[原著]Oral 5-Fluorouracil Therapy in Carcinoma of the Digestive Organs

Oral 5-Fluorouracil Therapy in Carcinoma of the Digestive Organs

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Recently, attention has been increasingly focused on the oral administration of anticancer agents in the patients with cancer of the digestive organs [1, 2, 3, 4, 5, 6]. Especially, oral administration of 5-Fluorouracil (5-FU) seems to be useful as maintenance treatment because it showes anticancer activity with low toxicity [1, 3, 4, 5, 6]. It is known that oral administration of 5-FU dry syrup in fasting patient, compared to intravenous injection of 5-FU, showes same mode of elevation of plasma 5-FU level[7]. Therefore, 5-FU dry syrup is useful, but 5-FU tablet which acts just like 5-FU dry syrup is also desired because some patients with cancer think 5-FU dry syrup which they drink in syrup suspicious and become nervous.

The authors report the experience of oral administration of 5-FU tablet in the patients with carcinoma of digestive organs.

Materials and Methods

Fourteen patients were referred consecutively from the Department of Second Surgery (Table 1). Six were male and eight were female. Their ages were distributed from 29 to 75 years old. Five patients had cancer of the sigmoid colon or rectum, one had cancer of the jejunum, seven had cancer of the stomach and one had cancer of the pancreas.

Of these, one patient with cancer of sigmoid colon (case 1) and two patients with cancer of the stomach (case 2 and 3) received 5-FU tablet preoperatively, and another eleven patients received it postoperatively.

Each tablet contained 100mg of 5-FU. It was given after the meal three times a day, therefore, all patients received 300mg of 5-FU per day except for case 5. In case 5 it was given also before he went to bed in the form of one more tablet (400mg per day).

Response to treatment was assessed from objective parameters, including tumor measurements and laboratory finding such as plasma CEA-Z level.

Table 1. Age, Sex, Disease Categories, Histologic Diagnosis, Mode of Administration of 5-Fluorouracil tablet, Response to Treatment and Toxicity in Oral 5-FU Treated Patients with Cancer of the Digestive Organs

Case No.	Age	Sex	Disease Categories	Histologic Diagnosis	Mode of Administration	Response	Toxicity	
1	51	M	sigmoid colon	adenocarcinoma papillotubulare	pre-op 15.6g in 52d	good	none	Dukes C
2	45	F	stomach	adenocarcinoma tubulare	pre-op 2.7g in 9d	fair	nausea vomiting in 9d (recovered by stopping the agent for 5d)	
3	45	M	stomach	adenocarcinoma mucocellulare	pre-op 3.0g in 10d	not decided	none	
4	58	F	rectum (Dukes B)	adenocarcinoma papillare	post-op 18.6g in 62d	follow up study is in progress	none	Miles'op 3 yrs ago. CEA-z 0.5 ng/ml. hypersalivation by 5-FU DS 300mg/d. nausea by FT207 800 mg/d.
5	62	M	rectum (Dukes B)	adenocarcinoma papillare	post-op 22.7g in 71d	follow up study is in progress	none	Miles'op 10m ago. CEA-z 2.3ng/ml
6	61	F	rectum (Dukes C)	adenocarcinoma tubulare	post-op 27.9g in 93d	follow up study is in progress	none	Miles'op 2yrs 6m ago CEA-z 1.4ng/ml
7	75	F	rectum (Dukes B)	adenocarcinoma papillare et muconodulare	post-op 8.4g in 28d	poor (CEAZ-5.1–6.7 ng/ml)	nausea (recovered by stopping the agent 1d)	Miles'op 3yrs ago
8	70	F	jejunum	adenocarcinoma tubulare	post-op 32.1g in 107d	fair (stable disease)	anorexia nausea epigastralgy	palliative resection of tumor 1yr ago
9	40	F	pancreas	acinar cell carcinoma	post-op 38.1g in 127d	fair	anorexia nausea vomiting	Whipple's op 2yrs ago no finding of recurrence of tumor
10	59	M	stomach ($P_0H_0S_1$)	adenocarcinoma mucocellulare	post-op 29.7g in 99d	follow up study is in progress	diarrhea	gastrectomy 2yrs 6m ago no finding of recurrence of carcinoma
11	55	M	stomach ($P_0H_0S_2$)	adenocarcinoma tubulare	post-op 21.9g in 73d	follow up study is in progress	anorexia sensation of abdominal distention in 10d (recovered by stopping the agent for 3d)	total gastrectomy 1yr 9m ago. no finding of recurrence of carcinoma

