Special Articles

Clinical Studies on Gastric Juice Secretion

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In carrying out clinical studies of gastric secretion, several directions of study can be enumerated, including studies of central (cerebral, psychogenic, and neural) and local (neural, humoral, and organic) secretory mechanisms and on endocrinological changes in connection with the concept of "stress ulcer" of Gray (1951).

Although the above-mentioned ways of studies are naturally closely associated with each other, the present studies were mainly directed to the systematic observations of gastric juice components in regard to non-parietal cell secretions, on which little clinical knowledges have been obtained so far, as compared to those of HCl secretion, the "singular physiological entity" (Hollander, 1932, 1952) of the parietal cell secretion. Analyses of pathological components in gastric juices resulting from pathological changes of gastric juice secretion were also carried out.

Before starting the studies, methods of gastric stimulation which serve the above purposes were scrutinized, and several useful methods were devised for testing gastric secretion. In the course of a study on basal secretion in miscellaneous diseases, remarkable changes were found especially in diabetes mellitus, diabetes insipidus and in several other disorders. These will be presented at the same time.

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1. Examination of methods for systematic observation of gastric secretory function—with special reference to methods of secretory stimulation

To obtain as much physiological secretion as possible, the list of gastric secretory stimulation methods utilized so far has mainly consisted of oral stimulation methods including Ewald-Boas's test meal, caffeine (Katsch-Kalk), and alcohol. These methods, however, have their limitations in simultaneous examination of various secretory components, because the fluid, test meal, or the drugs

themselves prevent the exact analyses. The present study, therefore, has started from a comparison of parenteral stimulation methods including histamine, histalog, insulin, and carnitine.

Secretory stimulation mechanism exerted by histamine or histalog naturally differs from that exerted by insulin. Thus polarographic protein wave activity and mucoprotein concentration will often decrease when secretion volume exceeds 20 ml./15 min. in the case of the former stimulation, while in the case of the latter stimulation they are roughly parallel to the secretion volume. This difference may be attributed to the "wash out effect" (Björkman) due to the effect of histamine which enhances the secretion rate of fluid. Such an effect is not encountered in the case of insulin stimulation.

Fig. 1a~c. Correlation diagrams of each constituent and S. V. R.

(a) acidity and S. V. R.

Histalog shows much stronger stimulatory effect on parietal cell secretion with less side effects than histamine. Carnitine, though less effective, also acts as a secretory stimulator.

Results of examination of various doses of histamine hydrochloride (H) led to the recommendation of 1.0 mg subcutaneous injection method to be suitable for the general screening test of Japanese, as doses exceeding 0.03 mg./kg. body weight will be accompanied by side effects, and is devoid of the above-mentioned parallelism of the secretory components. The side effects, however, are almost completely eliminated by the method of Kay (1953) who utilized anti-histaminic drugs, although the wash out effect is unavoidable when histamine dosage exceeds 0.4 mg./10 kg. body weight.

In the present report will be presented three methods for the examination of gastric secretory function, of which it is still almost unable to point out any reports of clinical application, although basic studies including animal experiments are already at hand.

One is the method in which secreted constituents are observed correlatively with secretion volume rate (SVR), after careful aspirations of gastric juice specimens at intervals of every 2 to 3 minutes (this intermittent aspiration is better than continuous aspiration owing to an unknown reason) after subcutaneous injection of H.

(b) peptic activity and S. V. R.

(c) electrolyte concentration and S. V. R.

(Fig. 1-a, b, and c).

The acidity apparently has a high linear correlation to SVR, indicating the same secretory origin of fluid and HCl, as well as the functional status of the two secretory components.

A relative decline of peptic activity (Anson) is observed when SVR exceeds 20 ml/15 min. Similar phenomenon is observed in con-

centration of mucoprotein (Glass, 1949).

In correlation diagrams of electrolytes and SVR, an antipodal mode of correlation is observed between Na^+ and basic Cl, statistically significant inverse correlation and correlation, respectively, being found, both of which coincide with the linear correlation between HCl concentration and SVR.

The second method of observation consists of repeated subcutaneous injections of a small dosage of H. at short intervals (0.15 mg. every 10 min.). Fundamental studies of this method have already been reported by Hollander (1956, 1960).

Fig. 2a~b. Repeated histamine stimulation method.

