PHARMACOLOGICAL, TOXICOLOGICAL AND CLINICAL DATA OF NEUSILIN, NEUSILIN A

(English translated version, Original in Japanese)

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CONTENTS

INTRODUCTION

Neusilin and Neusilin A have already been highly appraised at home and abroad as excellent antacid and have been used in large quantities as raw materials for gastrointestinal preparations.

Their outstanding remedial virtues are not only featured with being greater in acid consuming capacity, prompt in action and maintaining a pH of 3 to 5 for a long period of time, but also are derived from having an antipeptic action as well as a protective coating action on the gastric mucosa. In 1974, after OTC Drug Review for antacid products by F.D.A. of the United States of America, Neusilin and Neusilin A were considered safe and effective. Furthermore, the results of Drug Review for medical treatment (No. 16) on these substances were officially announced on July 16, 1979 and then its addendum No. 16-2 on March 22, 1980 by the Japanese Government, by which both substances are recognized as safe and effective as antacid.

This time, we prepare the literature by supplementing new data on pharmacological, safety and clinical studies to serve for your reference.

[Indication]
For antacid action and symptomatic improvement for the following diseases:
Gastric and duodenal ulcers, Gastritis (including acute and chronic gastritis, medicine-induced gastritis), Dysfunction of the upper part of the digestive tract (including neurotic anorexia, gastroptosis, hyperacidity).

[Dosage and Administration]
Normally 1.5 - 4 g, t.q.d, orally given for adult as magnesium aluminometasilicate or magnesium alumino silicate.

[Precautions]
1. Must be cautiously administered to the following patients.
a) Patient's with impaired renal function.
b) Patients with impaired cardiac function.
c) Patients of hypermagnesemia.

2. Side effects:
a) Abnormal metabolism - as hypermagnesemia may be caused by a long-term administration, a thorough observation should be made and on observation of abnormality, suitable measures such as decrease of dosage or discontinuance of administration should be taken.
b) Digestive organs - such symptoms as nausea, vomiting, constipation, diarrhea, thirst, etc. may occasionally occur.
c) Others - Itching may occasionally occur.

3. Interaction:
a) As the absorption of the antibiotics belonging to tetracycline will interfere, do not give simultaneously.
b) As the adsorptive action of these substances or rise of pH in the digestive tract and body fluid will affect the absorption and excretion of the combined drugs, administer with care.

Trade name: Magnesium aluminometasilicate/Neusilin
Magnesium aluminosilicate/Neusilin A

PHARMACOLOGICAL STUDIES OF NEUSILIN AND NEUSILIN A

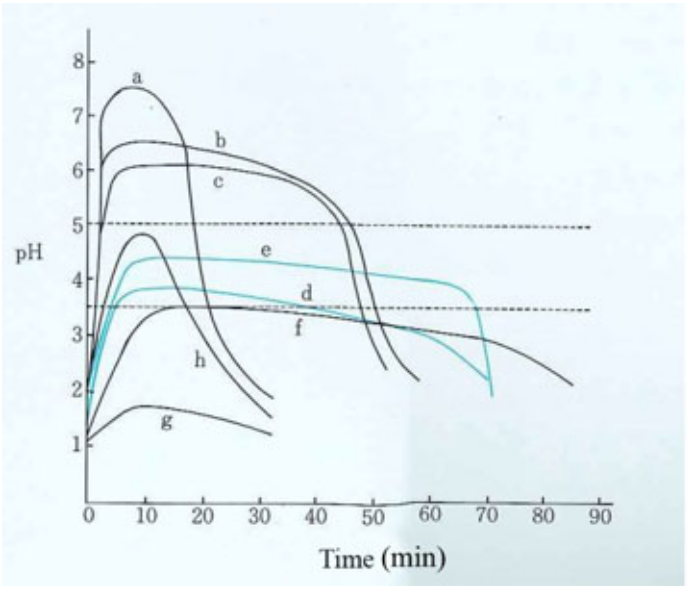
Neusilin (Magnesium aluminometasilicate) and Neusilin A (Magnesium aluminosilicate) are non-absorbent, maintain an optimum pH of gastric juice for long *in vitro* test (Fuchs method) and do not deteriorate with time. Also, in the clinico-pharmacological test (Katsh-Kalk method) the acidity of gastric juice has been proved to be lowered in almost all test cases. Further, as they have an antipeptic action as well as a protective coating action on the gastric mucosa, an apparent inhibitory effect has been observed in the experiment of antiulcer test (ligature of pylorus).

