STUDIES ON THE ABSORPTION OF VITAMIN B₁₂

III. INTRINSIC FACTOR SECRETION IN VARIOUS GASTRIC DISEASES WITH SPECIAL REFERENCE TO GASTRIC ATROPHIC CHANGES

SHIGEO UKYO

*The First Division, Department of Internal Medicine, Faculty of Medicine,
Kyoto University, Sakyo, Kyoto*

(Received February 3, 1962)

Castle's intrinsic factor which is assumed to be a substance secreted into the gastric lumen mainly by the cells located in the fundus and body of the stomach plays an essential part in the physiologic mechanism of the intestinal absorption of vitamin B₁₂ (B₁₂) (1). Therefore, it may reasonably be assumed that the diseases of the stomach may give rise to decreased output of intrinsic factor, but few investigations have been made on the production or secretion of intrinsic factor in the diseases. Meanwhile, atrophic changes of the gastric mucosa are frequently encountered in most cases of Addisonian pernicious anemia (2-8), and it is generally accepted that these changes are responsible for the deficient intrinsic factor secretion leading to pernicious anemia (7, 9-23). In order to investigate the existence of any disturbances in intrinsic factor secretion, the author studied the intestinal absorption of orally administered radioactive B₁₂ labeled with Co⁶⁰ in the patients suffering from gastric diseases such as gastric cancer, polyp, gastritis and peptic ulcer, *etc.*, by means of Schilling's urinary excretion test. Furthermore, studies were extended to the problem whether there may be any significant correlation between intrinsic factor secretion as estimated by Schilling's urinary excretion test and the findings of the gastric mucosa obtained by the gastroscope technique from the patients with above-mentioned diseases or pernicious anemia.

EXPERIMENTAL

1. Subjects Studied

Intestinal absorption of Co⁶⁰-B₁₂ was carried out on 7 patients with gastric cancer, 2 with gastric polyp, 12 with peptic ulcer associated or not associated with diverticle, 11 with gastritis and 24 with gastric atrophic changes.

2. Vitamin B₁₂ Absorption

For B₁₂ absorption study, the urinary excretion test introduced by Schilling (24) was carried out, because the test is more readily applied to relatively large series; 0.5 μ g of Co⁶⁰-B₁₂¹ of high specific activity was given by mouth to the patients

¹ Kindly supplied by Dr. Nathaniel Ritter, Merck and Co., Rahway, New Jersey, U. S. A.

in the fasting state. Two hours later, 1000 μ g of non-radioactive B₁₂ (Fresmin)² was injected intramuscularly, and the urine excreted during the subsequent 24 hours was collected. Counting of the radioactivity in the urine was made on the top of a well-type scintillation counter and urinary radioactivity was expressed as the percentage of the given radioactivity. The normal controls excreted 5.1 to 27.6 % of the given dose in the urine (average, 17.6 ± 6.8 %). The details have been described in the foregoing paper (25).

3. Gastrocamera Technique

Gastrocamera—The gastrocamera is an instrument with which the gastric mucosa of the patients with various conditions can be photographed as does the gastroscope. This instrument was originally devised in Japan. The advantage of the camera is to lessen the patients' distress by virtue of its high flexibility. In addition, the use of the instrument makes it possible to photograph the mucosa of the gastric antrum which is a blind area for the gastroscope. However, the cardiac and fundic area as well as the upper region of the posterior wall of the stomach remains as a blind area for the gastrocamera.