(a)

After 5 to 6 injections (at about 1 hr. after the first injection), constancies of concentrations of acid and electrolytes (*inter alia* Cl^- and Na^+) are obtained regardless of fluctuations of SVR, and the method proves itself to be more accurate than the method of a single H. injection. No clear-cut constancy is obtained even with this method in the case of peptic activity and mucoprotein. No side effect is encountered even when the number of injections is increased, and the constancy of SVR is finally obtained. As is indicated in the figure, this method is especially useful to deduce the pathological changes of the gastric mucosa (and especially the functional status of parietal cells and other components of the gland)

(b)

(Fig. 2-a, b).

The third method consists of vector-diagrammatic observations of the data obtained by the second method. As are indicated in Fig. 3-a, b and c, secretion volumes and the acidities are plotted in regions confronting on a diagonal line between each other, and a locus of intersecting points of the two values at given time points

Fig. 3a~c. Vector secretion diagram.

are found. The vector diagram thus obtained indicates a simple pattern in cases of normal controls, while it is remarkably extended and expanded in conditions with enhanced secretory function (e.g., peptic ulcer) and is remarkably compressed in conditions with lowered secretory function (e.g., atrophic gastritis and diabetes mellitus). Thus a glimpse of the diagram may suffice the differentiation of conditions of gastric secretory function.

2. On basal secretion

Although many reports can be found in respect to basal secretion of peptic ulcer, there is only a few limited number of reports on basal secretion in other diseases. This was studied with reference to nocturnal basal secretion and it was found that the highest secretion volume was that of a case of diabetes insipidus, in which result of Carter-Robbins test indicated the effect of pitressin upon gastric secretion volume in coincidence with the effect upon urinary volume.

Findings of special interests were encountered in several metabolic and endocrine diseases including diabetes mellitus and myxedema, both of which being characterized with exceedingly small secretion volumes. Patients with Addison's syndrome seemed to have variable amounts of secretion volumes, but most cases studied belonged to hyper-secretion group. Volumes in Fig. 4-a are those

Fig. 4a~b. Nocturnal gastric juice secretion.

(a) volumes aspirated at 1 hr. intervals and the distribution of incidences (%)

observed by aspirating every 30 or 60 minutes and are therefore smaller than those reported by others. Hydrochloric acid secretions in these cases were in complete agreement with secretion volumes as far as the nocturnal basal secretions are concerned.

Curves of secretion volume indicated fluctuations repeating at intervals of about 2 hours, and an over-all decrease of secretion during hours from midnight to the early morning.

(b) changes of blood sugar level of rabbit after injection of G. J.

This fluctuation is independent of blood sugar levels, but a close correlation between basal secretion and the sensitivity of autonomic nervous system was clearly demonstrated by studying the correlation between secretion volume and insulin sensitivity (Kuzuya, 1953) or adrenalin blood sugar curve (Barok, 1931).

When a direct elevation of blood sugar was achieved by continuous intravenous infusion of glucose, an undoubted decline of gastric juice secretion was obtained, and when the patient was forced to suffer the resulting urge of urination, an increase of secretion was obtained. It is conjectured that this indicates a compensatory regulation of water and sugar metabolism through homeostatic mechanism of the body via gastric secretion, in addition to the parasympathetic stimulation resulting from the impulse of urge of urination.

As Sutherland (1948) has extracted a glucagon-like substance from gastric mucosa, a hypothesis was given that a factor inducing the elevation of blood sugar level might exist in gastric juice. Gastric juice of patients with diabetes mellitus exerted a significant blood sugar elevation when injected intravenously to rabbits. This effective factor was recovered from the visible mucus fraction of gastric juice (Fig. 4-b).

Possible participation of non-specific stimulation was thoroughly

scrutinized, and diabetic gastric juice was found to have activity at least somewhat stronger than the activity of normal gastric juice.

3. On hydrochloric acid secretion

As so many reports on hydrochloric acid secretion are already at hand, the present study was carried out in three additional ways. In the first step, symptomless achlorhydria after injection of H. (0.5-1.0 mg.) was studied by observing the incidence of achlorhydria in mass screening medical examination. A part of 485 subjects of over 40 years of age were studied with tubeless method, and intubation methods were used for the other part of the subjects. Incidence of achlorhydria by the former method was as high as 42%, nearly half of which indicated evidence of acid secretion when the second examination was done by the use of intubation method. On the other hand, among 391 subjects who were studied by intubation method in the first examination, the incidence of achlorhydria was 24%. It may therefore be concluded that the incidence of achlorhydria in this study was as high as about 20%. It may partly result from possible co-existence of subjects who are with more or less conscious gastric symptoms. These achlorhydric subjects were further subjected to close examination, and gastro-camera study revealed atrophic gastritis in 17 case (16.5%), and chronic ulcer in 3 cases. A finding which merit attention was that 14 cases (13.6%) had diabetes mellitus.