Case No.	Age	Sex	Disease Categories	Histologic Diagnosis	Mode of Administration	Response	Toxicity	
12	29	F	Stomach ($P_0 H_0 S_2$)	scirrhous carcinoma	post-op 4.2g in 14d	follow up study is in progress	abdominal pain in 7d (recovered by stopping the agent for 3d)	tolal gastrectomy 10m ago. 5-FU 250mg/d IV for 30d had been given before no finding of recurrence of carcinoma
13	52	F	stomach ($P_0 H_0 S_2$)	adenocarcinoma mucocellulare	post-op 26.7g in 89d	follow up study is in progress	abdominal pain in 30d (recovered by stopping the agent for 2w) anorexia nausea vomiting in 83d	gastrectomy 10m ago no finding of recurrence of carcinoma
14	71	M	stomach	adenocarcinoma papillotubulare	4.5g in 15d	poor	skin eruption in 15d (recovered by stopping the agent)	terminal cancer

Treatment Effect and Toxicity in Preoperative Administration

Preoperative administration was done in three patients. The authors report these three patients.

Case 1. A 51 year-old male came to us because he noticed a big mass in the epigastrium. Barium enema revealed cancer of the sigmoid colon and the mass in the epigastrium seemed to be liver metastases. Needle biopsy of the liver revealed tubular adenocarcinoma, then 15.6g of 5-FU in the shape of tablet was given in 49 days preoperatively. No change was noticed in clinical course, physical findings and laboratory findings.

At operation, cancer of the sigmoid colon and multiple metastases in both lobes of the liver were found. Palliative resection of cancer of the colon and end-to end anastomosis of the colon were performed.

Light microscopic examination of specimen of the liver obtained by biopsy before administration of 5-FU revealed tubular adenocarcinoma which contained a lot of connective tissue. Cancer cells were high columnar cells and showed typical tubular arrangements (Fig. 1).

Light microscopic examination of surgical specimen after administration of 5-FU revealed papillary adenocarcinoma with ulcer formation, tubular arrangement in areas, and marked infiltration of cancer cells into all layers of colon and mesocolon. Remarkable coagulation necrosis was seen in the center of cancer nests. Some cancer nests showed complete replacement of cancer cells by necrotic substance (Fig. 2). Necrotic changes in various degrees, that is, pycnosis, deformation and pleomorphosis of nuclei of cancer cells were also noticed. Pycnosis of the nucleus means death of the cell, therefore, the above mentioned findings seem to be followed by coagulation necrosis (Fig. 3). Cytoplasm of cancer cell was scant, condensed and eosinophilic and these findings suggested also severe injury of cells. These findings of injury were seen in all layers of colon at same degree. Borderline between normal mucous membrane and cancer was clearly noticed and findings of injury

were seen in cancer cells only. Normal cells in normal mucous membrane did not show any findings of injury (Fig. 4).

In this case, it may be said that 5-FU tablet had good effect histologically. No toxicity was seen in the digestive organs and hematologic system, therefore, surgical operation was not disturbed by administration of this agent.

Case 2. A 45-year-old woman was hospitalized for jaundice. She had undergone subtotal gastrectomy for cancer of the stomach 2 years and 4 months before.

Percutaneous transhepatic cholangiography revealed a smooth semicircular defect of the choledochus which appeared to be coming from the lateral aspect only.

Administration of 5-FU tablet, 5-FU 2.7g in nine days, was done and it was abandoned because of anorexia, nausea and vomiting.

At operation, metastases of cancer was found in lymphnodes of the hepatoduodenal ligament and lymphnodes of head of the pancreas only. Pancreaticoduodenectomy was performed.

