Acta Medica Okayama

Volume 25, *Issue* 2 1971 *Article* 6

APRIL 1971

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Abstract

Three inoperable patients with primary hepatoma could be placed on gluconeogenic diets (minimum carbohydrate-high fat diets) for one to three months. A transient inhibition or a marked retardation of the tumor growth was observed with these patients and their entire clinical courses were fairly good. These results confirmed our previous observation with a metastatic liver tumor patient.

*PMID: 4333631 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **25**, 143—163 (1971)

EFFECT OF GLUCONEOGENIC DIET ON PRIMARY HEPATOMA PATIENTS

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Received for publication, February 25, 1971

In our previous study (1) attempted to extend the gluconeogenic dietary therapy of the Novikoff hepatoma (2) to humans, a transient but definite growth-inhibiting effect of a low carbohydrate-high fat diet was observed on a patient with hepatic metastases of malignant melanoma. Since the original observation was made with the hepatoma transplanted into the liver, the most pertinent subjects to be studied with the gluconeogenic diet would be primary hepatoma patients.

The present paper reports three cases of primary hepatoma placed on gluconeogenic diets for one to three months and then returned to balanced diets. The tumor growth was inhibited transiently or slowed considerably during the period of the low carbohydrate regimens.

METERIALS AND METHODS

The principle and practical techniques of placing hepatoma patients on gluconeogenic diets were essentially the same as those reported previously (1). Four inoperable primary hepatoma and one cystic liver patients admitted to the clinic of the University Department were the subjects of the present study. Except one primary hepatoma, these patients had cirrhosis of the liver. One of the hepatoma patients with cirrhosis of the liver could not tolerate the gluconeogenic diet and served as a control. The cystic liver patient was treated with the gluconeogenic diet as primary hepatoma before the diagnosis was established and was also included as another control to see the effect of the diet on cirrhotic patients.

Metabolite concentrations and enzyme activities in the blood or serum were determined as described in the previous paper (1) or according to the routine laboratory methods. Activities of liver and tumor hexokinase (3), glucose 6-phosphate dehydrogenase (1), and fructose 1, 6-diphosphatase (4) were also measured at 37°C in some of the patients on necropsied materials.

The days after starting the record of daily dietary intakes were referred to as the days of dietary treatment throughout the present paper.

OBSERVATIONS

Case 1. J. H., a 64-year-old male complaining of a fullness and pains in the right upper abdomen, was admitted and diagnosed by liver scinti-scanning and peritoneoscopy as primary hepatoma without cirrhosis of the liver. He noticed a swelling of the right upper abdomen about one month before admission. His appetite was normal but he was slightly emaciated; body weight 59 kg and height 170 cm. On admission he had no anemia, jaundice, and ascites. The abdomen was slightly distended and two groups of liver tumor mass were palpable; one below the right costal margin and the other below the xiphoid process (Fig. 1). Peritoneoscopically, most of the right liver lobe was occupied by the tumor mass and intrahepatic metastases in the right lobe were present. The rectal examination was negative.

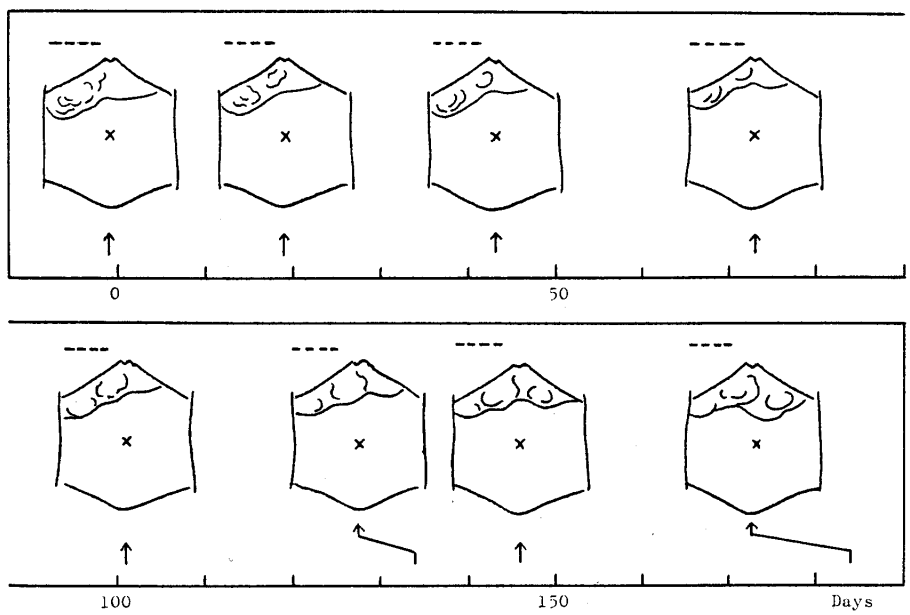


Fig. 1 Schematic representation of palpable hepatic tumors in Case 1. ···, The upper border of the liver surface. Arrows indicate the days of measurement.

Dietary intakes of this patient during the entire period of illness are presented in Fig. 2. The carbohydrate content could be reduced to 10 g per day for nearly three months without affecting the total caloric intake. A 3 kg loss of body weight in two weeks and no further loss in another one month were observed after starting the gluconeogenic dietary regimen.

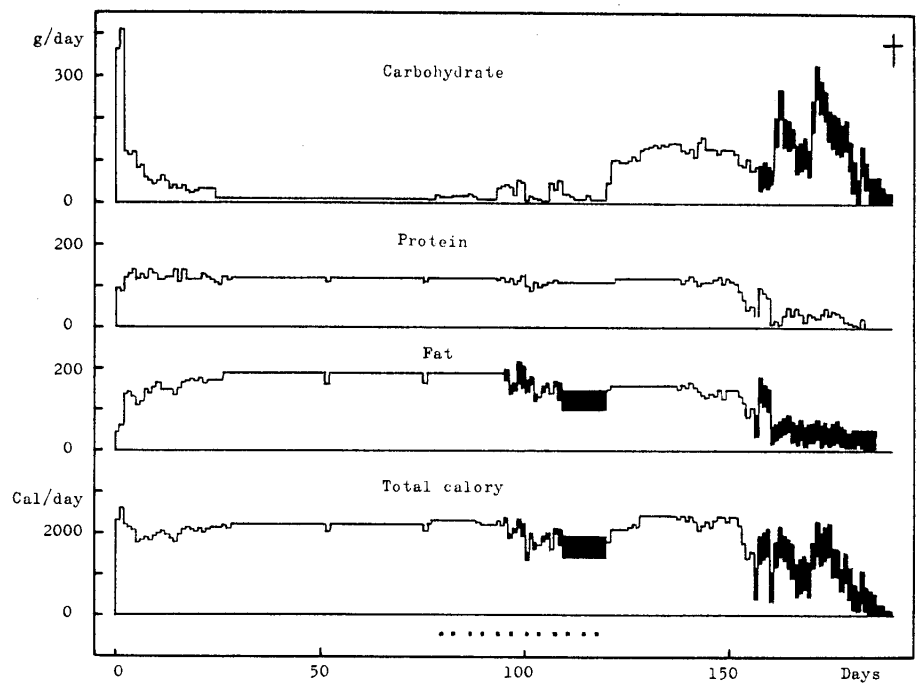


Fig. 2 Dietary intakes in Case 1. □, Oral administration; ■, parenteral administration. In this case the oral administration of medium-chain triglycerides was recorded as parenteral (from 95th to 110th day). The parenteral administrations of carbohydrate and fat refer to glucose and Intralipid, respectively, unless otherwise indicated. The small squares at the bottom indicate a combined antimetabolite therapy (5-fluorouracil, 500 mg; Mitomycin, 2 mg; Endoxan, 200 mg; and Toyomycin, 1 mg).