Procedure for the Gastrocamera Technique—The study with gastrocamera is performed in the fasting state (even smoking is prohibited). Lavage of the gastric contents is necessary, when the patients to be tested have pyloric obstruction. For the purpose of obtaining the clearer findings by ceasing the gastric secretion, 0.0005 mg of atropine sulfate or 20 mg of Buscopan (hyoscine-*n*-butylbromide) is injected subcutaneously to the patients. About 30 minutes after the injection, the patients were anesthetized by gargling with either 15 to 20 ml of 0.5 % solution of *p*-butylaminobenzoyl diethyl aminoethanol hydrochloride or 15 or 20 ml of 4.0 % solution of xylocain. Then the camera is introduced into the stomach. The introduction of the camera should be made very carefully so that the leading tip of the camera might avoid any pressure on the passing way. When the tip of the camera reached the cardia, a resistance is conveyed to the hand of the camera operator. After the tip had been passed through the cardiac region and introduced into the gastric lumen, the red light attached to the camera was switched on, so that the light often presents the contour of the stomach as a silhouette. The patients were then laid in the supine position. Now the tip can be felt with the operator's finger on the abdominal wall. When the tip had been advanced to the antrum of the stomach, 600 to 1000 ml of air was blown into the organ to inflate by use of an air-balloon to keep the adequate space between the gastric mucosa and the introduced camera, so that the mucosa was photographed in the natural state as it was. The mucosae of various parts of the stomach can be photographed by rotating the axis of the flexible tube attached to the camera, or by changing the angle of the tip to the axis of the tube or pulling up the camera toward the cardia. When the gastric mucosa was photographed all over, the camera was taken out of the body with care. About one hour later, the patients tested are allowed to take anything by mouth, because the anesthesia is worn off at this time.³

² Kindly furnished by Takeda Chemicals Co., Ltd., Osaka.

³ The details are described in the pamphlet, "Gastrocamera V: Direction for use, 1961", issued by the authoritative office of the Olympus Optical Co., Tokyo.

RESULTS

1. Cancer of the Stomach

Clinical and roentgenological examinations revealed, as summarized in Table I, that the tumor developed in the pyloric and/or fundic region of the stomach in 6 patients, while in the cardiac region in one case (Case No. 80, S. T.). Except for Case No. 80, S. T., percentage urinary excretions of all the patients were within the normal range, indicating no deficient secretion of intrinsic factor. In Case No. 80, S. T., however, urinary excretion was slightly decreased (2.8 %). This suggests the possibility that the cancerous condition of the stomach may be responsible for the decreased output of intrinsic factor.

TABLE I
*Urinary Excretions of Orally Administered Co⁶⁰-B₁₂ in
Gastric Cancer and Gastric Polyposis*

Case No.	Patient	Age	Sex	Diagnosis	B ₁₂ oral dose	Urinary excretion in hours					Total urin. excretion
						0—4	4—8	8—12	12—16	16—24	
					μg						per cent
80	S. T.	52	m	Gastric cancer	0.5	0.4		2.4		0	2.8
81	K. Z.	66	m	"	"	0	2.7	1.6	2.4	2.7	9.4
82	H. H.	53	m	"	"	0.8	2.6	2.0	0.8	0	6.2
83	K. H.	74	m	"	"	0.2	0.7	2.1	3.1	0.8	6.9
84	M. S.	51	m	"	"	0	5.1	9.4	4.6	2.1	21.2
85	Y. U.	76	m	"	"	0	3.1	2.9	3.1	2.2	11.3
86	Y. S.	55	m	"	"		1.6		6.4	2.6	10.6
87	Ki. T.	39	f	Gastric polyposis	"	0.3	4.0	3.4	3.3	0	11.0
88	Y. I.	62	f	"	"		2.5		4.3	2.0	8.8

2. Gastric Polyp

Gastric polyp was confirmed by the gastrocamera technique as well as X ray examination. In the two patients tested, as given in Table I, the urinary excretions were 8.8 and 11.0 %, respectively, indicating normal intrinsic factor secretion.

3. Peptic Ulcer

The diagnosis of peptic ulcer was made by the gastrocamera technique or X ray examination. Thus it was found, as shown in Table II, that the Case No. 65, Sh. T., was accompanied by duodenal diverticle. The urinary excretions of the oral Co⁶⁰-B₁₂ were found to be within the normal range in all the patients tested without any exception. It seemed possible that peptic ulcer did not affect the secretion of intrinsic factor.

4. Gastritis

All the 11 patients with acute or chronic gastritis excreted, as shown in Table III, normal amounts of the test dose in the urine, ranging from 8.4 to 27.0 %. This result suggests that the intrinsic factor secretory function can be well preserved, irrespective of the diseased stomach.

