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Histochemical studies on enzyme activities of gastric carcinoma. II. Dehydrogenases

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Abstract

With gastric carcinomas the activities of eight dehydrogenases; succmlC, lactic, malic, α glycerophosphate, glutamic, β-hydroxybutyric, glucose-6-phosphate and isocitric dehydrogenase were statistically estimated. Principal findings may be briefly summarized as follows. These enzymatic activities differed considerably even in the same claification of carcinomas and generally ranged from strong to weak in the following order: lactic, malic, glucose-6-phosphate, isocitric, succinic, α-glycerophosphate, glutamic and β-hydroxybutyric dehydrogenase. The activities of adenocarcinomas were stronger than those in simple ones, and these were not related appreciably to cell differentiation in adenocarcinomas except succinic, glutamic, glucose-6-phosphate and isocitric dehydrogenase. As for succinic dehydrogenase and NAD-linked dehydrogenases except for lactic dehydrogenase, the activities were strongest in intestinal metaplasia and early mucosal carcinomas, the next being in benign adenomatous polyps and weakest in the other carcinomas. As for NADP-linked dehydrogenases and lactic dehydronase, the activities were also strongest in intestinal metaplasia and early carcinomas, the second in the other carcinomas and the third in the benign polyps. Generally, these dehydrogenase activities were strongest in free carcinoma cells in blood and lymph veels and in actively growing part of several carcinomas and weakest in the central area of tumors, especially almost negative in the central necrotic area.

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HISTOCHEMICAL STUDIES ON ENZYME ACTIVITIES OF GASTRIC CARCINOMA
II. DEHYDROGENASES

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Statistical histochemical investigation on the hydrolytic enzymes in human gastric carcinomas was presented in our previous report[1]. However, systematic and statistical investigations on dehydrogenases of gastric carcinoma have not yet been reported precisely in the histochemical field. During the period from 1960 to 1966, 180 patients of gastric carcinomas, just as those in the previous report on hydrolytic enzymes served as the materials in the present investigation. Dehydrogenases used in our study were succinic, lactic, malic, α-glycerophosphate, glutamic, β-hydroxybutyric, glucose-6-phosphate and isocitric dehydrogenases. For the purpose of disseminating accurate statistics, the histological classification of the tumors in our paper was made on the basis of that established by the Japanese Pathological Society in 1962 (Table 1) as in the previous report in which the explanation of the classification was precisely described.

MATERIALS AND METHODS

The materials were human gastric carcinomas removed from 180 patients examined histochemically at Department of Surgery, Okayama University Medical School, from 1960 to 1965. All the specimens were frozen in the room kept at $-20°C$ immediately after the removal, and with these specimens serial sections of 20 microns thick were prepared in a cryostat. For the demonstration of dehydrogenases, the sections dried at room temperature were incubated with the following media. Succinic dehydrogenase: Incubation mixture was composed of 5 ml of 0.2 M sodium succinate, 5 ml of 0.2 M phosphate buffer at pH 7.6, to which 10 ml of nitro-BT aqueous solution (1 mg/1 ml) were added. The sections were incubated in the mixture at 37°C for 30 minutes, fixed in 10 per cent formalin and mounted in glycerin without dehydration. Lactic, glutamic, α-glycerophosphate and β-hydroxybutyric dehydrogenases: Incubating solution contained 4 ml of 1 M substrate solution, 3 ml of nitro-BT solution

Table 1 Morphologic Classification of Tumors

	CAT	SAT	INF	Structural pattern	Functional pattern	Stromal quantity
Adenocarcinoma	I, II, III	1, 2, 3	α, β, γ	tubular papillar acinar	muconodular mucocellular	medullar scirrhous
Carcinoma solidum simplex (simple carcinoma)	I, II, III	1, 2, 3	α, β, γ	macro- meso- micro- alveolar	mucocellular	medullar scirrhous
Epidermoid carcinoma	I, II, III	1, 2 3	α, β, γ	macro- meso- micro- alveolar	Keratoid	medullar scirrhous
Adenoacanthoma	I, II, III	1, 2, 3	α, β, γ	Mucosal carcinoma, early Ulcus carcinoma, early Polyp carcinoma, early Double carcinoma,		
Miscellaneous carcinoma	I, II, III	1, 2, 3	α, β, γ			

CAT: Cellular atypism
SAT: Structural atypism
INF: Carcinoma cell infiltration
I, 1 and α: slight grade
II, 2 and β: moderate grade
III, 3 and γ: heavy grade