The change in body weight thereafter was complicated by the accumulation of ascites. The ascites obtained on 86th day was chylous. The increased triglyceride content in the ascites was lowered considerably by reducing the dietary fat and by instituting oral administration of medium-chain triglycerides and intravenous infusion of a fat emulsion, Intralipid (Apoteksvarucentralen Vitrum, Sweden). Because of a loss of appetite and a limitation in parenteral administration of fat, the carbohydrate centent of diet was gradually increased. Around 150th day the patient became slightly icteric and markedly emaciated, and he died from gastrointestinal bleedings.

The change in hepatic tumor size is illustrated in Fig. 1. The tumor became slightly smaller and sharply defined following the reduction of carbohydrate content (days 50 to 70 of dietary therapy). Since an increase of the tumor in the epigastric region was noted around the 80th day of the treatment, an antimetabolite therapy was combined (see Fig. 2). The

tumor growth was not so marked during the period of the antimetabolite treatment, but he developed anorexia and general weakness. After discontinuing the chemotherapy and increasing the carbohydrate content in the diet, the tumor growth became marked and a metastatic tumor mass in the left lobe of the liver was palpable.

Liver scintigrams taken on 52nd and 136th days are shown in Fig. 3.

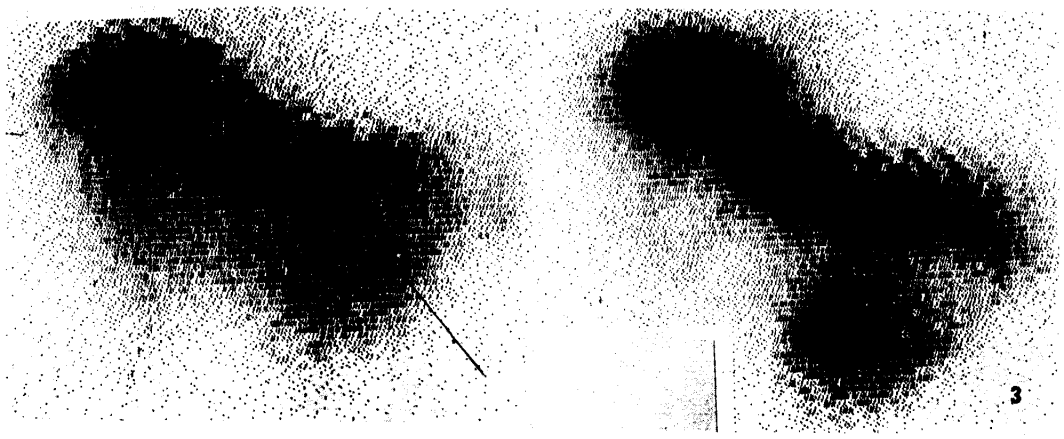


Fig. 3 Liver scintigrams in Case 1. The left, 52nd day and the right, 136th day.

The findings of a liver scintiscanning performed on 20th day, which is not presented in the figure, were essentially identical to those revealed on 52nd day, indicating no appreciable growth of the tumor during the initial half-period of the low carbohydrate regimen. The comparison of the two scintigrams in Fig. 3 confirmed the marked growth of the tumor observed during the latter half-period of the low carbohydrate dietary therapy.

The alterations in blood metabolite concentrations during the entire course of the therapy are shown in Fig. 4. At the time of admission the metabolite levels were all within the normal limit. No marked increases in blood citrate concentration were observed even with minimum carbohydrate diets until the patient became emaciated considerably, when a slow but gradual increase in tumor size was noted. At this time the fasting blood sugar level tended to fall below the normal lower limit and the postprandial levels were less than 90 mg/100ml. These abnormalities of the blood metabolites were corrected by increasing the dietary carbohydrate content. Although the NEFA concentration was slightly raised by the low carbohydrate diet, the acetone body reaction in the urine was negative in most occasions. The triglyceride concentration varied widely

Blood sugars (mg/100 ml)×10-2, ○; Blood citrate (mM) ×4, ●; Serum NEFA (mEq/l)×1, ▲; Serum triglyceride (mg/100 ml)×10-2, △

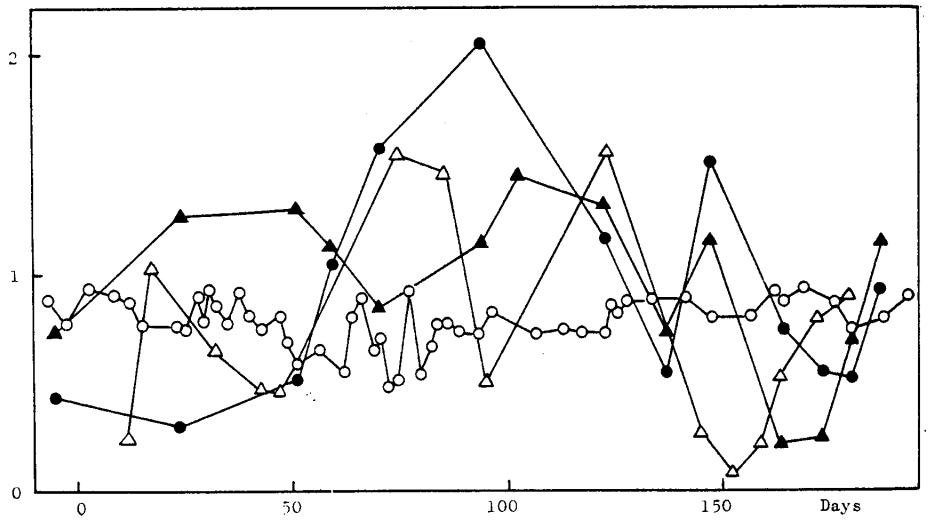


Fig. 4 Metabolite concentrations in the fasting blood and serum in Case 1. NEFA, Non-esterified fatty acids.

within the normal range. Fecal lipid contents were not abnormally increased.

GOT (K. U.)×10-2, ▲; GPT (K. U.)×10-2, △; ICDH (mU/hr/ml)×5×10-4, ×; Alkaline phosphatase (B. U.)×10-1, ○; LAP(G-R U.)×2×10-3, ●

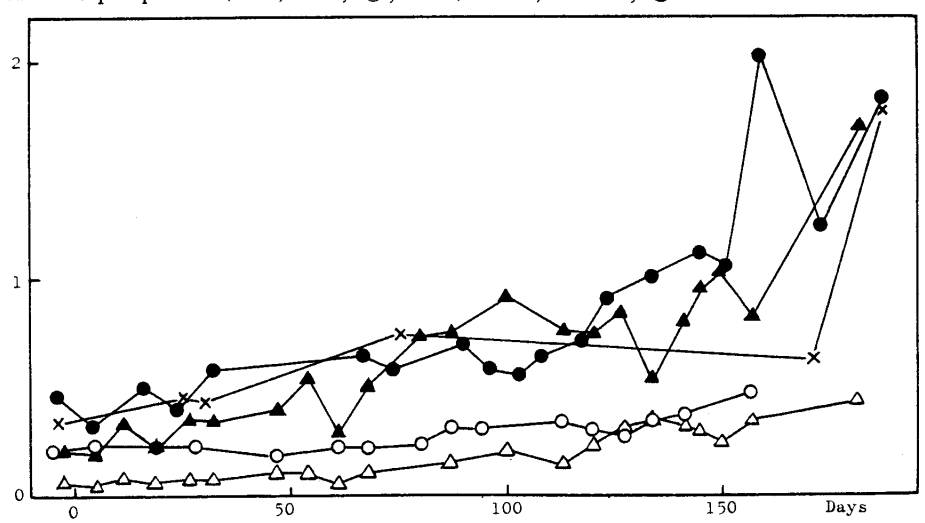


Fig. 5 Serum enzyme activities in Case 1. GOT, Glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; LAP, leucine aminopeptidase; and ICDH, TPN-dependent isocitrate dehydrogenase.