5. Gastric Atrophic Changes as Observed by the Gastrocamera Technique

"Gastric atrophy" used in the present study means the "atrophic" findings of

TABLE II
Urinary Excretions of Orally Administered Co⁶⁰-B₁₂ in Peptic Ulcer

Case No.	Patient	Age Sex	Diagnosis	B ₁₂ oral dose	Urinary excretions in hours					Total urinary excretion
					0—4	4—8	8—12	12—16	16—24	
				μg	per cent					per cent
63	S. T.	64 m	Ulcus duodeni	0.5	0.5	2.8	2.7	1.5	1.4	8.9
64	S. K.	65 m	" ventriculi	"	0	2.7	3.1	1.3	0.7	7.3
65	Sh. T.	48 f	Ulc. vent. with duod. diverticle	"		4.9		8.0	0.7	13.6
66	K. O.	49 f	Ulcus ventriculi	"		7.2		3.1	1.0	11.3
67	T. K.	43 m	" duodeni	"		2.6		6.6	1.0	10.2
68	S. M.	39 m	" ventriculi	"		2.5		5.9	0.6	9.0
69	H. K.	28 m	" duodeni	"		7.4		4.9	0	12.3
70	S. S.	51 m	" ventriculi	"	0.3	9.9	2.9	0.5	0.1	13.7
71	K. F.	54 m	"	"	0	4.2	4.8	3.6	4.2	16.8
72	S. F.	72 m	"	"		5.4		9.8	2.4	17.6
73	S. O.	57 f	"	"		2.2		7.1	2.9	12.2
74	Y. Y.	21 m	" duodeni	"		0.3		9.2	0.4	9.9

Range: 7.3—17.6; mean: 11.9

TABLE III
Urinary Excretions of Orally Administered Co⁶⁰-B₁₂ in Gastritis

Case No.	Patient	Age Sex	Diagnosis	B ₁₂ oral dose	Urinary excretions in hours			Total urinary excretion
					0—8	8—16	16—24	
				μg	per cent			per cent
52	M. I.	64 m	Antrum gastritis	0.5	2.3	5.5	0.6	8.4
53	S. K.	61 f	Acute "	"	4.1	9.2	0.6	13.9
54	I. K.	33 m	"	"	1.1	10.7	0.6	12.4
55	T. O.	55 m	Chronic "	"	2.7	8.1	1.7	12.5
56	S. T.	64 m	Acute "	"	3.2	7.0	3.9	14.1
57	O. Y.	35 m	Chronic "	"	0	12.7	1.4	14.1
58	U. S.	45 m	"	"	3.4	19.1	3.3	25.8
59	M. I.	27 m	"	"	4.9	15.0	7.1	27.0
60	T. T.	23 m	"	"	6.9	4.6	0.4	11.9
61	Te. H.	52 f	"	"	1.0	19.5	4.0	24.5
62	H. H.	36 m	"	"	0.3	10.4	1.7	12.4

Range: 8.4—27.0; mean: 16.1

gastric mucosa as observed by the the gastrocamera. Accordingly, the findings may not necessarily be identical with the histologic changes as revealed by gastric suction biopsy or with the results obtained by gastroscopy. At any rate, gastric atrophy thus diagnosed by the present author was divided into three grades, slight, moderate and severe, according to Schindler's classification of chronic atrophic gastritis which was made on the basis of (a) the discoloration of the mucosa, (b) the thinning of the mucosa, and (c) the appearance of blood vessels (26). The group of severe atrophy includes three patients with Addisonian pernicious anemia.

Thus, Schilling's urinary excretion test was carried out in 24 cases of gastric atrophy consisting of 8 cases of slight, 10 moderate and 6 severe atrophy. As shown in Table IV, it was confirmed that all the cases of slight and moderate atrophy excreted normal amounts of the radioactivity in the urine, whereas urinary radioactivity in three cases of pernicious anemia with severe gastric atrophy was