On the other hand, Neusilin and Neusilin A do not cause alkalosis as sodium bicarbonate does. Besides, even if they are given in combination with aspirin or sulfanylamide, they do not affect the absorption of the latter medicinal substances and in case of compounding Neusilin with various kinds of digestive enzymes Neusilin does not inhibit amylase and protease activities.

Acid consuming capacity test

In vitro test: Acid consuming capacity of Neusilin and Neusilin A is respectively not less than 200 ml and 250 ml of O.1N HCl per gram[1,2)]. When examining the acid consuming capacity of Neusilin with Fuchs or its modified method, 1 g of Neusilin neutralizes 0.1N HCl rapidly to pH of over 3 and maintains pH of 3 to 5 for more than 50 to 60 minutes in the simulated gastric fluid *in vitro* tests.
Fuch's curves of various antacids are shown in Fig. 1[3,4,5)]

Fig. 1- Fuchs curve (test substances-1g each)



a. Sodium bicarbonate
b. Magnesium carbonate
c. Precipitated calcium carbonate
d. NEUSILIN
e. NEUSILIN A
f. Dried aluminum hydroxide gel
g. Synthetic aluminum silicate
h. Magnesium silicate

Clinico-pharmacological study

In performing an inspection of gastric juice by Katsh-Kalk method on patients of various diseases, Neusilin or Neusilin A has been administered to them and several experiments have then been performed to compare the gastric acidity prior to and after the administration. As a result, lowering of acidity has been observed in almost all cases.[6,7,8,9,10,11] In the experiment for comparing the acidity by the inspection of histamine-induced gastric juice prior to and after the administration of Neusilin, a sharp decrease has been observed in 5 out of 7 cases and a moderate lowering in one case.[45] Furthermore, when measuring a pH value in the stomach by radio capsule after taking 1 g of Neusilin, the rise of pH has been explicitly observed.

Clinical Study 1 – To study the influence of Neusilin, Neusilin A on acidity of gastric juice and peptic action[10]

Measurement of acidity of gastric juice: By Katsh-Kalk Caffeine method, collect the gastric juice at an interval of 10 minutes for 2 hours and measure.

Measurement of peptic activity: In accordance with Gruetzner's method measure prior to and after the administration of the test solution as well as 1 and 2 hours after the administration respectively.

The result of measuring
(1) Acidity and peptic action of gastric juice prior to the administration of Neusilin
(2) Acidity and peptic activity after administration of Neusilin – (mix 1g of Neusilin in caffeine solution to administer and collect gastric juice) and
(3) Acidity and peptic activity after the consecutive administration of Neusilin for 4 weeks (administered 3 g of Neusilin daily between meals) on 2 cases is shown in Fig. 2 and 3, and the change in acidity of gastric juice and peptic activity after long-term administration is shown in Table 1.