The changes in serum enzyme activities are presented in Fig. 5. Alkaline phosphatase levels remained normal during the strict gluconeogenic dietary therapy, whereas the activities of LAP, GOT, and ICDH increased gradually above normal even with the gluconeogenic diet and markedly rose by allowing more carbohydrate ingestions, particularly when the general conditions of the patient became worse before death. The GPT activity changed similarly within the normal range.

Postmortem examinations revealed a main pathological diagnosis of primary hepatoma and its metastases to the lungs, myocardium, peritoneal lymph nodes, adrenal grands, and descending colon. Multiple stomach ulcers and esophageal varices were also detected. The hepatic tumor tissue occupied most of the right lobe. The remaining intact liver in the left lobe was hypertrophic. The tumor was histologically hepatocellular carcinoma.

Case 2. T. M. was a 70-year-old male admitted with the diagnosis of primary hepatoma with cirrhosis of the liver. He had complained of a lassitude and a slight loss of appetite over six months. A weight loss of 10 kg was noted during this period. At the time of admission the weight was 65 kg and the height was 166 cm. The anemia, jaundice, enlarged liver or palpable tumor, and ascites were not present. Repeated fecal examina-

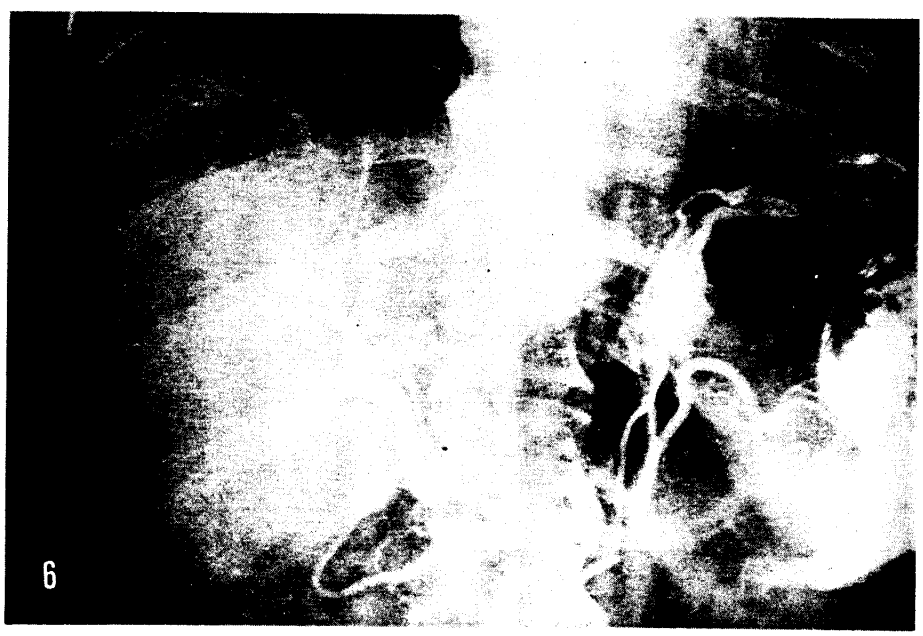


Fig. 6 A coeliacogram of Case 2.

tions gave positive occult blood, but X-ray examination of the upper gastrointestinal tract failed to disclose esophageal valices, gastric ulcer or cancer. The chest roentogenogram showed a slight elevation of the right diaphragm, suggesting the presence of a hepatic tumor. The diagnosis of primary hepatoma with cirrhosis of the liver was established by liver scintiscanning and coeliacography (Fig. 6). A large defect suggestive of the tumor occupied nearly half of the lateral upper part of the right liver lobe. Liver function tests gave results indicative of an advanced cirrhosis of the liver. Based on these findings, conservative treatments rather than a radical operation were chosen.

After placing the patient on gluconeogenic diets, a loss in body weight of 2 kg was observed in the first one month. The body weight was restored to the original in next one month and increased 2 kg over the initial weight thereafter. Parallel increases in the skinfold were also noted. Ascites was not detected during the course of the dietary therapy. The profile of dietary intakes is shown in Fig. 7. The carbohydrate content could be reduced to as low as 40 g per day without appreciable loss of

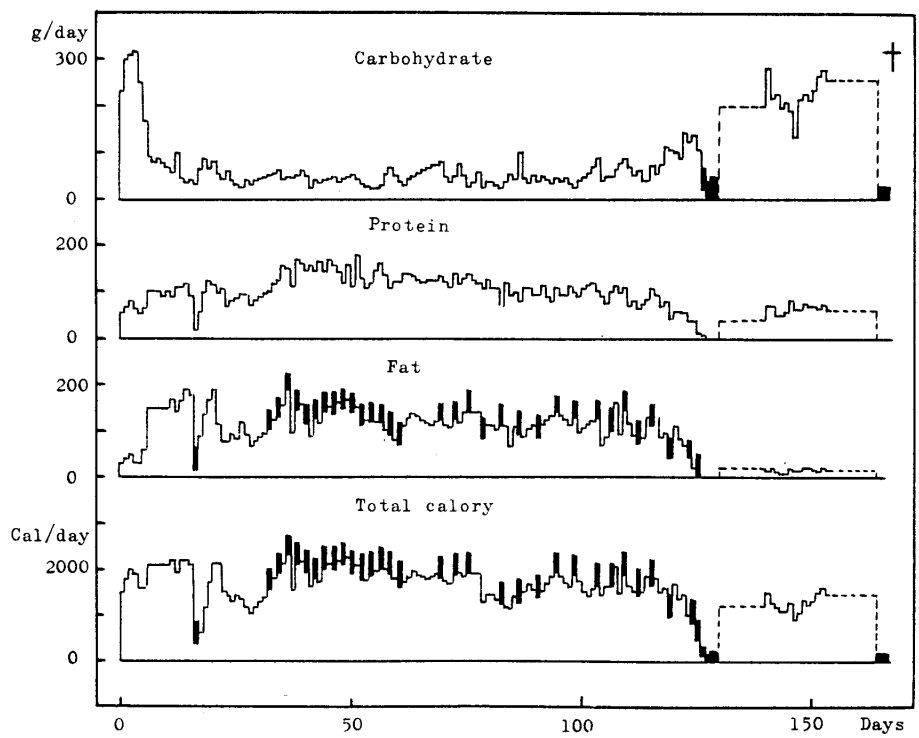


Fig. 7 Dietary intakes in Case 2. □ and ■, See the legend to Fig. 2.

appetite. Increases of dietary fat as well as intravenous infusion of Intralipid were necessary to maintain the initially recorded total caloric intake. The parenteral administration of the lipid caused a marked hyperlipemia; the serum triglyceride content, which was initially in the normal range, was elevated as high as 690 mg/100 ml. However, the lipid infusion was continued as far as the serum turbidity had been cleared. The general condition of the patient was considerably good until the 120th day of the dietary treatment, when he developed anorexia and had a right hypochondrial pain. Total serum bilirubin level increased to 1.95 mg/100 ml. The gluconeogenic diet was discontinued at this time. On 127th day he experienced a melena, which continued few days. After he recovered, he consumed diets of 1200-1500 Cal/day including 200-250 g of carbohydrate. The raised serum bilirubin level was not lowered by the relatively high carbohydrate diets. From 150th day of the therapy, a tumor became palpable below the costal margin. Serum alkaline phosphatase level also increased markedly, and the patient died from repeated gastrointestinal bleedings.