(5 mg/3ml), 11 ml of 0.1 M phosphate buffer at pH 7.6, 2.5 mg of NAD (100 per cent), 2 ml of 0.1 M KCN and adjusted at pH 7.6 with 0.5 M HCl. Malic dehydrogenase: Incubating solution was composed of 5 ml of 1 M sodium malate, 3 ml of nitro-BT solution (5 mg/3 ml), 10 ml of phosphate buffer (0.1 M) at pH 7.4, 2.5 g of NAD, 2 ml of 0.1 M KCN and adjusted at pH 7.4 with 0.5 M HCl. Glucose-6-phosphate dehydrogenase: Incubation mixture was consisted of 4 ml of 0.002 M disodium glucose-6-phosphate, 3 ml of nitro-BT solution (5 mg/3 ml), 11 ml of 0.1 M Veronal buffer at pH 7.6, 3 ml each of 0.01 M $MgCl_2$, and 0.5 M $MnCl_2$ solutions and with 7 mg of NADP. Isocitric dehydrogenase: Incubation mixture was consisted of 4 ml of 0.1 M sodium isocitrate, 3 ml of nitro-BT solution (5 mg/3 ml), 11 ml of 0.1 M Veronal buffer at pH 7.4, 2 ml each of 0.01 M $MgCl_2$, and 0.5 M $MnCl_2$, solutions and with 2.5 mg of NADP. For the lactic and malic dehydrogenases, incubation was carried out at 37°C for 30 minutes, and for the other NAD-and NADP-linked dehydrogenases one hour.

RESULTS

The statistical estimation of the histochemistry on gastric carcinoma is shown by a graph in columns of Fig. 2, and that on the fibrous stromal elements of

Fig. 1 Activity on Gastric Carcinoma

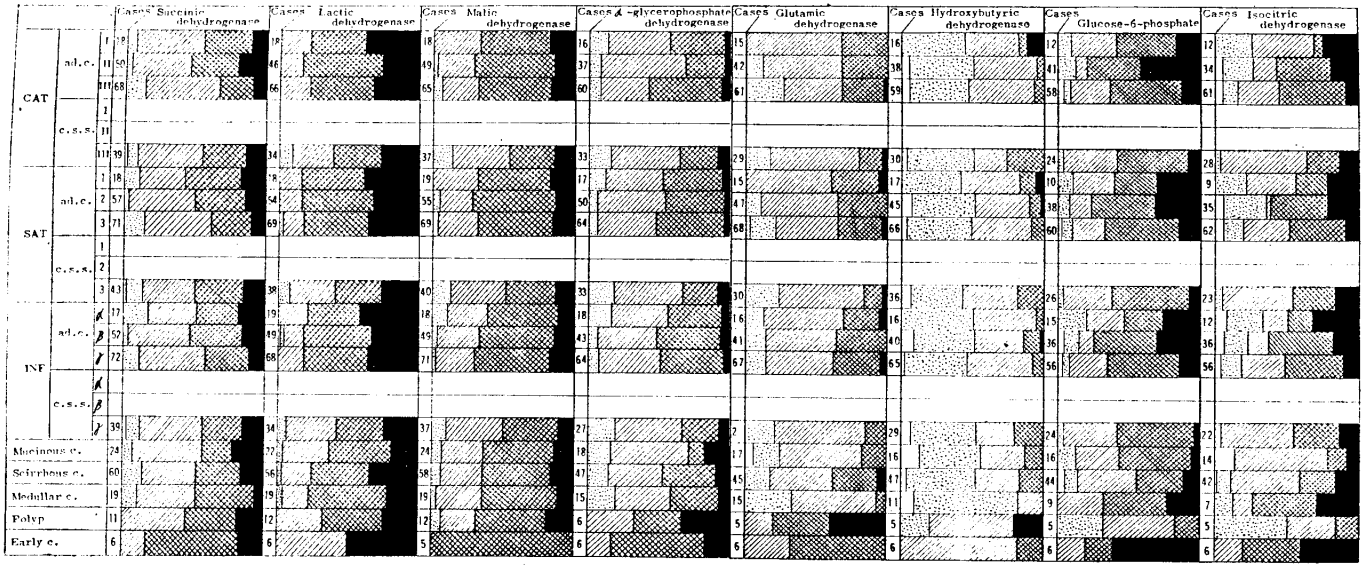
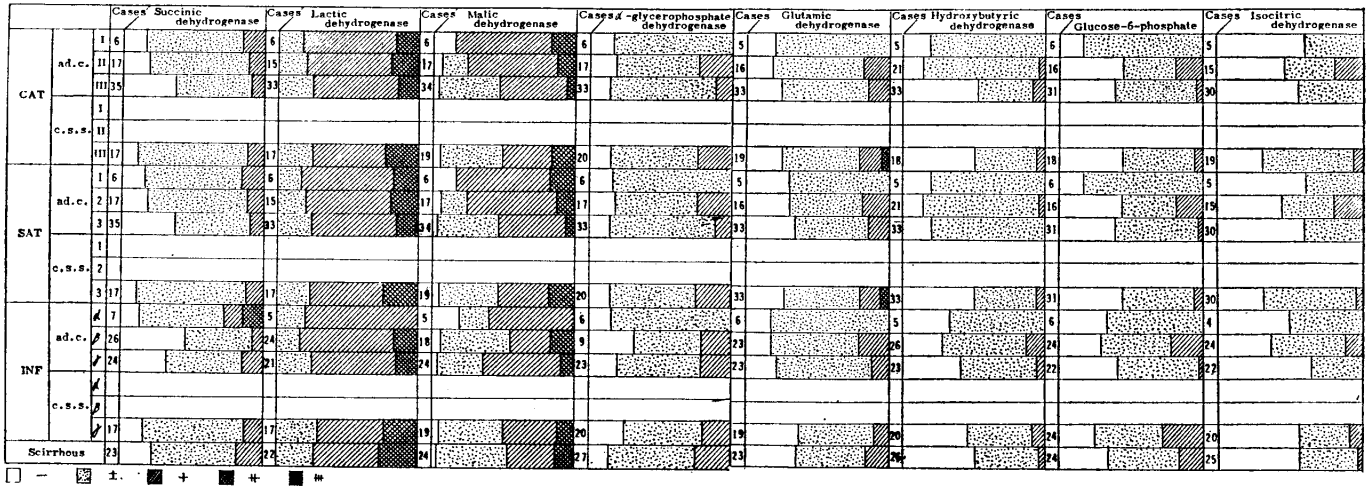