Fig. 2 - Gastric ulcer and Gastroptosis

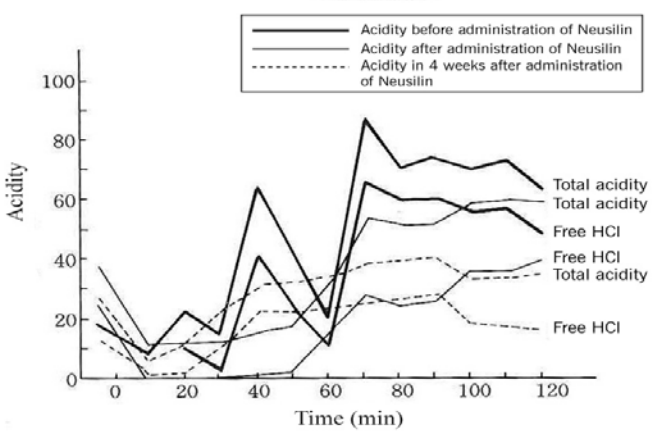


Fig. 3 - Duodenal ulcer

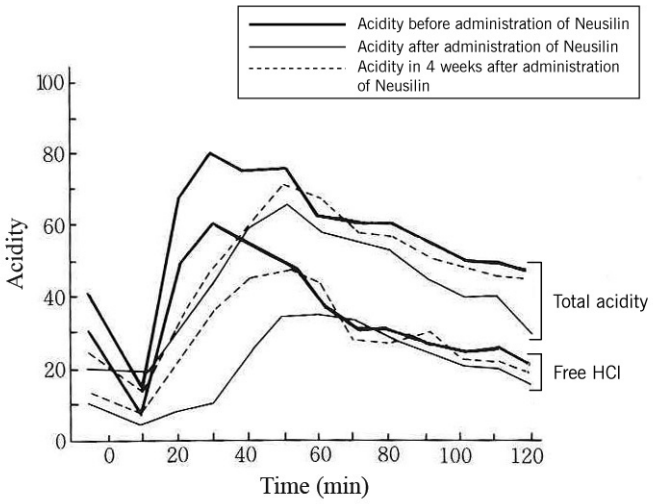


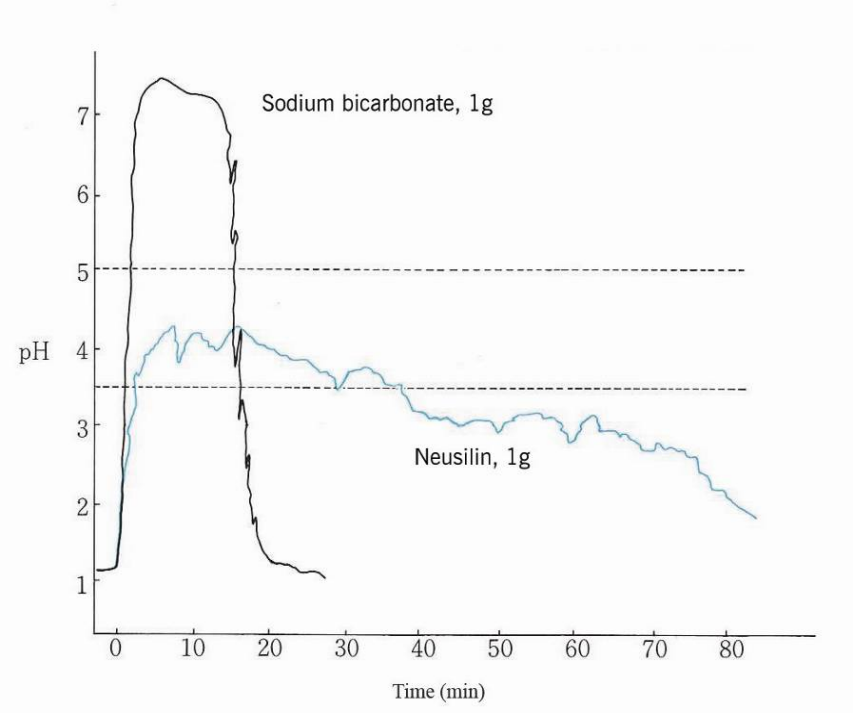
Table 1. Neusilin Long-term administration trials