The second step of study was a follow-up observation of 208 cases who had been diagnosed as having hypo- or achlorhydria during seven years since 1954. Japanese literatures contain few reports of this type of study, although there are several at hand in other countries including that of Bloomfield & Pollard (1935). None of the 208 cases indicated conversion to normo- or hyperchlorhydria, and 12% were found to be converted from the earlier hypochlorhydria into achlorhydria. Furthermore, a recent survey disclosed four deaths (including one from gastric carcinoma) out of the whole cases, and 59% had gastrointestinal symptom of some kind or other.

Another group of 147 subjects was found to contain 32 cases of

achlorhydria by histamine 1 mg. test, and complete apeptic achlorhydria was found in 4 (11.1%) of them when peptic activity of gastric juice was examined with Anson's method. Close re-examination of the four cases disclosed that 3 of them had atrophic gastritis, and the remaining one had gastric ulcer complicated with atrophic gastritis.

It is concluded that the significance of the screening test by the use of 1 mg. histamine method is great, at least when subjects of over 40 years of age are concerned.

The third step of study was a comparison of gastric secretory function between Japanese and American subjects. Although it is still on the stage of interim report, result of a comparison between data of 276 American subjects and those of this institute indicated that American subjects are generally characterized with higher volume and acid secretory functions in all diagnostic classifications except atrophic gastritis and gastric ulcer. Although it is premature to give conclusive remarks as the survey was limited to a small number of cases selected from localized areas as California and Hokkaido, environmental and constitutional conditions must be borne in mind.

4. On enzyme secretion

When peptic activities of gastric juice specimens classified under diagnoses were studied by the use of Anson's method, correlations with acidity and with secretion volume were demonstrated as were already reported by many authors, and no characteristic which is specific for each diagnostic criterion was demonstrated.

Taylor (1959, 1960) however reported that diversity of proteolytic activity of gastric juice was demonstrable when peptic activity was measured with albumin substrate and with pH conditions corrected in several values between 1 and 5. This was re-examined in diseases of the stomach, and it was reaffirmed that specimens from control and ulcer subjects were characterized with 3 to 4 peaks of activity with the maximum peak in each case at a low pH value. In atrophic gastritis, essential hypochromic anemia and in gastric carcinoma, the number of peaks and the degree of activity

in each case were reduced, and the optimal pH value was often higher than that of the control specimen. This phenomenon was compared with rennin activity and it was found that the latter activity had an apparent correlation with proteolytic activity at pH values above 4, while no correlation was found between rennin activity and proteolytic activity at pH values under 3.5. Further enzymological study will be needed to determine whether the two enzyme activities are exerted by a single enzyme or by different enzymes, and to elucidate the nature of proteolytic activity of gastric juice.

Continuous paper electrophoretic fractionation of lyophilized specimen demonstrated a sharp separation of peptic activity into two fractions in the anodic component, while cation exchange resin chromatography of the same specimen demonstrated a broad elution band of the activity in the acidic fraction.

These results may coincide with the demonstration of the above-mentioned diversity of peptic activity. However, when crossing electrophoresis was carried out using gastric juice and commercial pepsin, interaction of materials was demonstrated exclusively between the utmost anodic fraction and commercial pepsin. When paper electrophoresis was carried out using a mixture of gastric juice and commercial pepsin, the electrophoretic mobility of the utmost anodic fraction of gastric juice was apparently enhanced. These results indicate that the main peptic activity of gastric juice is contained in the anodic fraction.

Lysozyme titers were relatively high in chronic gastritis and in gastric carcinoma, and a decline of activity was found to occur after application of secretory stimulation. Lysozyme titer has an inverse correlation with secretion volume rate, and also has a significant inverse correlation with the acidity of the specimen. Correlations were demonstrated between lysozyme titer and both of visible mucus volume (estimated as relative volumes of gastric secretion) and viscosity of the soluble fraction of gastric juice. These results indicate that lysozyme is a non-secretory, biologically active substance which has a close connection with changes of gastric mucosa, and diagnostic significance is thus speculated.