Light microscopic examination of surgical specimen revealed scirrhous adenocarcinoma which involved severly the duodenum and the pancreas. Cancer cells showed atypical tubular arrangement or cord-like structures. Marked infiltration of round cells which chiefly consist of lymphcyte were seen in interstitial connective tissue (Fig. 5). In areas, findings of marked injury of cancer cell, that is, blured borderline of each cancer cell, pycnosis and light stained nucleus of cancer cell were seen. In there areas, some cancer cells seemed to be replaced by connective tissue and it was difficult to differentiate cancer cell from connective tissue (Fig. 6). In general, although growth and invasion of cancer cells were marked, here and there, the findings of injury of cancer nests were seen and these suggested the treatment effect of anticancer chemotherapy. Metastases in lymphnode showed similar appearance and scirrhous cancer with hyperplasia of connective tissue showed above mentioned findings of injury.

Before administration of this agent, laboratory studies included serum total bilirubin 9.2mg/dl, SGOT 57 IU, SGPT 54 IU, LDH 96 U, BUN 13mg/dl, nevertheless, hepatic, renal and hematologic toxicity were not found.

Surgical operation was not disturbed by administration of 5-FU tablet.

It may be said that this patient showed histologically fair response to this treatment.

Case 3. A 45-year-old man was hospitalized for discomfort in epigastrium. Upper GI series revealed II c type of gastric carcinoma near the cardia. Biopsy confirmed this conditiona and 5-FU tablet, 5-FU 3.0g in 10 days, was given. Clinical course, physical examination and laboratory examination revealed no change.

At operation, total gastrectomy was done.

Light microscopic examination of the specimen of biopsy of the stomach before the treatment revealed tubular adenocarcinoma and, in areas, signet ring cells. Cancer cells were found in mucous membrane only. Tumor formation was not found (Fig. 7). Light microscopic examination of surgical specimen revealed severe atrophic gastritis and scattered cancer cells in the mucous membrane. Cancer cells showed mucoid degeneration, and some of them had eosinophilic cytoplasm and blured cell membrane.

In this patient, however, it was impossible to estimate quantitatively the treatment effect of this agent by means of assessment of size of cancer nest or estimation of severity of necrosis, because cancer cells of this patient did not form nest nor tumor (Fig. 8).

Therefore, reponse of this patient to this treatment could not be estimated histologically. Surgical operation was not disturbed by administration of this agent.

Treatment Effect and Toxicity in Postoperative Administration

Postoperative administration of 5-FU tablet was done in eleven patients. Of these, four patients had cancer of the rectum (Dukes B or C) which had been removed by abdomino-perineal resection of the lower bowel 10 months to 3 years before. In case 7, 4, 5 and 6, 8.4g, 18.6g, 22.7g of 5-FU was given in 28 days, 62 days, 71 days and 93 days respectively.

In case 4, 5 and 6, plasma CEA-Z levels were in normal range, that is, less than 0.5, 2.3, 1.4 (ng/ml) respectively, and these three patients did not show any findings of recurrence of malignancy. Treatment effect of this agent for these patients will be determined not in the present time but in future by long term follow up study.

In case 7, plasma CEA-Z levels which were assessed three times before administration of this agent showed gradual elevation up to 5.1ng/ml and after administration of 5-FU, 8.4g in 28days it was as high as 6.7ng/ml.

Treatment effect could not be found in this patient.

Case 8. A 70-year-old woman was hospitalized for epigastralgy. Upper GI series revealed a defect of the jejunum near the ligament of Treitz.

At operation, carcinoma of the jejunum which invaded the retroperitoneal space was found. Palliative resection of the lesion and end-to-end anastomosis of the jejunum was performed.

Postoperatively, the patient received one time a combination of mitomycin C, 4mg, cylocide, 40mg, 5-FU, 500mg, by drip infusion, but it was abandoned becaused of the anorexia and nausea. Then, she received 46.2g of 5-FU in 154 days in the shape of dry syrup, thereafter, 32.1g of 5-FU in 107 days in the shape of tablet. Oral administration of these agents seemed to be effective because the mass in the epigastrium, which was 10 cm x 7 cm in size on palpation, did not show growing nor obstruction of the bowel.