Fig. 2 Activity on Stromal Elements



The enzymatic activities of specimens stained histochemically were graded microscopically on the basis of color reaction in − to ⫲ by inspection of all cells; complete negative −, faint ±, slight, +, moderate ⫲, and intense ⫲, and shown by graph in column.

neighboring epithelium of the stomach carcinomas is shown in Fig. 3. The activities of succinic dehydrogenase and NAD-linked dehydrogenases were strongest in parietal cells and moderate to faint in the other epithelial cells of normal gastric mucous membrane. While on the contrary, NADP-linked dehydrogenases were strongest in normal superficial epithelium of gastric mucous membrane and faint to negative in the other epithelial elements[2~7]. As mentioned above, the normal tissues showed a constant activity of dehydrogenases, but their activities were often not so uniform even in carcinoma that the average intensity was adopted in these tables. Variation in these dehydrogenase activities with pathological tissues of the stomach was so common that something common among them was mentioned at first as follows.

In general, all of these dehydrogenase activities were strongest in free carcinoma cells in blood and lymph vessels and in the actively growing part of several carcinomas and weakest in the central part, especially the activity being almost negative in the central necrotic portion. However, weaker reaction in the growing part was found in exceptional cases. Where the mucous epithelium was hypertrophic around the tumor, the activities of dehydrogenases were mainly a little increased. In metaplastic area all of the dehydrogenases showed a strong activity as duodenal villi showed. Being adenomatous polyps exhibited a rather strong tendency of these enzymatic reaction as a whole than epithelial elements near the polyps. The NADP-linked dehydrogenase activities of gastric carcinomas were clearly more intense than those of the mucous epithelium and benign polyps, particularly mucosal carcinomas in early stage were most intense. As for the other dehydrogenases, the activity in the carcinomas was similar in degree as that in the polyps or a little weaker than that in the polyps and that in early mucosal carcinoma strongest. In carcinomas excepting ones in early stage, when two different types of carcinomas were found morphologically in a same specimen, the activity of these eight dehydrogenases in two different patterns mostly resembled each other. In the other specimens with two different patterns of tumor, the dehydrogenase activities were weaker in poorly differentiated area than in well differentiated area. And in the same specimen of adenocarcinomas, these enzyme reactions were occasionally more intense in the area showing papillary pattern than in the tubular area, and also were often more intense in the part of smaller pseudoluminal formations than in that of larger ones. The enzyme reaction in stromal elements was very similar to that of the elements in normal tissues, but sometimes it was slightly increased in newly forming part of fibrous stroma in the gastric carcinomas In the fibrous stroma generally the activity in carcinomatous tissue did not differ from that around the carcinoma. In these areas, it was found that fibroblasts and young fibrocytes were more intensely reactive for succinic dehydrogenase and NAD-linked dehydrogenases

than the fibrocytes that matured in normal tissue. In blood vessels, smooth muscles and wander cells in the carcinomatous tissues, the activities of these eight dehydrogenases were similar to that in the inflammatory area of gastric mucosa and rather strong than that in the other inflammatory tissues.