5. On electrolyte secretion

Stimulation of gastric secretion results in a decline of Na^+ and an increase of Cl^- . K^+ was found to increase slightly and Ca^{++} to decrease, although the last two tendencies were less significant. As was already mentioned, electrolyte concentrations have similar tendencies both when observed in relation to the secretion volume rate and after repeated histamine stimulations. Accurate information of hydrochloric acid secretory function is therefore to be expected only when systematic observations of results of the above various methods are achieved.

6. On 17-ketosteroid

Zicha (1960) reported on gastric secretion of corticoid and 17-ketosteroid, to which a part of the present report has dedicated itself. Although accurate determination of absolute secretory output of 17-ketosteroid is impossible, it was found to increase after secretory stimulation with histamine, and it was also found that the highest gastric excretion for male and female subjects were encountered in 20-39 and 20-29 years of age, respectively. Among disease of the stomach, gastric atony was found to be accompanied with lower 17-ketosteroid levels in gastric juice as compared with those of healthy controls, while most of other gastric diseases were found to have elevated levels. The decrease in case of gastric atony is an interesting observation, and may be a characteristic which indicates a side of pathological endocrine function of this condition. Remarkably low levels were encountered in cases where continued cortisone therapy was applied, and also in cases with Addison's syndrome. It may be possible to speculate that 17-ketosteroid in gastric juice is adrenal dependent, although the coefficient of correlation was not examined because determination of absolute output of 17-ketosteroid into the stomach was impossible.

7. On visible mucus

Considerable difficulties are encountered in the determination of visible mucus when the method of Wolf (1948) and Glass (1953),

which utilize tyrosine estimation after alkaline hydrolysis, are used. In the present study, therefore, the amount of visible mucus was expressed in terms of per cent volume of total gastric juice, aspirated after rinse of the stomach. A trial was also made to determine the relative concentrations of components by the use of Dische's (1960) partial hydrolysis with trichloroacetic acid. The amount of visible mucus naturally increases in relation with morbid changes of gastric mucosa and a finding which merit attention was an astonishing decrease in cases where continued cortisone therapy had been applied. This may be another evidence of participation of side effect of cortisone in the causation of disorders of the stomach. An even more interesting finding was that gastric carcinoma was accompanied by strongly increased sialic acid, while diabetes mellitus was characterized with increases of hexose and hexosamine, when relative concentrations of components were determined with the present methods.

Miller and Dunber (1933) reported that the viscosity of mucus will be maximum at its isoelectric point. This phenomenon was applied in the analysis of visible mucus which had been pooled under different diagnoses. The alteration of relative viscosity resulting from the change in acidity was investigated, and differences of pH value, and the rate of increase of relative viscosity, at the isoelectric point were clearly demonstrated to occur between different diseases (Fig. 5-a, b). It is conjectured that there is a disparity of the relative concentrations of acid, isoelectric and alkaline mucinates between various conditions of the stomach, and that the disparity in one way or another has a connection with the aforementioned differences of relative concentrations of the chemical components. Inhibition of the increase of viscosity at the isoelectric point of course indicates the decline of defence mechanism of mucosa. On the other hand, when acid-binding capacity of mucus was titrimetrically determined, similar disparity between diseases, and between samples, was demonstrated. Although disease-specificity is difficult to be demonstrated, since the samples used were pooled specimens, disparity of chemical defence mechanism is thus evidenced.

Fig. 5a~b. Change of Natures of Visible Mucus in Several Gastric Diseases.

(a) change of viscosities by pH correction

(b) acid binding capacities

8. On secretion of soluble protein

Soluble fraction of gastric juice was assayed for tyrosine (Folin method), protein-bound hexose (orcinol method), hexosamine (Elson-Morgan method) and sialic acid (Svennerholm method). It was found that all of these components were generally elevated in gastric carcinoma and in chronic gastritis, and the values were in inverse correlation with the acidities of gastric juice.

Components other than hexosamine, and in a limited number of cases those other than hexose and hexosamine, roughly paralleled the

secretion volume rate in control subjects and in peptic ulcer cases. However, in low secretion group, which covered gastric carcinoma, gastritis and diabetes mellitus, the values were distributed in narrow regions with lower secretion volume rate. Since, therefore, the values represent two or more components including physiological secretory, in addition to pathologically enhanced, ingredients, it is almost impossible to utilize the individual value for the diagnosis of diseases of the stomach, even if conditions such as gastric carcinoma was found to be characterized with high values.