The scintiphotographs shown in Fig. 8 indicated a relatively small increase of the tumor during the initial period of the gluconeogenic dietary

Fig. 8 Liver scintiphotographs in Case 2. The left, 12 days before starting the gluconeogenic diet and the right, 37th day of the dietary therapy.

therapy. The levels of blood metabolites and serum enzymes in the entire course of illness are given in Figs. 9 and 10, respectively. Following the reduction of carbohydrate and the increase of fat, the NEFA concentration varied over a wide range, probably depending on the period of time after the intravenous infusion of the lipid. The citrate level was consistently raised during the period of the strict gluconeogenic diet. No marked

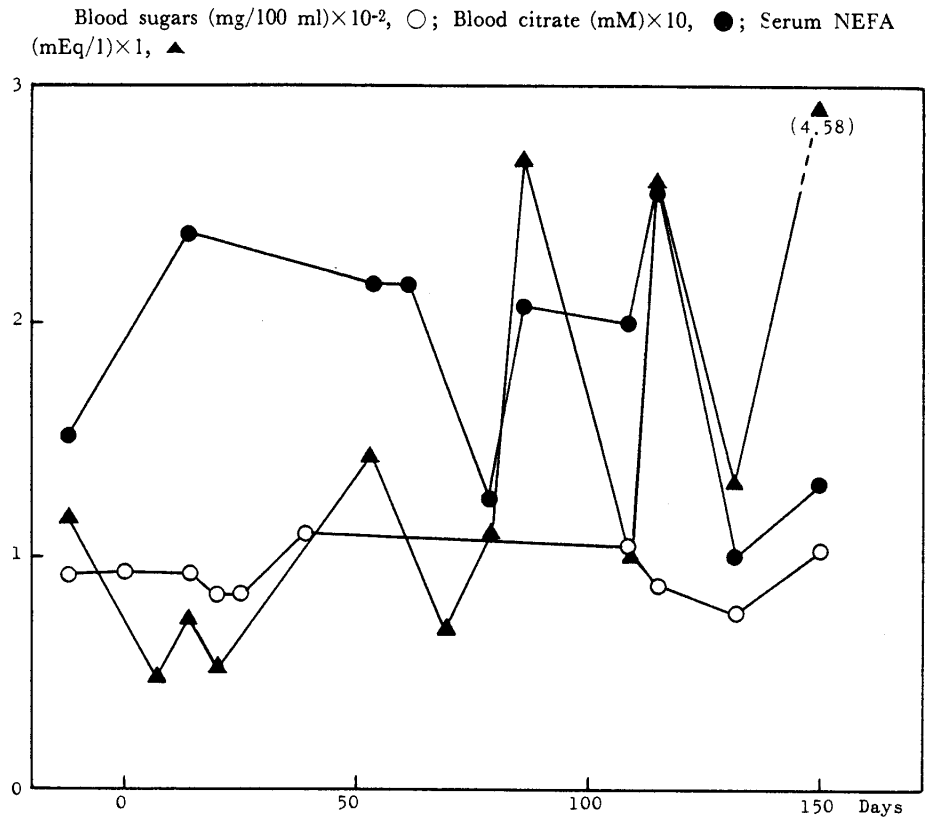


Fig. 9 Metabolite concentrations in the fasting blood and serum in Case 2.

changes in blood sugar concentration were observed during the whole therapeutic period. Serum alkaline phosphatase, GOT, GPT, and ICDH levels were initially slightly high and further increased with the low carbohydrate-high fat diet. These enzyme levels tended to decrease slightly after restoring regular dietary regimen except for alkaline phosphatase, which elevated markedly after the dietary carbohydrate content was increased and the tumor became papable. The change in activity of LAP was similar to that of alkaline phosphatase.

By postmortem examinations, the cause of the melena was indicated to be due to a valix bleeding in the cardiac region of the stomach. The tumor occupied nearly 80 per cent of the enlarged cirrhotic liver. Intrahepatic metastases of the tumor were also detected. The tumor was histologically well differentiated hepatocellular carcinoma and the cirrhosis was of Type B.

GOT (K. U.)×10-2, ▲; GPT (K. U.)×10-2, △; ICDH (mU/hr/ml)×10-3, ×; Alkaline phosphatase (B. U.)×10-1, ○

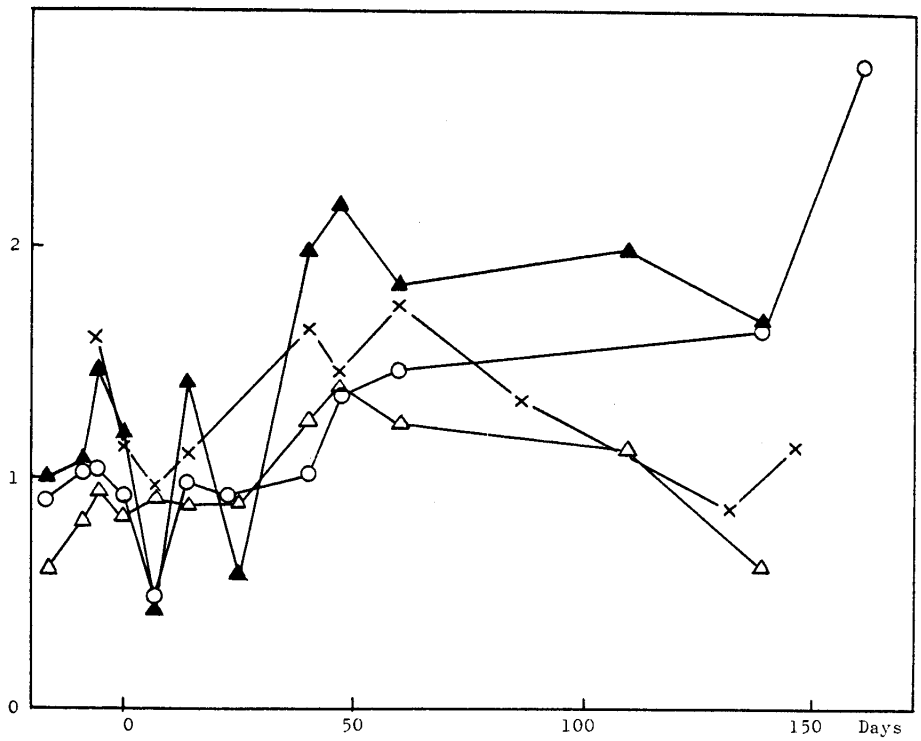
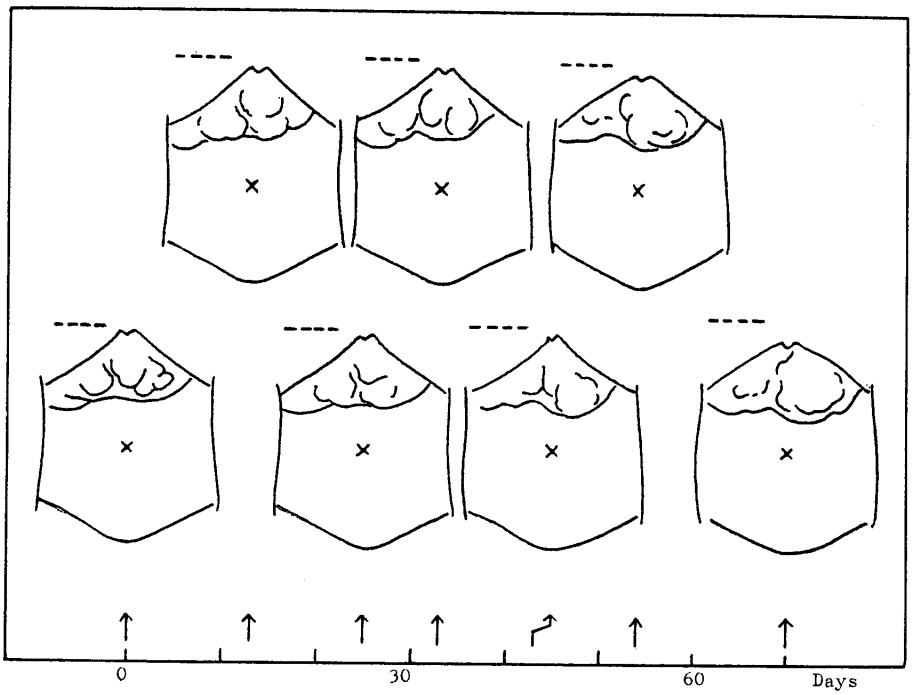