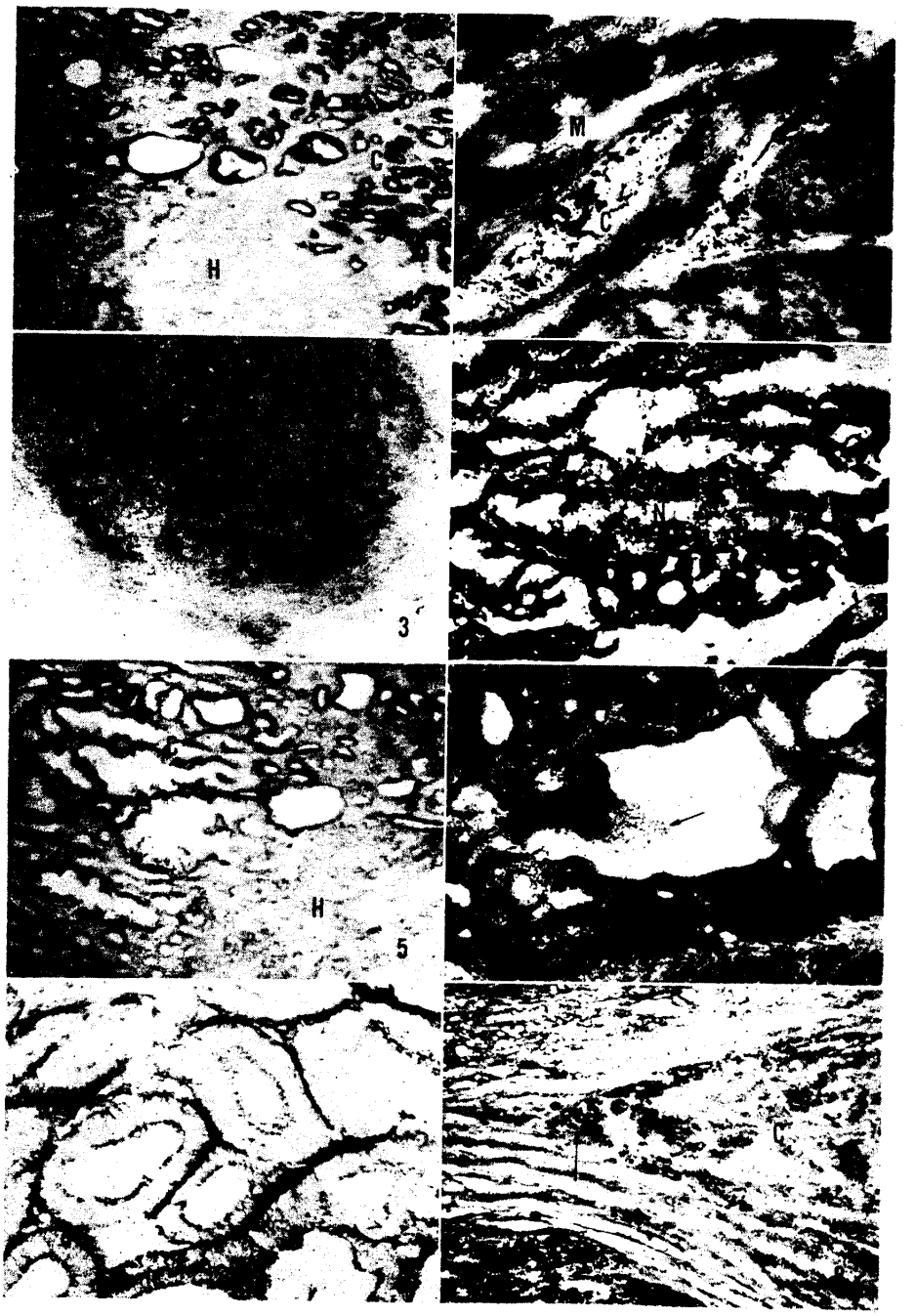
Succinic dehydrogenase : The majority of gastric carcinomas was weakly or moderately reactive for this enzyme in the tumor cells and faintly active in the stromal elements. In the tissues of adenocarcinomas, a rather weak tendency of the dehydrogenase reaction for the high grade of atypism of the cell, the structure, and the growing pattern, that is carcinoma cell infiltration, was observed in both carcinoma cells and fibrous stromas. The activity of simple carcinomas, carcinoma solidum simplex, was about the same with undifferentiated adenocarcinomas. An interesting finding was that early mucosal carcinomas generally revealed a stronger activity than all other carcinomas.

Lactic dehydrogenase : The activity of this enzyme in tumor cells was most predominant of all eight enzymes and ranged from slight to intense, and that of fibrous stroma was slight. Adenocarcinomas did not depend on the grade of cellular and structural atypism and that of tumor cell infiltration. But comparing the simple carcinomas, they statistically showed a rather strong enzyme activity. In general, the activity in early mucosal carcinomas was strongest of all the carcinoma specimens.

Malic dehydrogenase : In the carcinomas, moderate reaction unaffected by the cellular and structural atypism was often observed. On the grade of growing pattern shown as the quantity of the tumor cell infiltration around the main tumor, a slightly stronger tendency of the dehydrogenase reaction for the high grade was obtained. The activity of simple carcinomas was mainly weaker than that of adenocarcinomas. All of early mucoal carcinomas were moderately reactive. Fibrous stroma showed often a slight activity.