Case No.	Diseases	Sex	Age	Time of Inspection	Av. Acidity (free HCl)	Total Acidity (Average)	Pepsin (Average)
1	Duodenal Ulcer	M	25	Before administration	35.6	54.3	6829x
				After 84g dosage	35.0	47.8	5120x
2	Gastric Ulcer	F	25	Before administration	33.2	47.6	4266x
				After 84g dosage	22.1	32.9	3413x
3	Chronic gastritis	M	29	Before administration	31.8	50.1	2987x
				After 84g dosage	49.7	61.1	3413x
4	Chronic gastritis and gastroptosis	F	38	Before administration	31.3	45.2	4266x
				After 84g dosage	15.3	28.9	3413x

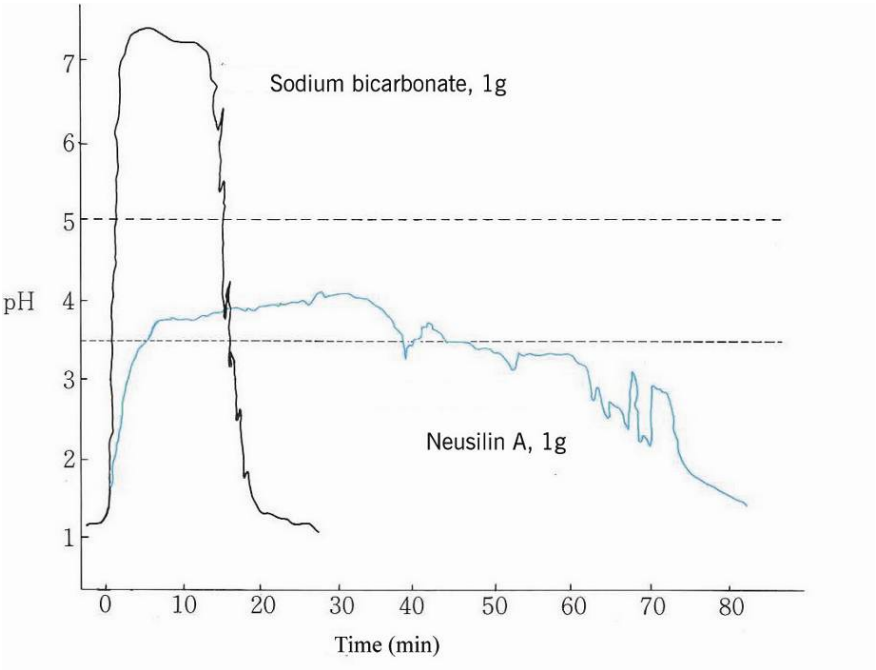
Clinical Study 2 - Measurement of pH in the stomach by radio capsule[12)]

Fig. 4 and 5 are the results of measuring the change of pH in the stomach by radio capsule after administering Neusilin and Neusilin A. It was found that the acid neutralizing action sustains over an extremely long time when compared with sodium bicarbonate.

Fig. 4 - Change of pH in the stomach by the administration of Neusilin



Fig, 5 - Change of pH in the stomach by the administration of Neusilin A



Protective action of gastric mucosa

When comparing the gastric emptying time of barium sulfate in the stomach by taking an X-ray photograph between a combined administration of barium sulfate with Neusilin and a single administration of barium sulfate, it was observed that barium sulfate stayed longer in case of a combined administration with Neusilin, from which it was presumed that Neusilin has a protective action on the gastric mucosa.[12)]

Further, when mixing various antacids with the gastric juice of the patient of gastritis, it was observed that while sodium bicarbonate dissolved the mucus, Neusilin adsorbed the mucus to produce a gelatinous precipitate and became turbid in white, and it was then conceivable that the aforesaid precipitate exerted a protective action on the gastric mucosa.[13)]

Clinical Study 1 - On the influence on the gastric emptying time of barium sulfate in the stomach[12)]

The X-ray photographs were taken from 30 to 120 minutes after administering the test substance obtained by suspending 50 g of barium sulfate in 100 ml of water and a suspension obtained by adding 1 g of Neusilin to that test substance. The adhesive state to the stomach mucosa is shown in Table 2 and when comparing a single administration of barium sulfate with a combined administration of barium sulfate with Neusilin a significant difference was observed in their remaining amount and time in the stomach.

