad per diem (Case No. 4). Lesions in the cancerous tissue infiltrating into the gastric subserosal layer: Essentially this case is adenocarcinoma, but the cancer cells lose often pattern of the epithelial arrangement and show atrophic degeneration as well as atypical giant cell formation.

Fig. 2. Specimen after 100,000 units of Carzinophilin (Case No. 9). Essentially this is cubic-epithelial adenocarcinoma but the cancer cells infiltrating into the sumbucosa show dissociation and degeneration and are in a polymorphocellular pattern.
Fig. 3. Specimen after intraperitoneal injection of 1,000 mg of Nitromin and 30 mc of Au$^{198}$ (Case No. 1). Essentially this case adenocarcinoma, but the cancer cells notably changed by variation in size, dissociation, degeneration and necrosis. The stromatic connective tissue is edematous and poor in inflammatory cell reaction.

Fig. 4. The same specimen as in Fig. 2. The adenocarcinoma tissue is markedly degenerated and dissolved. Round-cell infiltration obvious in the stroma.
Fig. 5. Specimen after intraperitoneal injection of 1,655 mg of Alanin-nitrogen-mustard and 330,000 units of Carzinophilin (Case No. 6).

The case treated for the longest duration; the cells in the cancerous focus infiltrating into the stomach serosa have become free cells, and show disparity in size, eccentric localization of nuclei and such variegated changes.

Fig. 6. Specimen after 100,000 units of Carzinophilin (Case No. 10).

Stomach cancer metastasized in the liver. Findings of adenocarcinoma are apparent in the stomach wall, but in the liver, the tendency to squamous cell metaplasia is manifest here.
Fig. 7. The same specimen as in Fig. 3.
Stomach cancer metastasized in the liver. Disintegration and necrosis are conspicuous in the cancer focus, particularly so in the marginal part adjoining the hepatic tissue.

Fig. 8. Specimen after 165,000 units of Carzinophilin (Case No. 7).
Necrosis is conspicuous in the cancer tissue of metastatic focus in the liver adjoining the liver tissue.
Fig. 9. Liver of the specimen shown in Fig. 1. Necrotic focus formed at the center of a liver lobule; edema around the capillaries is also marked.

Fig. 10. Adrenal gland of the specimen after 85,000 units of Carzinophilin (Case No. 12). Dissociation and coagulative necrosis of the cortex prominent.
Fig. 11. Adrenal gland of the specimen after 78,000 units of Carzinophilin and 220 units of ACTH (Case No. 11). The cortex is kept comparatively intact and the cells are solidly filled with cytoplasmic granules.

Fig. 12. Adrenal gland of the specimen in Fig. 3. Pseudo-cavity formation and differentiation of the light and dark cells are noted in the zone glomerulosa adult and the cells in the fascicular zone show focal atrophy and dissociation.