TABLE IV
Urinary Excretions of Orally Administered Co⁶⁰-B₁₂ in Gastric Atrophy

Case No.	Patient	Age	Sex	Degree of atrophy	B ₁₂ oral dose	Urinary excretions in hours					Total urinary excretions
						0-4	4-8	8-12	12-16	16-24	
					μ g				per cent		per cent
88	S. T.	48	f	Slight	0.5		4.9		8.0	0.7	13.6
89	M. I.	64	m	"	"		2.3		5.5	0.6	8.4
90	I. K.	33	m	"	"		1.1		10.7	0.6	12.4
91	Y. Y.	21	m	"	"		0.3		9.2	0.4	9.9
92	S. M.	39	m	"	"		2.5		5.9	0.6	9.0
93	Y. M.	30	f	"	"		7.7		12.1	0.7	20.5
94	S. F.	72	m	"	"		5.4		9.8	2.4	17.6
95	T. T.	23	m	"	"		6.9		4.6	0.4	11.9
96	Sh. T.	64	m	Moderate	"		0.5		5.5	2.9	8.9
97	Ki. T.	39	f	"	"	0.3	4.0	3.4	3.3	0	11.0
98	T. K.	43	m	"	"		2.6		6.6	1.0	10.2
99	T. O.	55	m	"	"		2.7		8.1	1.7	12.5
100	H. H.	53	m	"	"	0.8	2.6	2.0	0.8	0	6.2
101	I. S.	37	m	"	"	0.4	5.4	4.9	1.9	2.1	14.7
102	K. H.	74	m	"	"	0.2	0.7	2.1	3.1	0.8	6.9
103	C. A.	56	f	"	"		5.2		13.9	3.2	22.3
104	S. O.	57	f	"	"		2.2		7.1	2.9	12.2
105	H. S.	52	f	"	"		6.5		14.4	3.6	24.5
106	T. H.	36	m	Severe	0.5		0.3		10.4	1.7	12.4
22	T. N.	46	f	" (PA)	"	0	0.4	0.5	0.2	0	1.1
21	T. K.	33	m	" (PA)	"	0	0	0	0	0	0
75	T. Ka.	61	m	" (PA)	"	0	0	0	0	0	0
107	A. M.	26	m	"	"		11.4		12.1	2.5	26.0
108	M. M.	48	m	"	"		3.9		14.3	2.4	20.6

Atrophic lesion of the gastric mucosa was classified according to the degree of the lesion observed by gastrocamera technique.

PA, pernicious anemia.

none or very little, unless hog intrinsic factor was added. However, in the remaining three cases of severe atrophy, in whom pernicious anemia is not the underlying disease, normal amounts of the radioactivity were detected in the urine.

In brief, intrinsic factor-secretory function is absolutely well preserved in all the cases of gastric atrophy excluding the three cases of pernicious anemia. This result points out that the atrophic changes in pernicious anemia and those in gastric diseases other than pernicious anemia may be substantially different in nature and the gastrocamera is unable to serve as a means to differentiate the former from the latter, no matter how similar the findings as observed by the gastrocamera technique may be.

DISCUSSION

Castle's hypothesis put forward in 1929 that intrinsic factor secreted into the gastric lumen plays an important role in the intestinal absorption of B₁₂ is generally accepted through a large body of researches over the subsequent years. Now that the stomach is the very source from which intrinsic factor is secreted, it is quite reasonably assumed that gastrectomy, *i. e.*, the removal of the source may result in the decrease of intrinsic factor secretion and impaired B₁₂ absorption. This problem was studied by the author (27) as well as by many workers in the world. However,

few investigations have been made on the influence of gastric diseases upon intrinsic factor secretion. In other word, B₁₂ absorption study has been made only in the stage where gastrectomy had already been achieved, while the absorption on unoperated patients remains almost unclarified, despite the increasing frequency with which the patients with gastric diseases have been encountered and not always operated.

According to the results of Schilling's urinary excretion test, most patients with various gastric diseases could absorb normal amounts of the oral dose. These results indicate that the diseased conditions of the stomach may not involve the secretion of intrinsic factor. Lowenstein (31) studied B₁₂ absorption in patients with peptic ulcer before and after subtotal gastrectomy, and found that impaired B₁₂ absorption was generally unusual before the operation, thus supporting the author's view. Okuda *et al.* (28) claimed in an *in vitro* experiment that normal B₁₂ absorption occurred if the B₁₂-intrinsic factor ratio were kept less than 50 mμg : 0.1 mg or 1 : 2000 on a weight basis. It is very convenient to speculate in the light of this finding that a little amount of intrinsic factor can well serve in promoting the intestinal absorption of physiologic amounts of B₁₂, and the patients tested did not show any impairment of B₁₂ absorption. Nevertheless, a patient with cancer in the cardiac region (Case No. 80, S.T.) did show a slightly impaired B₁₂ absorption. This impairment may be well accounted for by the possibility that the abolished secretion of intrinsic factor from the cardia resulted from the tissue destruction due to cancer thereof. Indeed the main site of production of intrinsic factor is the fundus and body of the stomach, but the cardia is likewise the site to produce the factor, though in a small amount (29, 30). Moreover, it is quite probable to speculate that the cancer of this case might have spread over the other part of the stomach and this condition might have been responsible for the abolished intrinsic factor secretion.