α-glycerophosphate dehydrogenase : Judging from the intensity of this enzyme reaction in the carcinoma cells by the appearance, it was similar to that of succinic dehydrogenase, but statically it was considerably different when the tumors were graded as shown in Table 1. In adenocarcinomas the activity was strongest in the poorest group of cellular and structural atypism, and then that was similarly stronger in the high grade of carcinoma cell infiltration. Simple carcinomas were rather weakly reactive than adenocarcinomas. In benign adenomatous polyps and early mucosal carcinomas, the activity was stronger than that in the other carcinomas. Fibrous elements mostly showed a faint reaction.

Glutamic dehydrogenase : Most of the tumor cells displayed a slight or moderate reaction of this enzyme. On this enzyme, the reaction of adenomatous polyps were strongest, that of early mucosal carcinomas the second, that of well differentiated carcinomas the third, and that of undifferentiated carcinomas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weakest. Unexpectedly, the activity was not changed due to the grade of carcinoma cell infiltration. And between the scirrhous carcinomas and medullar carcinomas, the latter revealed a very weak activity at times. The activity in their fibrous stroma was mainly faint.

β-hydroxybutyric dehydrogenase : The activity was faint or slight in carcinoma cells and weakest of all of eight dehydrogenases. In carcinoma cells, there was observed no significant change in the activity of this enzyme caused by cell differentiation of the tumors, excepting adenomatous polyps and early mucosal carcinomas which showed considerable activities. In fibrous stromal elements, the activity was faint or negative and the rate of negative cases was about a half in undifferentiated carcinomas and in scirrhous type.

Glucose-6-phosphate dehydrogenase : This enzyme activity was slight to strong in carcinoma cells and negative or faint in fibrous stromal elements. The fibrous stromal elements of well differentiated carcinomas which were of the first grade of cellular and structural atypism displayed faint reaction in most cases, but those of the other carcinomas did react faintly in about 60 cases. The strongest activity of tumor cells was observed in early mucosal carcinomas, while the weakest activity of them in benign adenomatous polyps. According to the present classification, the activity was more intense in the intermediate grade of cellular atypism than in the other grades, and on the enzymatic evaluation of the structural atypism in the grade of carcinoma cell infiltration, the carcinomas with the high grade showed weaker activity than those of the other grades. Scirrhous carcinomas showed generally weaker activity than medullar ones, and in adenocarcinomas the activity was stronger than in simple carcinomas.

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1 Succinic dehydrogenase stain, ×20, early adenocarcinoma: Lateral hyperplasy(H) often keeps simillar activity to non-hyperplastic area. Carcinoma(C) had very strong activity, especially in small pseudoluminal part.

2 Succinic dehydrogenase stain, ×50, scirrhous simple carcinoma: Strong activity is often seen at infiltrating area of carcinoma(C) in muscle layer(M)

3 Succinic dehydrogenase stain, ×20, simple carcinoma: Occasionally the activity in central portion of carcinoma cell nestle is weaker than that of peripheral area.