Case 9. A 40-year-old woman had a huge mass of 7 cm in diameter in the head of the pancreas. It was removed by Whipple's maneuver 2 years before. Light microscopic examination of the surgical specimen revealed acinar cell carcinoma of the pancreas. Postoperatively, the patient received 21g of 5-FU by drip infusion, 79.8g of 5-FU in 266 days in the shape of dry syrup and 38.1g of 5-FU in 127 days in the shape of tablet and at the present time no finding of recurrence of carcinoma is observed.

Administration of these agents seems to be effective as maintenance treatment.

5 patients of case 10, 11, 12, 13 and 14 had cancer of the stomach. In case 10, 11, 12 and 13, gastrectomy was performed for the lesion (P_0, H_0, $S_1 - S_2$) 10 months to 2 years and 6 months ago. These 4 patients received 5-FU tablet recently and follow up study is in progress. Nobody of these four patients showes the findings of recurrence of malignancy.

Two patients, case 12 and 14, could not receive sufficient does of 5-FU tablet because of its toxicity such as abdominal pain and skin eruption.

Of 11 patients who received 5-FU tablet postoperatively, nausea, anorexia and sensation of abdominal distention was seen in two patients, vomiting was observed in one patient, abdominal

pain was reported in three patients and diarrhea was seen in one patient. All patients except for case 12 recovered when the agent was stopped for a while, therefore, maintenance treatment with this agent for nine patients for a long time was possible. The patient of case 12 had been able to receive 5-FU 250mg per day for 30 days consecutively by drip infusion formerly, but she could not receive 5-FU tablet more than 15 days because of severe abdominal pain which was reported when she received it for seven days and the pain appeared after each administration of 5-FU tablet. The patient of case 5 received 5-FU in the shape of tablet 400mg per day for 14 days, and then, discomfort of the epigastrium with nausea is reported. The complaint disappeared when the agent was stopped for 3 days. However, when he received the agent 400mg per day for three days again, sensation of abdominal distention was appeared again. Thereafter, he could receive the agent three tablet per day with no toxicity. Reddish skin eruption appeared diffusely in one patient, case 14. This was seen when the patient had received 5-FU tablet for 15 days and disappeared gradually by stopping administration of the agent.

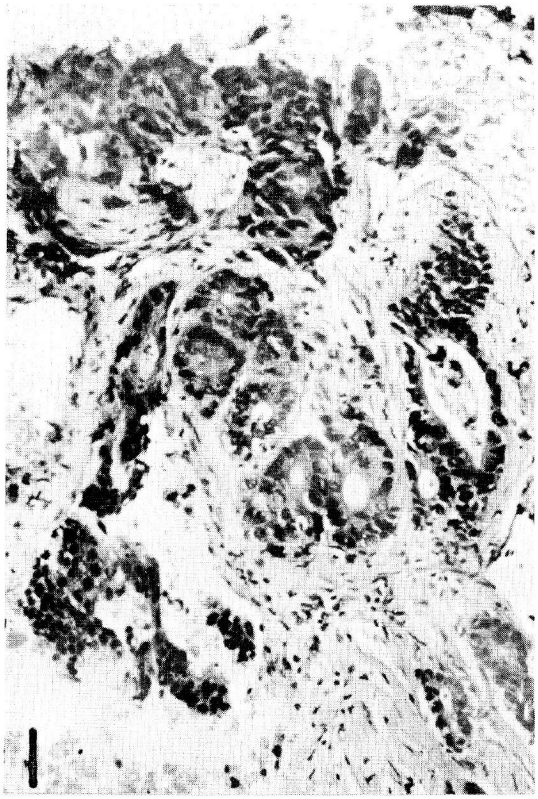
Hepatic, renal and hematologic toxicity were not seen.

Discussion

Fourteen patients with carcinoma of the digestive organs received 5-FU 300mg per day in the shape of tablet. Of these, three patients received the agent preoperatively and light microscopic examination of their surgical specimen revealed good response in one patient with cancer of the sigmoid colon, fair response in one patient with cancer of the stomach.