It is a well known fact that atrophic changes of the gastric mucosa are frequently associated with subtotally resected stomach, peptic ulcer, gastric cancer, polyp and gastritis, *etc.* (32, 33) and are responsible for deficient intrinsic factor secretion (2-23). In the present study, all the patients except for pernicious anemia patients, in whom atrophic changes were accompanied by underlying gastric diseases, excreted normal amounts of Co⁶⁰-B₁₂, indicating that there is no involvement of intrinsic factor secretion. However, despite the fact that severe atrophic changes of the gastric mucosa was likewise confirmed with the gastroscope in pernicious anemia patients as well, any radioactivity could not be detected in the urine unless hog intrinsic factor was given together with the oral Co⁶⁰-B₁₂, presenting the evidence that there is abolished intrinsic factor secretion in pernicious anemia. An emphasis, therefore, should be put on the use of gastroscope for detecting the atrophic changes of the mucosa in the interpretation of the above-described discrepancy of the results concerning the positive secretion of intrinsic factor. Glass *et al.* (17) claimed that gastric suction biopsy could contribute more than any other techniques such as gastroscopy to the elimination of misconceptions as to the frequency, symptomatology, and clinical significance of atrophic lesions of the gastric mucosa, reviewing the literatures over the past years that the techniques other than gastric suction biopsy could occasionally give misdiagnosis of gastric atrophic lesions. Siurala *et al.* (22, 23) have also taken up gastric suction biopsy as a more reliable means

for detecting gastric atrophy on the basis of histology. If this is taken into consideration, the name of "gastric atrophy" given by the present author is fallacious and meaningless after all; gastric atrophy has been diagnosed on inadequate grounds in this study. As a matter of fact, the gastrocamera technique is unable to provide any genuine informations on histology of the gastric mucosa, but can only present the superficial findings such as the color or the thinning of the mucosa and the aspect of blood vessels. Accordingly, it is absolutely justifiable to consider that there is a substantial or fundamental difference in the natures of the gastric atrophic changes between pernicious anemia and other gastric diseases, and the difference can not be revealed by gastrocamera technique. Thus it is concluded that gastrocamera technique fails to differentiate the gastric atrophy of pernicious anemia, in which intrinsic factor secretion is abolished, from the similar findings of the mucosa of other gastric diseases, in which the secretion is still preserved. In addition, it seems probable that the combination of gastric suction biopsy with gastrocamera technique could provide a more exact informations on atrophic lesions of the gastric mucosa. Another problem is the relation between the gastric atrophy of pernicious anemia and cancer of the stomach. Pernicious anemia is a rare disease in Japan (34, 35). Instead, cancer of the stomach is said to be frequently associated with atrophic changes of the gastric mucosa and *vice versa* in this country. Yoshida (36), and Setsuda *et al.* (37) reported a case of pernicious anemia associated with cancer of the stomach. Generally speaking, views so far put forward as to the causative relation between pernicious anemia and cancer of the stomach may be classified as follows: (a) there develops primarily cancer of the stomach which may result in deficient intrinsic factor secretion and the deficient output of intrinsic factor may secondarily lead to the development of pernicious anemia, (b) the gastric atrophic changes of pernicious anemia may be the cause of gastric cancer, (c) there may exist some causative factors commonly responsible for the occurrence of both diseases, and (d) both diseases may develop independently, but may coexist in an individual by chance. Today's general acceptance is the third view, a common causative factor view (38—40). As the common factor, there come hereditary influence, chronic gastritis, habitus, achlorhydria, *etc.*