Fig. 10 Serum enzyme activities in Case 2.

Case 3. S. O., a 51-year-old male, had complained of anorexia and fullness in the upper abdomen for several months and noticed a swelling in the epigastric region one month before admission. Two kg of weight loss in two months were also noted. On admission the weight was 46 kg and the height was 155 cm. Physical examinations revealed no anemia, jaundice, and ascites. The liver was enlarged and tumor masses were palpable (Fig. 11). The spleen was also enlarged below the costal margin. The diagnosis of primary hepatoma with cirrhosis of the liver was made by liver scintiscanning (Fig. 12) and by peritoneoscopy. The latter examination disclosed a large tumor mass in the right liver lobe and its intrahepatic metastases.

Inspite of a reduced appetite, this patient could be placed on a gluconeogenic diet with minimum carbohydrate contents of less than 10 g per day by aid of a parenteral lipid administration (Fig. 13). The loss of weight during the period of the minimum carbohydrate diet was 2 kg;



Fig, 11 Schematic representation of palpable hepatic tumors in Case 3. ···, See the legend to Fig. 1.

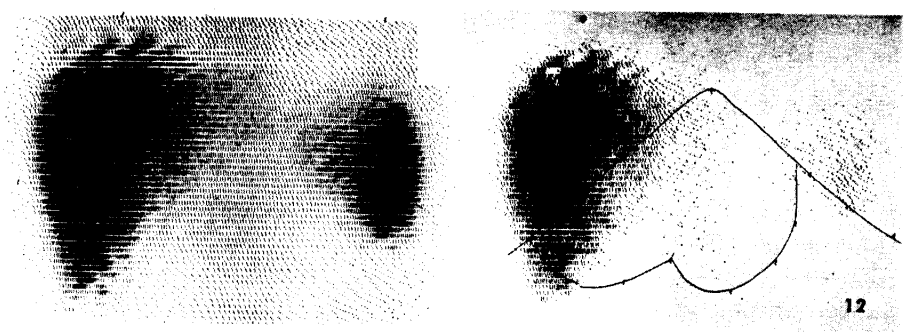


Fig. 12 Liver scintigrams in Case 3. The left, 11th day and the right, 47th day.

but the net loss would be more than that in considering the gradual accumulation of ascites and the marked decrease in skinfold. The basal metabolic rate was +57 per cent with the normal Triosorb test before instituting the low carbohydrate diet. Measurements of the nitrogen balance gave a mean value of −7 g per day in the control period with a regular diet and a value of +1 g per day during the period of the strict

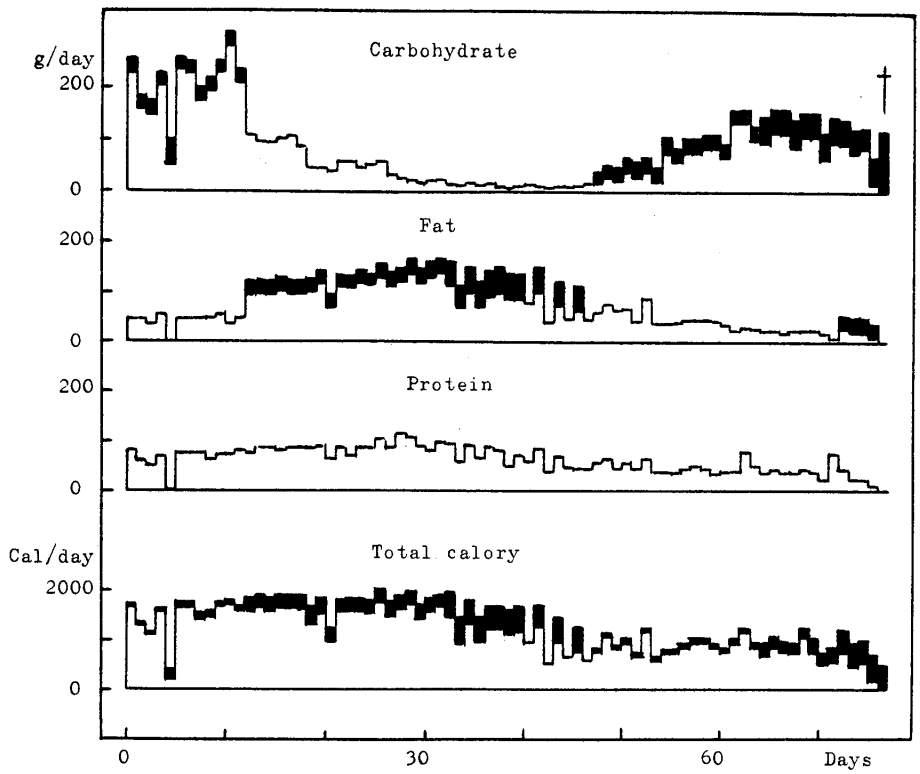


Fig. 13 Dietary intakes in Case 3. □ and ■, See the legend to Fig. 2. In this patient xylitol (25 g/day) was intravenously infused from 48th to 62nd day and recorded as carbohydrate for convenience.

gluconeogenic dietary therapy. Fecal loss of lipids was not abnormally increased during this period. By the dietary treatment, the full sensation of the upper abdomen was transiently relieved. However, the low carbohydrate-high fat diet was discontinued due to a marked hyperlipemia. The change of diet corrected the increased levels of blood lipids, although the general conditions were not improved, and the jaundice became apparent. The emaciation, ascites, and jaundice were progressively increased, and the patient died from the cardiac arrest.

As schematically illustrated in Fig. 11, the size of palpable hepatic tumor increased gradually during the period of the minimum carbohydrate therapy, although the increase was not apparent from the results of liver scintiscanning (Fig. 12). The tumor mass below the costal margin started increasing rapidly around 50th day of the therapy despite the fact that the dietary carbohydrate content was kept below 10 g per day. After allowing carbohydrate intake *at libitum* due to the hyperlipemia, the tumor growth

appeared to be accelerated, causing a deformity of the left costal margin.