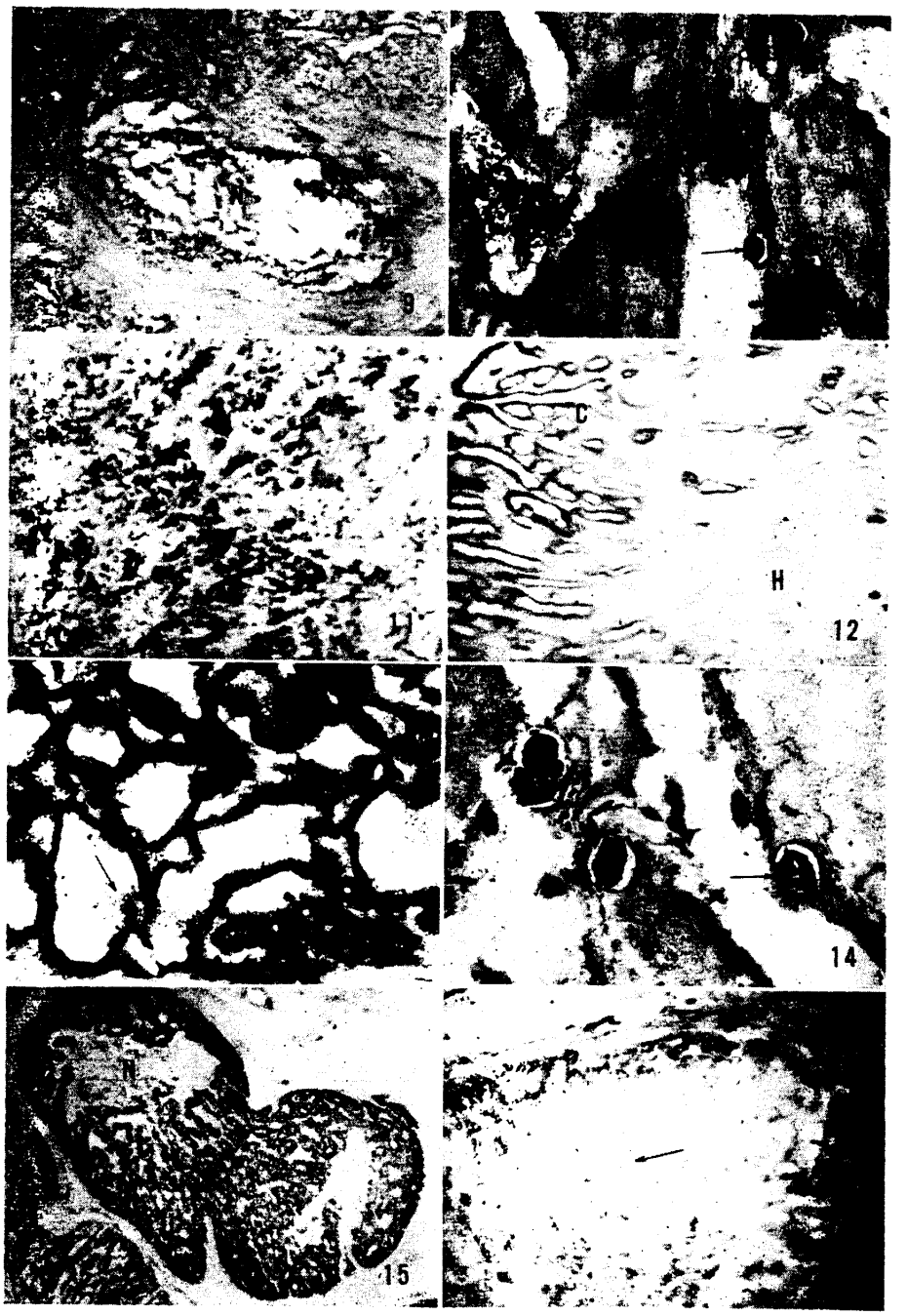
4 Succinic dehydrogenase stain, ×50, adenocarcinoma: Necrotic part shows decreased activity (N).

5 Lactic dehydrogenase stain, ×20, early adenocarcinoma: Comparing with 1, lactic dehydrogenase activity is not appreciably increased in carcinoma(C).

6 Lactic dehydrogenase stain, ×50, adenocarcinoma: Rare case, the activity is rather weak in actively growing part(↑) of carcinoma than the other part.

7 Malic dehydrogenase stain, ×100, adenocarcinoma: In the vicinity of basement membrane strong activity is found at times.

8 Malic dehydrogenase stain, ×50, adenocarcinoma: Invading part of carcinoma(↑) is sometimes strongly reactive for the enzyme, the same pattern is found in the other dehydrogenases.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Isocitric dehydrogenase : This dehydrogenase exhibited similar activity to glucose-6-phosphate dehydrogenase in the carcinomatous tissues but somewhat weaker, in spite of member belonging to different metabolic pathways. The strongest activity was in the early mucosal carcinomas of all of these tumors, and the weakest was in adenomatous polyps. In the adenocarcinomas a decreasing tendency of strong positive reaction for the high grade of cellular atypism, structural atypism and tumor cell infiltration. And also the mucinous carcinomas, carcinoma muconodulare et mucocellulare, presented a weak activity but the medullar ones a strong reaction.

DISCUSSION

WACHSTEIN *et al.*[8] found distinct staining of succinic dehydrogenase in the more immature carcinomas, and also some faint activity in the scirrhous carcinomas. But SCHOLL *et al.*[9], IMANISHI *et al.*[10], MONIS *et al.*[11], KITAMURA[12], OGATA *et al.*[13], JINNAI *et al.*[14] and TANAKA *et al.*[15,16] stated that the succinic dehydrogenase activity was similar to normal mucosa or reduced in well differentiated adenocarcinoma and was significantly diminished according to the degree of differentiation as to whether being poorly differentiated or not in human gastric carcinomas. The mucinous carcinomas showed feeble reaction of succinic dehydrogenase. However, in the present paper, as varying intensities of the reaction were observed in individual cells of each mucous epithelium, namely, superficial epithelium, neck cells, zymogenic cells and parietal cells of fundocorpus gland and superficial epithelium and pyloric gland cells of the pyloric gland, it was difficult to use them as the control for the gastric carcinomas.

9 Malic dehydrogenase stain, ×50, adenocarcinoma : Central necrotic area(N) with decreased activity is noticed, but the border part between necrotic area and non-necrotic carcinoma with strong activity.