Of 11 patients who received 5-FU tablet postoperatively, treatment effect seemed to be noticed in two patients, one patient had cancer of the jejunum and one patient had cancer of the pancreas. On the contrary, two patients were non-responders. In the remaining seven patients, follow up study is in progress. In the patients who had received the agent preoperatively, toxicity did not disturbe the performance of surgical operation. In the patients who received the agent postoperatively, anorexia, nausea, vomiting, diarrhea or abdominal pain was reported in seven patients, skin eruption was seen in one patient. Hepatic, renal or hematologic toxicity was not encountered. Although two patients could not receive the agent more than 15 days because of toxicity, the patient of case 4 who had complained of nausea when he had received FT-207, 800mg per day and hypersalivation when he had received 5-FU dry syrup (5-FU 300mg per day) could receive 5-FU tablet without toxicity.

It appears to be essential to select a proper agent and a proper mode of administration for each patient.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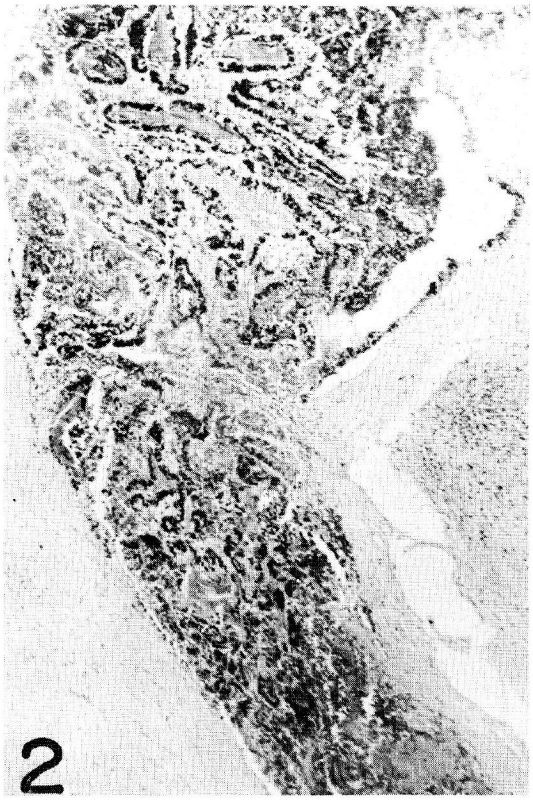
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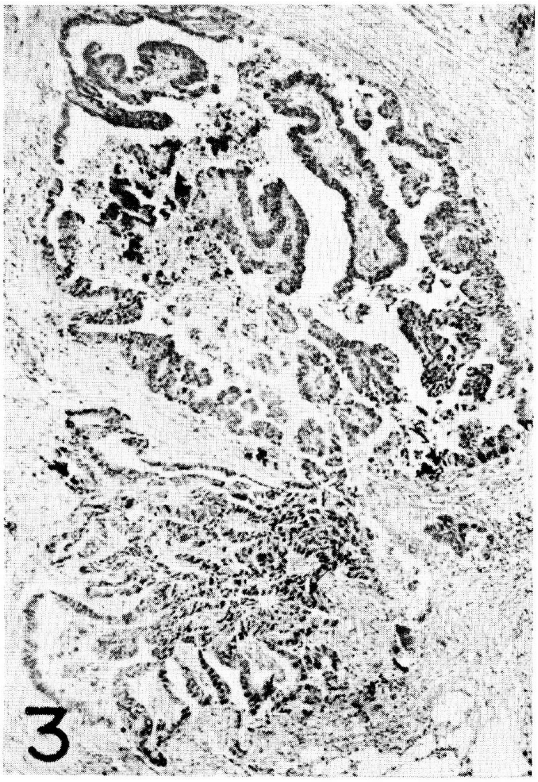
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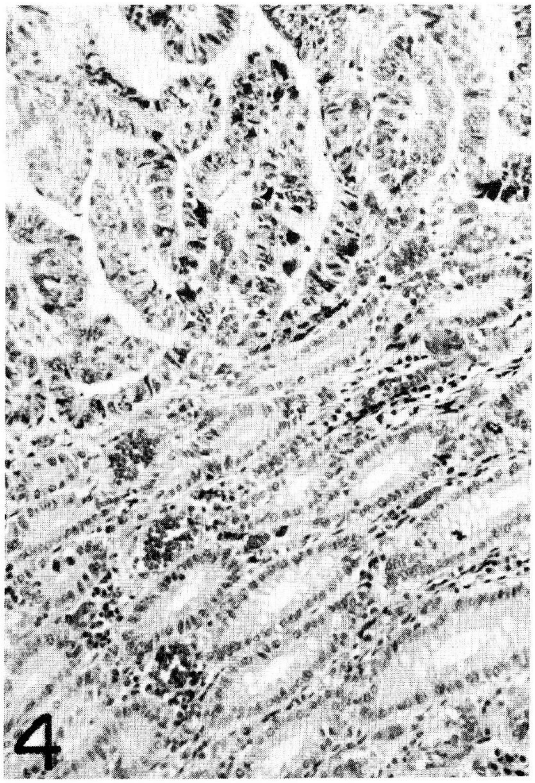
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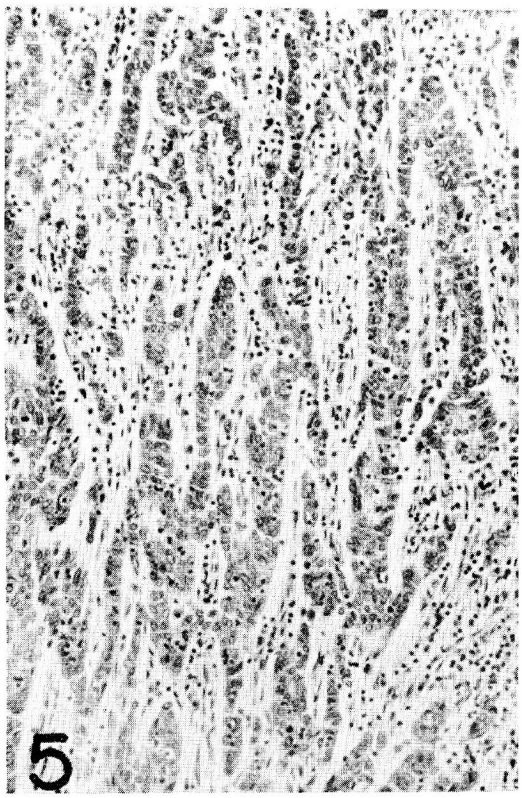