Mosbech (40) reported that many relatives of the parents of pernicious anemia died of cancer. Siurala *et al.* (23) have also reported that the incidence of pernicious anemia and gastric cancer in the relatives of pernicious anemia patients was largely the same as in the patients with severe atrophic gastritis. Kaplan and Rigler (39) stated that pernicious anemia and gastric cancer were combined each other by a common hereditary influence. The hypothesis was once put forward that gastric atrophy as seen in pernicious anemia may be a precancerous state, and in contrast, recent evidences (17, 22, 23) suggest that gastric atrophy or atrophic gastritis as proved by gastric suction biopsy may develop to pernicious anemia in the countries where this disease is not so rare.

At any rate, in view of the low incidence of pernicious anemia and high incidence of gastric cancer in Japan, various possibilities should be taken into consideration; for instance, (a) in Japan, it may be unable to find in the patients the so-called gastric atrophy as seen in other countries, (b) even if such genuine atrophy exists in Japanese patients, the patients with gastric atrophy may be eventually led by

unknown causes to gastric cancer rather than to pernicious anemia, (c) in fact, it is often observed on operation that gastric cancer is accompanied by atrophic gastritis, and this phenomenon is generally interpreted in Japan by the possibility that cancer occurs first and atrophic changes follows, but the latter does not precede the former. After all, the difference in the substantial development of gastric atrophy to pernicious anemia or to gastric cancer between Japanese patients and those of other countries may be ascribable to the species difference. Further investigations are needed for the elucidation of this problem.

SUMMARY

In order to investigate the secretion of intrinsic factor in patients with gastric diseases, intestinal absorption of $\text{Co}^{60}\text{-B}_{12}$ was studied by means of Schilling's urinary excretion test. Additional study was made as well on the relation between intrinsic factor secretion and the findings of the gastric mucosa as observed by gastroscope.

1. Intrinsic factor secretion was well preserved in all the patients with gastric cancer, polyp, ulcer and gastritis, with only one exceptional case of cancer. Thus it was suggested that these gastric diseases did not necessarily involve the intrinsic factor secretion.

2. The exception was a case of cancer of the cardia. A slight decrease of intrinsic factor secretion was noted in this case. But the decreased output of intrinsic factor may have resulted from the tissue destruction of the cardia due to cancer. The possible spread of the cancer over other part of the stomach may account for the decrease as well.

3. For detecting the atrophic changes of the gastric mucosa, gastroscope was employed in this study. But because of its inability to differentiate gastric atrophy of pernicious anemia from the similar findings of other gastric diseases, the interpretation of whether intrinsic factor secretion is preserved or not was sometimes confused. That is, in all the patients with various gastric diseases, in whom gastric atrophic changes were observed, urinary excretions were within the normal range, while three pernicious anemia patients could not excrete normal amounts of radioactivity in the urine unless hog intrinsic factor was added.

4. Some comments were made on the significance of the diagnosis of gastric atrophy as made by gastroscope technique.

5. Additional discussions were made on the relation between gastric atrophy and pernicious anemia or gastric cancer. However, further studies are needed for the clarification of the problem.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Professor Gyoichi Wakisaka for his constant interest and helpful guidance in this study. Grateful acknowledgement is also given to Assistant Professor Eisuke Katsura and Instructor Haruto Uchino for their careful criticism and useful comments. The author is deeply indebted to Dr. Nathaniel Ritter, Merck and Co., U. S. A., for his kind supply of Co^{60} -labeled vitamin B_{12} , and also to Dr. Kenneth Thompson, Organon Inc., U. S. A., for his generous supply of hog intrinsic factor, "Bifactor". To the

authoritative officers of Takeda Chemicals Co., Ltd., Osaka, the author greatly appreciate their kind supply of "Fresmin", non-radioactive vitamin B₁₂. This study was carried out in part by a grant-in-aid for scientific research from the Educational Ministry of Japan.