The blood metabolite profiles summarized in Fig. 14 demonstrated

Blood sugars (mg/100 ml)×5×10-2, ○; Blood citrate (mM)×10, ●; Serum NEFA (mEq/l)×5, ▲; Serum triglyceride (mg/100 ml)×10-2, △

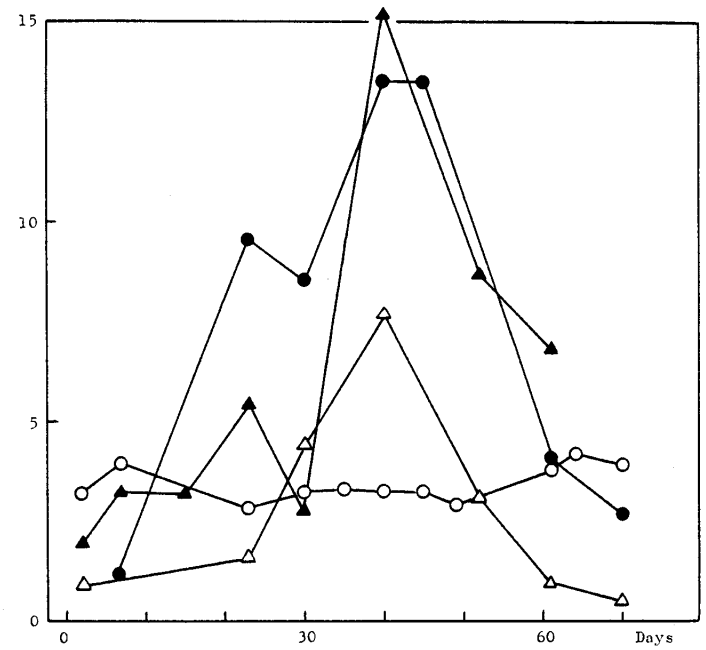


Fig. 14 Metabolite concentrations in the fasting blood and serum in Case 3.

that citrate, NEFA, and triglyceride concentrations, which were initially within the normal, rose to extraordinary high levels with the minimum carbohydrate-high fat diet. On the 45th day, the values for serum cholesterol, blood acetoacetate, and β-hydroxybutyrate were 439 mg/100 ml, 920 mμmoles/g, and 2.15 μmoles/g, respectviely; the extent of the increases of the latter two was approximately 50 fold of the normal values. Uninary ketone bodies were slightly to moderately positive as measured by Ketostix. These high metabolite levels returned toward the normal after increasing carbohydrate and reducing fat contents.

The data in Fig. 15 show that the values of GOT and GPT increased over the normal range after initiation of the gluconeogenic therapy. The serum LAP activity, which was slightly elevated before starting the specific dietary treatment, tended to decrease during the initial period of the dietary therapy. The serum alkaline phosphatase activity was also decreased following the carbohydrate reduction, although the changes were

GOT (K. U.)×10-2, ▲; GPT (K, U.)×10-2, △; Alkaline phosphatase (B. U.)×10-1, ○; LAP (G-R U.)×10-2, ●

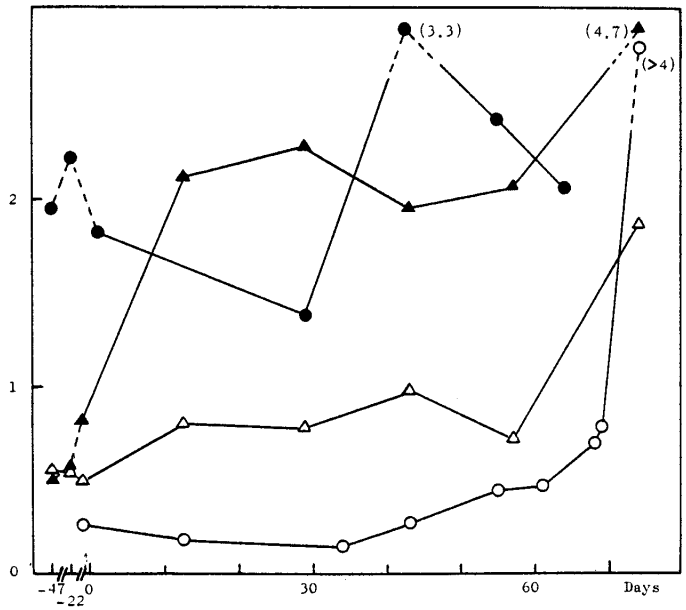


Fig. 15 Serum enzyme activities in Case 3.

within the normal range, and started to increase rapidly following the increase in carbohydrate content in the diet.

Percutaneous necropsy performed as a postmortem examination revealed hepatocellular carcinoma and cirrhosis of the liver (Type B).

Case 4. K. K., a 59-year-old male, with a history of hepatitis at the age of 50 years was admitted with the chief complaint of epigastric pains lasting about three months. A marked loss of body weight, 3 kg in one month, was noted. At the time of admission the weight was 71 kg and the height was 166 cm. Slight anemia and jaundice were noticed but ascites was not detected. The liver edge with a tumor mass was palpable 10 cm below the xiphoid process. The results of liver function tests and other examinations were suggestive of primary hepatoma with cirrhosis of the liver. This diagnosis was confirmed by peritoneoscopy. The tumor was in the left lobe of the liver.

Due to a marked loss of appetite and a strong desire for carbohydrate-containing diets in this patient, he could not tolerate the low carbohydrate diet. His average carbohydrate intake was 100 g per day and the total caloric intake was also decreased (Fig. 16). After around 40th day the palpation of the liver tumor became difficult because of a marked accumu-

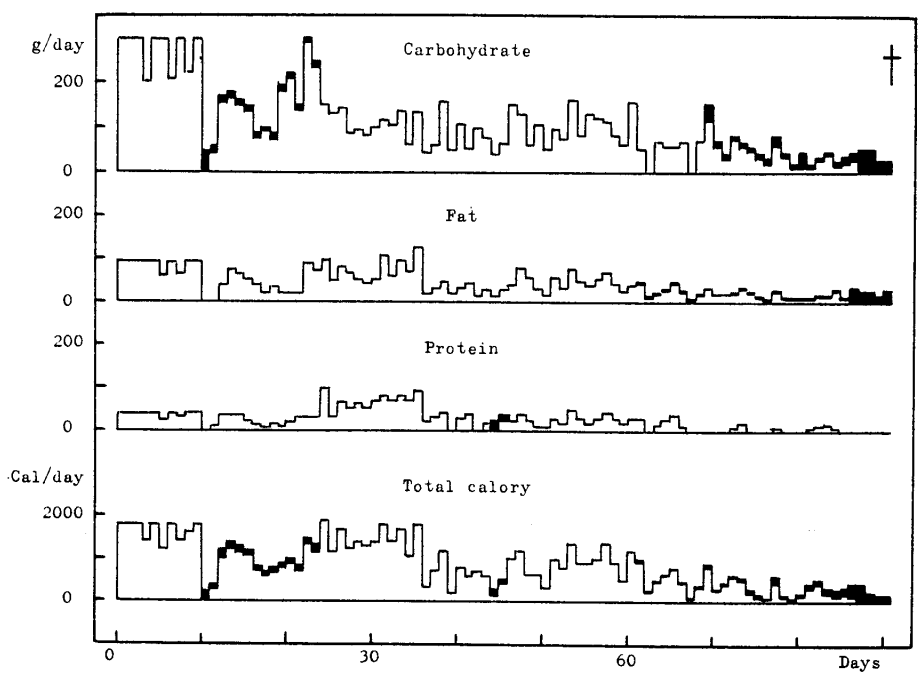


Fig. 16 Dietary intakes in Case 4. □ and ■, See the legend to Fig. 2. Intravenous infusion of amino acids is recorded as parenteral administrations of protein.