With respect to gastric juice mucoprotein (Mp), many reports have been presented by Glass (1948-1961), who holds an opinion that among three main fractions of gastric juice, glandular Mp is the only secretory component. In the present report, correlation of Mp with secretion volume rate, and the levels of Mp after repeated histamine stimulations, were studied, and a remarkable secretory response was found in controls and in subjects with hypersecretory conditions, whereas hypochlorhydric, hyposecretory group was found to show a different secretory response when studied with the same method, indicating the necessity of methodological re-examination.

The difference between physiological and pathological Mp was also clearly demonstrated by the use of electrophoretic examination of isolated fractions (Fig. 6), indicating the necessity of pH correction of the starting materials in carrying out the chemical fractionation procedures. It was also demonstrated that the supernatant fraction of trichloroacetic acid and acetone treatments (F_5) has a greater diagnostic value in gastric carcinoma, in which many substances of diagnostic value, e. g., sialic acid and substances responsible to diphenylamine reaction, were recovered from this fraction.

In addition to the above, polarographic protein wave of individual specimen was studied, together with electrophoresis in various buffers and with various supporting media. These, however, are only indirectly related with the present study and will be omitted.

In collaboration with Drs. Carpenter and Heiskell of University of California at Los Angeles and with Drs. Stempien and Dagradi of Long Beach Veterans Administration Hospital of the U. S. A., applicability of the immunochemical techniques for the analyses of gastric juice was investigated. Immunological differentiation and

Fig. 6. Electrophoregrams of mucoprotein and mucoprotease (Glass-Boyd).

characterization between secretory protein moiety of the stomach and contaminating protein moieties originated from sources other than stomach mucosa were attended, and the diagnostic value of the method was studied.

The results of gel-diffusion precipitation (GDP) with antisera against human whole serum, crystalline albumin and against gamma-globulin have demonstrated incidence of serum protein contamination in gastric juices obtained from cases with carcinoma of the stomach and with atrophic gastritis to be as high as 77% and 64.5%, respectively.

Table 1. Incidence of Serum Protein Contamination in G. J. by G. D. P.

Diagnosis	No. of cases	Incidence of positive serum protein			Negative reaction
		(+)	(+)	sum	
Gastric carcinoma	26	10 (38.5)	10 (38.5)	20 (77.0)	6 (23.0)
Chronic gastritis	31	13 (42.0)	7 (22.5)	20 (64.5)	11 (35.5)
Gastric ulcer	20	1 (5.0)	2 (10.0)	3 (15.0)	17 (85.0)
Duodenal ulcer	34	1 (2.9)	6 (17.6)	7 (20.5)	27 (79.5)
Others	17	0 (0)	0 (0)	0 (0)	17 (100)

The amount of serum protein detected in each sample apparently lacked correlation with the degree of hemorrhages tested with benzidine reaction. Inverse correlations were found between the degree of serum protein contamination and either of acidity or secretion volume.

The highest serum content found in native gastric juice was estimated to be over 1 gm. % with immune diffusion technique.

Patterns of immunoelectrophoresis of gastric juices with anti-human serum agreed with the results of the above gel-diffusion precipitation. When gastric juice specimens with weak GDP reaction were tested, only trace amounts of albumin and of gamma-globulin could be detected. The numbers and intensities of precipitating lines increased with the degree of GDP reaction, and in extreme cases such as atrophic gastritis, six to eight precipitation lines, including intense lines of albumin and gamma-globulin, together with faint lines of orosomucoid, alpha₂-globulins, ceruloplasmin, transferrin and of beta-globulins, were found.

Specific antiserum against gastric juice was also allowed to react with various gastric juice specimens. Although there is considerable variability in these patterns, main components of gastric juice protein were found to appear between beta- and gamma-globulin positions, and these components differed antigenically between acidic and anacidic samples. Studies on the incidence of this component and its specificity to certain pathologic changes of gastric mucosa are in progress.

The same samples were simultaneously subjected to the ultracentrifugal analysis. Specimens obtained from cases with gastric car-

cinoma and with atrophic gastritis showed presence of serum protein peaks and of gastric juice protein peaks, the latter being different in S values from the former. On the contrary, most of the ulcer specimens failed to show any sedimenting peak and only the specimen with positive GDP reaction developed a small peak with S value of 9.7.

It is therefore apparent that serum protein does appear in a considerable percentage of the gastric juice specimens, especially in cases with atrophic gastritis and with carcinoma of the stomach.