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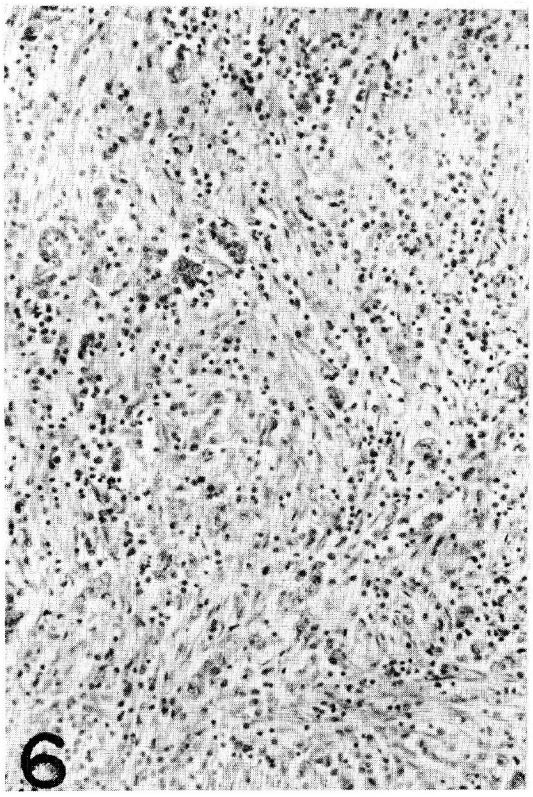