GOT (K. U.)×10-2, ▲; GPT (K. U).×10-2, △; Alkaline phosphatase (B. U.)×10-1, ○

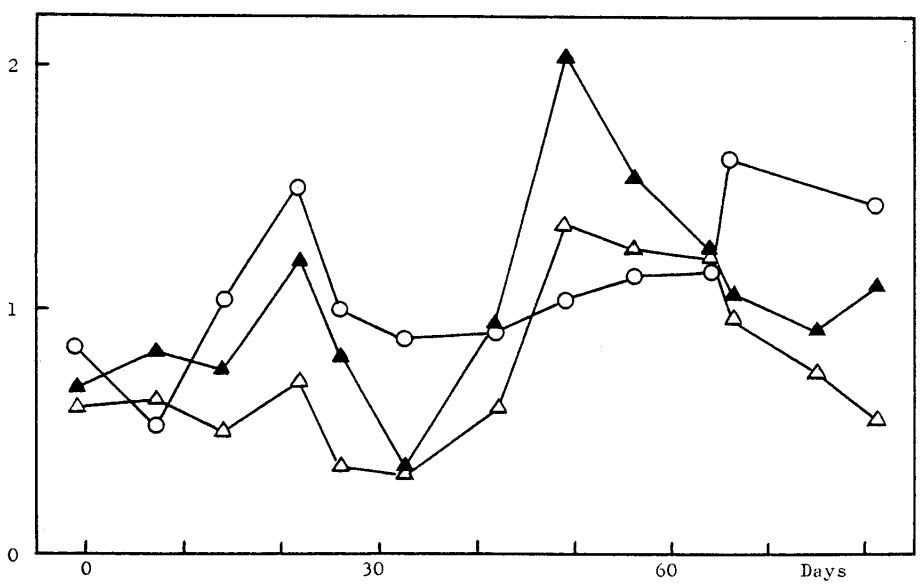


Fig. 17 Serum enzyme activities in Case 4.

lation of ascites. The serum bilirubin level also increased rapidly. Symptomatic treatments failed to improve the general conditions, and the patient expired as a result of the cachexia.

The serum NEFA concentration was normal but the blood sugar and citrate levels were slightly high. These metabolite levels were not altered significantly throughout the course of illness. Urinary acetone bodies were also negative. These results suggested that the gluconeogenic metabolic state was not attained in this case. Slightly increased serum GOT, GPT, and alkaline phosphatase activities at the time of admission showed fluctuation during the course of illness (Fig. 17).

Postmortem examinations revealed necrotic tumor masses occupying most of the markedly increased liver. Histologically the tumor was hepatocellular carcinoma associated with Type A' cirrhosis of the liver.

Case 5. W. S., a 44-year-old male, had been treated under the diagnoses of cirrhosis of the liver and diabetes mellitus. Because of the presence of palpable hard nodules on the liver, malignant hepatic tumors were suspected. On admission the weight was 60 kg and the height was 161 cm. Physical findings were normal except for the enlarged liver with the tumors. The liver edge was palpated 9 cm below the costal margin.

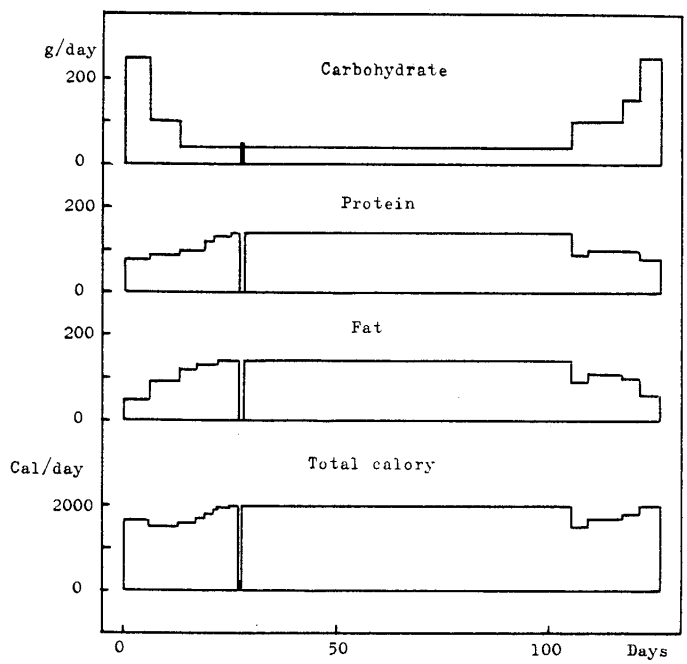


Fig. 18 Dietary intakes in Case 5. □ and ■, See the legend to Fig. 2.

Laboratory data were indicative of cirrhosis of the liver. The blood citrate level and serum ICDH and LAP activities were slightly increased. Oral glucose tolerance test gave a normal result.

The carbohydrate content of diet was reduced to 40 g per day (Fig. 18) before the diagnosis of cystic liver associated with cirrhosis was established. This caused a body weight loss of 5 kg. During the period of the gluconeogenic diet, the concentrations of serum citrate, NEFA, and triglyceride were markedly elevated (Fig. 19), while those of blood lactate, pyruvate, and α-ketoglutarate were inversely reduced. The result of glucose tolerance test was diabetic. These were indicative of a gluconeogenic metabolic state, which was attained by the low carbohydrate diet. Serum enzyme levels, particularly GOT, GPT, and ICDH, also increased during this period (Fig. 20). These alterations in metabolite, glucose tolerance, enzyme activity, and body weight all returned to normal or the initial values after resuming the regular diet. The liver and tumor sizes did not change significantly throughout the period of hospitalization.

Blood sugars (mg/100 ml)×10-2, ○; Blood citrate (mM)×5, ●; Serum NEFA (mEq/l)×2, ▲; Serum triglyceride (mg/100 ml)×10-2, △

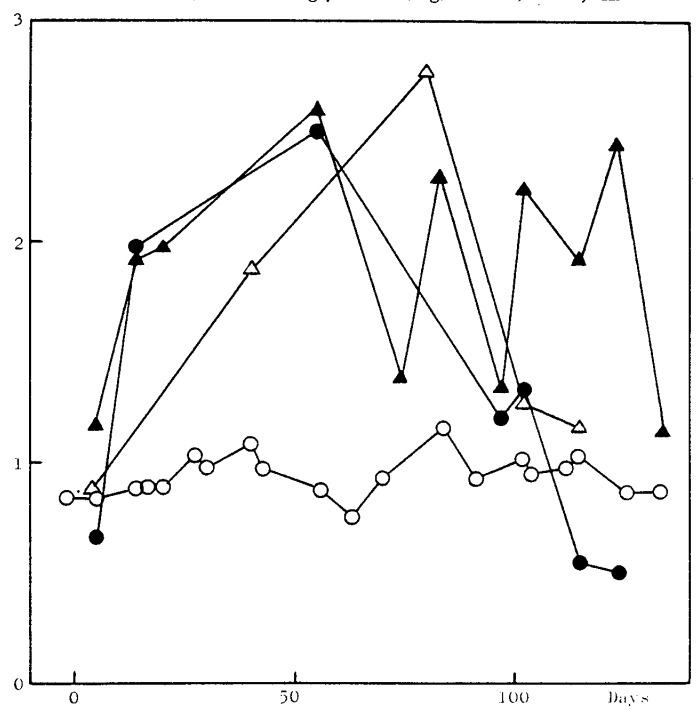


Fig. 19 Metabolite concentrations in the fasting blood and serum in Case 5.