10 α-glycerophosphate dehydrogenase stain, ×50, adenocarcinoma : Strong activity is observed in carcinoma cells in lymph vessel(↑).

11 α-glycerophosphate dehydrogenase stain, ×50, mucinous carcinoma : The activity of carcinoma is strong.

12 Glucose-6-pohsphate dehydrogenase stain, ×20, early adenocarcinoma : Hyperplastic glands (H) keep original activity but carcinoma(C) reveals similar activity to that of the superficial epithelium.

13 Glucose-6-phosphate dehydrogenase stain, ×50, adenocarcinoma : Rare case, proliferating portion(↑) of carcinoma with rather weaker activity is observed than the other part.

14 Glucose-6-phosphate dehydrogenase stain, ×50, adenocarcinoma : Strong reaction of carcinoma cells in lymph vessel is often found ↑).

15 Glucose-6-phosphate dehydrogenase stain, ×50, adenocarcinoma : In necrosis(N) the activity is distinctly decreased.

16 Isocitric dehydrogenase stain, ×20, adenocarcinoma : The activity sometimes appeared in capillary wall (↑) in carcinoma. The same observation is noticed on the demonstration of glucose-6-phosphate dehydrogenase.

Therefore, benign adenomatous polyp in the stomach was employed as a control in our study. Adenomatous polyps usually showed a stronger reaction than mucinous epithelium around the polyps. Generally, the activity of early carcinomas was stronger, that of well differentiated adenocarcinomas was similar to or rather weaker and that of poorly differentiated carcinomas weaker than that of polyps. Mucinous carcinomas showed the level of activity similar to the others. The stromal activity of succinic dehydrogenase was mostly negative or faint.

MONIS *et al.*[11] found lactic dehydrogenase activity in human tumors which was distributed almost as extensively as NAD-diaphorase activity, and OGATA *et al.*[13] and JINNAI *et al.*[14] found a decreasing tendency of activity for poorly differentiated carcinomas except for several scirrhous ones which showed a marked activity. TANAKA *et al.*[16] reported that the activity was generally marked and tended to be strong for less differentiated carcinoma cells. In contrast, in our study, there was observed hardly any difference in the activities between well differentiated adenocarcinomas and poorly differentiated ones. The activity of simple carcinomas resembling that of adenomatous polyps was weaker than that of adenocarcinoma. A noteworthy finding was the strong activity in early carcinomas.

Other NAD-linked dehydrogenases; MONIS *et al.*[11], KITAMURA[12], OGATA *et al.*[13], JINNAI *et al.*[14], TANAKA *et al.*[15,16] and MORI *et al.*[17] reported about the activities of malic, α-glycerophosphate, glutamic and β-hydroxybutyric dehydrogenase. MONIS *et al.*[11] stated that the staining intensity of these enzymes was not related to the histochemical structure or to the degree of morphological differentiation of neoplasmas, nor any significant difference was found between benign and malignant growths. But KITAMURA[12], OGATA *et al.*[13] and JINNAI *et al.*[14] reported some correlationships between carcinoma cell differentiation and thier NAD-linked dehydrogenase activities and concluded that there is a decreasing tendency of these activities for poorly differentiated carcinomas except for the activity of scirrhous ones. On the other hand, TANAKA *et al.*[15,16] reported statistically a rather reverse tendency as compared with their reports or the results similar to MONIS *et al.*[11] as above described. Accordingly, malic dehydrogenase was slightly less active than lactic dehydrogenase, and α-glycerophosphate, glutamic dehydrogenase and β-hydroxybutyric dehydrogenase were all less active in most of the tumors. In the present observation activity of these enzymes showed some variation from case to case, but generally weaker than that of succinic dehydrogenase. However, adenomatous polyps showed the strongest activity and early cancer the second, well differentiated adenocarcinoma the third and undifferentiated adenocarcinoma the fourth, simple carcinoma the weakest. According to the classification, in our paper, the activity

was a little more reactive for malic dehydrogenase for high grades of carcinoma cell infiltration of adenocarcinoma. α-glycerophosphate dehydrogenase had the same tendency for the grade of cellular and structural atypism and of carcinoma cell infiltration as malic dehydrogenase and glutamic and β-hydroxybutyric dehydrogenase showed a similar tendency in the grades of cellular and structural atypism, but a little significant correlation between these four dehydrogenase activities and cell differentiation. Simple carcinoma revealed a weak reaction for these NAD-dependent dehydrogenases. These enzyme activities in scirrhrous carcinomas were clearly stronger than those in medullar ones. Our results almost coincided with those reported by TANAKA *et al.*[15,16]. Stromal elements showed a weak or no activity on the demonstration of all of NAD-linked dehydrogenases, and the activity was noticed in the stroma in the following descending order: lactic, malic, glutamic, α-glycerophosphate and β-hydroxybutyric dehydrogenase.