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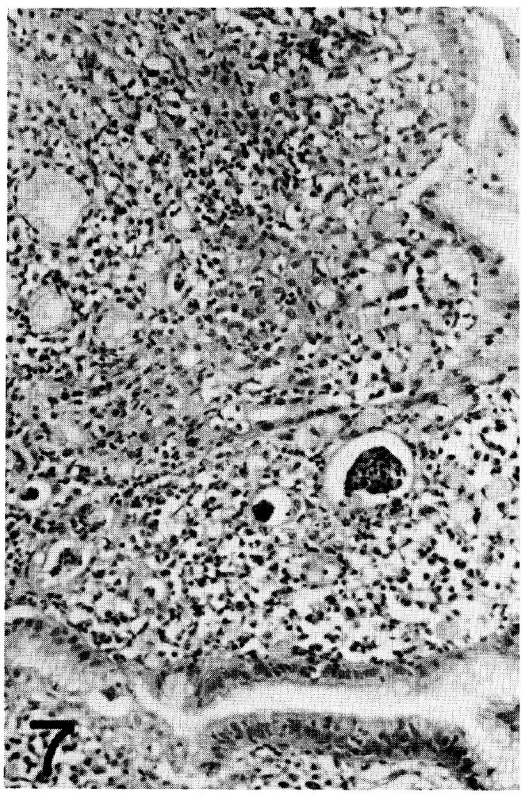

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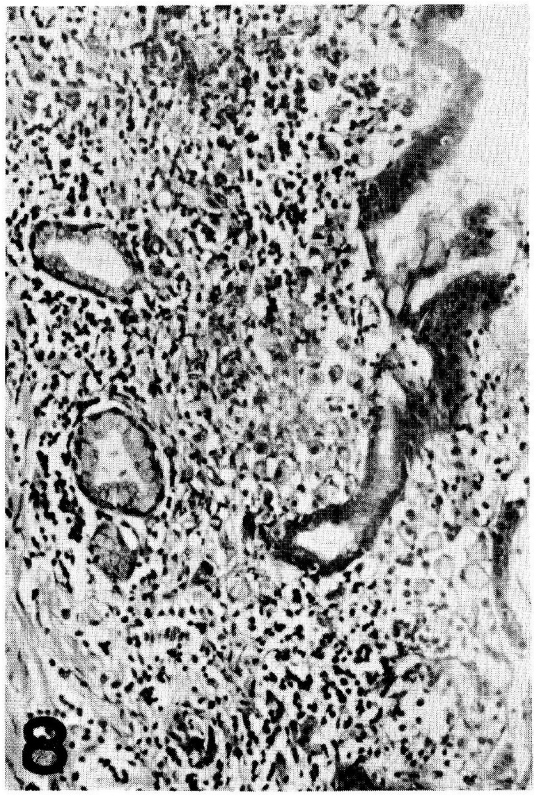

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REFERENCES

1) Bateman, J.R., Pugh, R.P., Cassidy, F.R., Marshall, G.J., and Irwin, L.E. : 5-Fluorouracil given once weekly: Comparison of intravenous and oral administration. Cancer 28, 907–913, 1971.
2) Link, J.S., Bateman, J.R., Paroly, W.S., Durkin, W.J., and Peters, R.L. : 5-Fluorouracil in hepatocellular carcinoma: Report of twenty-one cases. Cancer 39, 1936–1939, 1977.
3) Kennedy, P.S., Lehane, D.E., Smith, F.E., and Lane, M. : Oral fluorouracil therapy of hepatoma. Cancer 39, 1930–1935, 1977.
4) Lahiri, S.R., Boileau, G., and Hall, T.C. : Treatment of metastatic colorectal carcinoma with 5-Fluorouracil by mouth. Cancer 28, 902–906, 1971.
5) Mishina, T., Watanabe, H., Miyakoda, K., Araki, H., Fujiwara, T. and Kobayashi, T. : Absorption of 5-Fluorouracil through gastric epithelium. Tohoku J. Exp. Med. 125, 303–304, 1978.
6) Kitade, F., Honda, H., Sekimoto, T., Kawashima, Y., Tranishi, S. and Itaya, H. : A study on the preoperative administration of anticancer drug against gastric cancer. Cancer and Chemotherapy 3,751–755, 1976. (in Jpn)
7) Tamura, M., Koyama, R. and Fukuda M. : Clinical trial of the oral carcinostatica, 5-Fluorouracil Dry Syrup, with special reference to plasma and tissue concentrations of the drug. Cancer and Chemotherapy 2, 297–303, 1975.