GOT (K. U.)×10-2, ▲; GPT (K. U.)×10-2, △; ICDH (mU/hr/ml)×2×10-3, ×; Alkaline phosphatase (B, U.)×10-1, ○; LAP (G-R U.)×2×10-3, ●

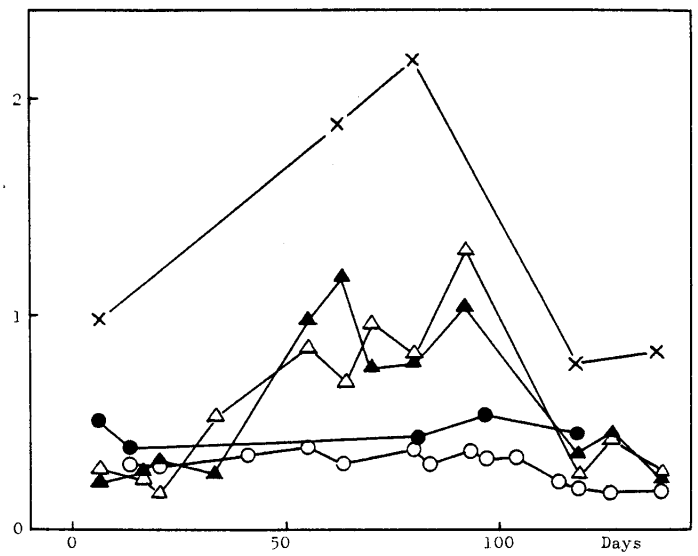


Fig. 20 Serum enzyme activities in Case 5.

Activities of relatively stable enzymes, hexokinase, glucose 6-phosphate dehydrogenase, and fructose 1, 6-diphosphatase, were measured on necropsied tumor and non-tumor liver tissues (Table 1). Higher activities

TABLE 1. ENZYME ACTIVITIES IN LIVER AND TUMOR TISSUES

	Non-tumor liver			Tumor tissue		
	HK	G6PDH	FDPase	HK	G6PDH	FDPase
Normal control (Mean±S. D.)	2.9 ±0.2	21.5 ± 3.6	95.8 ±15.8			
Case 1	0.9	28.2	118	5.7	8.9	0
Case 2	17.8	51.6	85	24.5	77.8	18.9
Case 4	—	38.6	138	—	250.0	10.4

HK, hexokinase; G6PDH, glucose 6-phosphate dehydrogenase; FDPase, fructose 1,6-diphosphatase. Enzyme activities are expressed as mμmoles/min/mg protein.

of hexokinase and glucose 6-phosphate dehydrogenase were found with the tumor and non-tumor tissues of cirrhotic patients. The activity of fructose 1, 6-diphosphatase was absent or very small in all the hepatoma tissues.

COMMENTS

The effects of gluconeogenic diets on three cases of primary hepatoma in the present study were essentially identical to those observed in our previous study on the patient with hepatic metastases of malignant melanoma (1); namely, 1) a transient inhibition or marked retardation of the tumor growth, 2) decreases or slower increases in alkaline phosphatase and LAP activities in serum, and 3) subjective improvements and a fairly good clinical course of the illness. These results were derived from comparing the above parameters during the gluconeogenic period with those after returning to the regular diet and also with those of the control patients treated with regular diets.

In Case 1, who had primary hepatoma without complication of cirrhosis of the liver, a small but definite decrease in the tumor size in the early stage of the low carbohydrate diet was observed and the serum enzyme activities were maintained at relatively low levels. In Cases 2 and 3, who had cirrhosis of the liver in addition to the hepatoma, the growth of the tumor was only partially inhibited, whereas serum alkaline phosphatase or LAP activity was even decreased temporarily. Those effects were neither apparent in the hepatoma Case 4, whose metabolic patterns were not gluconeogenic, nor in the control without malignant tumor, Case 5, who had definitely enhanced gluconeogenic patterns of metabolism. Incidentally, marked rises in serum GOT, GPT, and ICDH activities were found only in patients having cirrhosis of the liver; thus these parameters can not be regarded as an exact measure of tumor growth when underlying cirrhosis is present. Hyperlipemia developed also in cirrhotic patients under conditions with high fat diets, indicating a difficulty of treating tumor patients having cirrhosis of the liver with gluconeogenic diets.

It is of some interest that the decrease in tumor size was found with the hepatoma lacking fructose 1, 6-diphosphatase activity (Case 1) and that the tumor growth could not be completely inhibited with the well differentiated hepatoma, which retained considerable fructose 1, 6-diphosphatase activity (Case 2), in view of the fact that the growth-inhibiting effect of the gluconeogenic diet was originally observed with the Novikoff hepatoma, which had no detectable fructose 1, 6-diphosphatase activity (5).

The increased level of blood citrate, which was considered as related to the inhibitory effect of the gluconeogenic diet on the tumor growth (1), appeared to have no relevance to the presently observed inhibition or retardation of tumor growth. Since the gluconeogenic diet has a higher value of specific dynamic action compared with the balanced diet, the

isocaloric, low carbohydrate diet may partially inhibit the tumor growth by decreasing energy supply (6). This effect would be accentuated by the increased requirement of calory in the tumor-bearing host as may be seen in Case 3, who revealed an increase in the basal metabolic rate with normal thyroid function. However, it could be also stated that the administration of the isocaloric, gluconeogenic diet is still better than not to give it and to cause a severe or near total starvation in a sense that the former prevents the patient from cachexia by supplying additional calories and body constituents (7).

Since the clinical course of human hepatoma varies widely with individual cases, general conclusions as to the effect of the gluconeogenic diet on the survival time must wait further studies.

SUMMARY

Three inoperable patients with primary hepatoma could be placed on gluconeogenic diets (minimum carbohydrate-high fat diets) for one to three months. A transient inhibition or a marked retardation of the tumor growth was observed with these patients and their entire clinical courses were fairly good. These results confirmed our previous observation with a metastatic liver tumor patient.

ACKNOWLEDGEMENT

This work was carried out in collaboration with Dr. B. M. POGELL, Department of Microbiology, St. Louis University School of Medicine, St. Louis, Missouri, U. S. A. The authors wish to express thanks to attending doctors of the present cases for their cooperation and interest in carrying out the gluconeogenic dietary therapy. Grateful acknowledgement is also due to Miss K. NISHIMURA, the chief nutritionist in Okayama University Hospital, for her active cooperation in the present dietary therapy.

REFERENCES

1. TAKETA, K., MIYATA, E. and KOSAKA, K.: Treatment of hepatic cancer patients with a gluconeogenic diet: report of a case with hepatic metastases of malignant melanoma. *Acta Med. Okayama* **21**, 213, 1967
2. HUBBARD, J. D. and POGELL, B. M.: Differential effect of carbohydrate deprivation on growth of Novikoff hepatoma in liver and peritoneum. *Proc. Amer. Assoc. Cancer Res.* **8**, 32d, 1967
3. VIÑUELA, E, SALAS, M. and SOLS, A.: Glucokinase and hexokinase in liver in relation to glycogen synthesis. *J. Biol. Chem.* **238**, PC1175, 1963
4. TAKETA, K. and POGELL, B. M.: Allosteric inhibition of rat liver fructose 1,6-diphosphatase by adenosine 5'-monophosphate. *J. Biol. Chem.* **240**, 651, 1965
5. POGELL, B. M., TANAKA, A. and SIDDONS, R, C.: Natural activators for liver fructose

1,6-diphosphatase and the reversal of adenosine 5′-monophosphate inhibition by muscle phosphofructokinase. *J. Biol. Chem.* **243**, 1356, 1968

6. TANNENBAUM, A. and SILVERSTONE, H.: Nutrition in relation to cancer. *Adv. in Cancer Res.* **1**, 451, 1953
7. MIDER, G. B.: Some aspects of nitrogen and energy metabolism in cancerous subjects: a review. *Cancer Res.* **11**, 821, 1951