REFERENCES

1. Castle, W. B., *New England J. Med.* **249**, 603 (1953).
2. Brown, M. R., *ibid* **210**, 473 (1934).
3. Cox, A. J., *Am. J. Path.* **19**, 491 (1943).
4. Magnus, H. A., and Ungley, C. C., *Lancet* **1**, 420 (1938).
5. Meulengracht, E., *Am. J. Med. Sci.* **197**, 201 (1939).
6. Meyers, W. C., *Gastroenterology* **10**, 923 (1948).
7. Motteram, R. J., *J. Path. Bact.* **63**, 389 (1951).
8. Siurala, M., *Acta Med. Scand. Suppl.* **151**, (1954).
9. Finckh, E. S., and Wood, L. J., *Gastroenterology* **25**, 48 (1953).
10. Murphy, W. P., *J. Amer. Med. Assoc.* **149**, 907 (1952).
11. Ungley, C. C., *Gastroenterologia* **79**, 338 (1953).
12. Badenoch, J., *Proc. Roy. Soc. Med.* **47**, 426 (1954).
13. Badenoch, J., Evans, J. R., Richards, W. C. D., and Witts, L. J., *Brit. J. Haemat.* **1**, 339 (1955).
14. Callender, S. T., and Denborough, M. A., *ibid.* **3**, 88 (1957).
15. Gerner, G., and Henning, N., *Gastroenterology* **30**, 37 (1956).
16. Glass, G. B. J., *ibid.* **30**, 37 (1956).
17. Glass, G. B. J., Speer, F. D., Xieburgs, H. E., Ishimori, A., Jones, E. L., Baker, H., Schwarwarth, S. A., and Smith, R., *ibid.* **39**, 429 (1960).
18. Gräsbeck, R., and Siurala, M., *Acta Med. Scand.* **161**, 181 (1958).
19. Klayman, M. I., and Brandborg, L., *New England J. Med.* **253**, 808 (1955).
20. MacLean, L. D., *Gastroenterology* **29**, 653 (1955).
21. Mollin, D. L., Booth, C. C., and Baker, S. J., *Brit. J. Haemat.* **3**, 412 (1957).
22. Siurala, M., and Nyberg, W., *Acta Med. Scand.* **157**, 436 (1957).
23. Siurala, M., Erämaa, E., and Nyberg, W., *ibid.* **166**, 213 (1960).
24. Schilling, R. F., *J. Lab. Clin. Med.* **42**, 860 (1953).
25. Ukyo, S., *J. Vitaminol.* (Report I) (1962).
26. Schindler, R., *Gastroscopy: The Endoscopic Study of Gastric Pathology*, Second Edition, p. 225, The University of Chicago Press, Chicago, Illinois, U. S. A.
27. Ukyo, S., *J. Vitaminol.* (Report II) (1962).
28. Okuda, K., Wider, J. A., and Chow, B. F., *J. Lab. Clin. Med.* **54**, 535 (1959).
29. Ungley, C. C., and Moffett, R., *Lancet* **230**, 1232 (1936).
30. Fox, H. J., and Castle, W. B., *Am. J. Med. Sci.* **203**, 18 (1942).
31. Lowenstein, F., *Blood* **13**, 339 (1958).
32. Ricketts, W. E., Kirsner, J. B., and Palmer, W. L., *Am. J. Med. Sci.* **217**, 542 (1949).
33. Cromer, H. E., Jr., Comfort, M. W., and Butt, H. R., *J. Nat. Cancer Inst.* **10**, 505 (1949).
34. Otsuka, S., Okiishi, Y., Naruto, K., and Kumai, K., *Saishin Igaku* **11**, 952 (1956).
35. Wakisaka, G., Uchino, H., Ukyo, S., Akazawa, Y., Yamamoto, S., Ando, H., Sotobayashi, H., and Adachi, A., *Naika* **6**, 12 (1960).
36. Yoshida, Y., *Nagoya Igaku-Kai Zasshi* **44**, 1192 (1936).
37. Setsuda, T., Takayama, H., Tsunoda, O., Tsuda, H., Komatsu, S., and Murakami, H., *Jap. Arch. Int. Med.* (Japanese) **2**, 711 (1955).
38. Jener, A. W. F., *Acta Med. Scand.* **102**, 529 (1939).
39. Kaplan, H. S., and Rigler, L. G., *J. Amer. Med. Assoc.*, **128**, 426 (1945).
40. Mosbech, J., *Acta Med. Scand.* **148**, 310 (1954).