MORI *et al.*[18]described a slight or moderate activity of glucose-6-phosphate dehydrogenase in gastric cancers and no enzymatic reaction in stromal elements, and he and his associates[19] also stated isocitric dehydrogenase activity to be only in trace in 34% and low to moderate in 53% of 38 cases of gastric adenocarcinomas. The reports on these two enzymes by OGATA *et al.*[13], JINNAI *et al.*[14] and TANAKA *et al.*[15,16] gave the results very similar to the present ones. In our report, cancer cells of the stomach showed mainly slight or moderate activity of the NADP-linked dehydrogenases with a considerable variation in the activity from case to case and distinctly weaker one in the cases with high grade of cellular and structural atypism and cancer cell infiltration of adenocarcinoma. As for these two dehydrogenases, in simple carcinoma the activities were weak. Actually, the activities of glucose-6-phosphate and isocitric dehydrogenase in adenomatous polyps were very weak, while carcinomas, especially early ones revealed stronger activities than adenomatous polyps. In brief, benign adenomatous polyp had a weaker NAD-linked dehydrogenase activity, a rather weak lactic dehydrogenase activity, a slightly weak succinic dehydrogenase activity, and similar or rather stronger malic, α-glycerophosphate, glutamic and β-hydroxybutyric dehydrogenase activities than early carcinomas had. In early carcinomas, glucose-6-phosphate, isocitric, lactic, and succinic dehydrogenase activities were strongest of all of the benign and malignant tumors and moderately or slightly less in the other carcinomas. Even for malic, α-glycerophosphate, gluatmic and β-hydroxybutyric dehydrogenases this tendency was also observed.

From these findings, it might be presumed that the activity of these eight dehydrogenase is stronger in benign adenomatous polyp than in the non-tumor epithelium, strongest in the early carcinoma of all of the gastric tumors and the reduced in the carcinoma compared with the early cancers and polyps. Although

these results support WARBURG's theory[20] as definitely increased activities of lactic and glucose-6-phosphate dehydrogenase, but also these results can not defy WEINHAUSE's theory[21] in early carcinomas, in actively growing part of the tumors which revealed stronger activities of these eight enzymes and in free condition of the tumors. The same opinion by histochemical study was already presented by SEITO[22] using human intestinal tumors. Concerning the increased activity of dehydrogenases in actively growing area, PEARSE[23], TANAKA *et al.*[15,16] and ABE *et al.*[24] already reported on lactic and NADP-linked dehydrogenases in some tumors. Recently SEITO[22] reported that most of dehydrogenases show an increased activity in growing area of human intestinal carcinomas as gastric ones did in the present study.

In our study, all of these dehydrogenase reactions were changed even in a single specimen of carcinoma specimens and mostly they increased together in actively growing part at times, and necrotic area revealed lesser or no activity.

In any event, the activity of stromal elements were almost unchanged as compared with that of normal tissue. In collateral hyperplastic mucosa and accompanying gastritis, enzyme activities were generally a little increased, while in atrophic gastritis it was rather descreased. PLANTEYDT *et al.*[2] IMANISHI *et al.*[10] TANAKA *et al.*[15,16] YOSHITOSHI *et al.*[7] and KAWASHIMA *et al.*[6] noticed that intestinal metaplasia resemble a small intestinal epithelium, both morphologically and enzymatically in most cases and had a correlation between the severity of the process and several enzyme activities. In this study, all of these dehydrogenase activities were strong in metaplastic area. It indicates some correlationship between intestinal metaplasia and the early carcinoma.

SUMMARY

With gastric carcinomas the activities of eight dehydrogenases; succinic, lactic, malic, α-glycerophosphate, glutamic, β-hydroxybutyric, glucose-6-phosphate and isocitric dehydrogenase were statistically estimated. Principal findings may be briefly summarized as follows.

These enzymatic activities differed considerably even in the same classification of carcinomas and generally ranged from strong to weak in the following order: lactic, malic, glucose-6-phosphate, isocitric, succinic, α-glycerophosphate, glutamic and β-hydroxybutyric dehydrogenase.

The activities of adenocarcinomas were stronger than those in simple ones, and these were not related appreciably to cell differentiation in adenocarcinomas except succinic, glutamic, glucose-6-phosphate and isocitric dehydrogenase.

As for succinic dehydrogenase and NAD-linked dehydrogenases except for lactic dehydrogenase, the activities were strongest in intestinal metaplasia and

early mucosal carcinomas, the next being in benign adenomatous polyps and weakest in the other carcinomas. As for NADP-linked dehydrogenases and lactic dehydronase, the activities were also strongest in intestinal metaplasia and early carcinomas, the second in the other carcinomas and the third in the benign polyps.

Generally, these dehydrogenase activities were strongest in free carcinoma cells in blood and lymph vessels and in actively growing part of several carcinomas and weakest in the central area of tumors, especially almost negative in the central necrotic area.

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