9. On contamination of gastric juice with serum protein

A newly found evidence of existence of serum protein in gastric juice has attracted general attention recently, and Wetterfors (1960) reported clinical findings in gastric ulcer and in gastric carcinoma. The present author also studied this problem utilizing I^{131} -albumin technique. Control subjects and patients, who had been treated with iodine to saturate the thyroid gland, were given $50\mu\text{c}$ of I^{131} -albumin (RISA) intravenously after rinsing the stomach with phosphate buffer (pH 7.2, $\mu=0.1$) to neutralize the gastric juice. Post-injection specimens of gastric juice, which were also neutralized and aspirated continuously, were collected and total I^{131} , PBI^{131} and free I^{131} were determined. Total albumin excretion was calculated from the above data corrected with secretion volumes. Total circulating plasma volume, urinary I^{131} output, I^{131} -albumin turnover rate and I^{131} thyroidal uptake were estimated simultaneously.

(1) Intragastric I^{131} -albumin excretion rate

Both PBI^{131} and free I^{131} in gastric juices reached their maxima 40 to 60 minutes after stimulation with 1 mg. histamine, followed by gradual declines. Very small amounts of radioactivity were detected in control specimens, while the activity in atrophic gastritis with metaplasia showed the peak excretion level as high as above 1,500 cpm, and the value in gastric ulcer was around 500 cpm.

The ratio PBI^{131} versus total I^{131} in each case, which reached a constant level after about 40 minutes, was between 40 and 70 per cent. The mean value of calculated 24 hour excretion of PBI^{131} was 3 per cent of the tracer dose in this experiment. However, the

Fig. 7a~b. Assays of excretion of intravenously injected I^{131} albumin into gastric juice. (a) radioactivities (CPM) of PBI^{131} and free I^{131} in G. J.

above value is a calculation from the post-stimulation data, and practically it will be much smaller in ordinary conditions. There was no correlation between circulating plasma volume and estimated intragastric albumin excretion. Mean turnover rate was 16.3 gm./day, which was roughly equivalent to the report of Starling (1951), in which mean normal value was 16 gm./day. From circulating plasma albumin and estimated PBI^{131} excretion rate, 24 hour intragastric excretion of albumin was calculated to be 4.8 gm. In agreement with the results of gel-diffusion precipitation, most of cases with high intragastric albumin excretion had atrophic gastritis. However, there was no definite correlation between urinary I^{131} excretion and

(b) radioactivity of total I¹³¹ and excretion ratio of I¹³¹ in G. J.

intragastric I¹³¹ excretion. When lyophilized gastric juice specimens were fractionated with Pevecon C-870 block electrophoresis and the radioactivities in the fractions were assayed, the highest radioactivity was found in a fraction in which an albumin arc was demonstrated with gel-diffusion precipitation.

(2) Effect of serum contamination of gastric juice upon chemical analyses of the components

The problem coming next is the effect of serum contamination of gastric juice upon chemical analyses of the components. Summarizing up the possible errors in chemical analyses, it was concluded that serum contamination above 0.25% of gastric juice may significantly interfere with the results. It must be borne in mind that in gastric carcinoma and in atrophic gastritis, especially in

histamine refractory achlorhydric specimens, the amount of serum in gastric juice may often exceed the said concentration. However, this is of diagnostic value in itself and, as the results of gel-diffusion precipitation have indicated, control cases and cases with peptic ulcer will by no means accompany contaminations of more than 0.25% albumin. It may be concluded, therefore, that the significance of serum contamination as possible sources of analytical error is not worth due consideration in itself.

10. Conclusion

Clinical concept of gastric juice secretion has so far been liable to be biased towards hydrochloric acid secretion. The present study, therefore, was directed to the systematic observation of the problem covering secretions of other gastric juice components. In the course of the study on basal secretion, secretory abnormalities were demonstrated in several endocrine disorders including diabetes mellitus, and an opinion for this from morbid physiological viewpoints was stated, in which the significance of clinical follow-up observations of histamine refractory achlorhydria was emphasized. For the study of gastric secretory ability, a method which aims the survey of correlation between given component and secretion volume rate was recommended, together with repeated histamine stimulation method and its vector-diagrammatic observations.

In addition, analysis of constituents of protein led to the discussion of changes in gastric juice components which ensue the morbid changes of secretory mechanism. Contamination of gastric juice with serum protein was demonstrated by uses of gel-diffusion precipitation, immunoelectrophoresis and I^{131} -labeled albumin experiments, and the clinical significance of the observation was discussed.