Table 2. Adhesion of Neusilin to the gastric mucosa

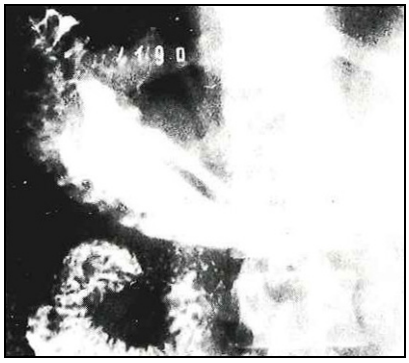
	Test substance	Single administration of barium sulfate			Combined administration with Neusilin		
	Photographing position	Erect	Supine	Prone	Erect	Supine	Prone
Observation time	Right after administration	+++	+++	+++	+++	+++	+++
	30 min. after	++	++	++	+++	+++	+++
	60 min. after	+	+	+	++	++	++
	90 min. after	-	-	-	++	++	++
	120 min. after	-	-	-	+	+	+

+ indicates the remaining state of Barium sulfate in the stomach

Photographs 1 and 2 indicate the state after 90 minutes.

Photograph 1 - A single administration of Barium sulfate

Photograph.2 - A combined administration of Barium sulfate with Neusilin



Clinical Study 2 - Influence of various antacids on the gastric mucosa[13)]

Add 0.1g each of various antacids to 5 ml of gastric juice of the patient of gastritis, mix with shaking, allow to stand at 38°C for 2 hours. Then, filter with a wrinkled filter paper of 4.5 cm in dia. while examining the solubility of the gastric mucus and its time is measured.

Sodium bicarbonate: dissolved the mucus to become transparent. The filtering time was also curtailed and the residual amount was small.

Magnesium oxide: became turbid in white by mixing with shaking, but the supernatant was opaque. The filtering time remained unchanged and the residue was much.

Neusilin: became distinctly turbid in white by mixing with shaking and when allowed to stand the supernatant became clear. The filtering time was fairly curtailed.

As described above, it is conceivable that Neusilin is not dissolved in the gastric juice nor does it dissolve the mucus, but as it adsorbs the mucus to produce a gelatinous precipitate it has a protective action on the gastric mucosa.

Inhibitory action on the experimental ulcer

Test. 1 Antiulcer Test[14)]

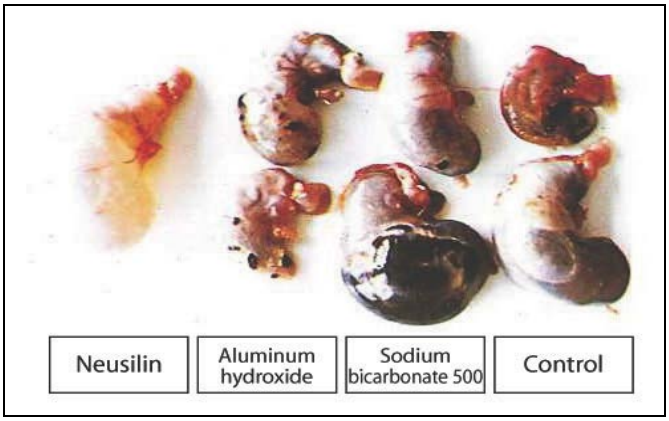
Using the method of Shay *et al*. (1945) Neusilin was orally administered to Wister male rats to perform the inhibitory test of the experimental ulcer. As a result, a distinct difference in the antiulcer action was observed between the groups given 500 and 1,000 mg/kg of Neusilin and the group given 500 mg/kg of sodium bicarbonate including the control group.

Table 3 – Antiulcer test of Neusilin

Test substance (mg/Kg)	No. of Ulcers formed/No. of animals tested	Occurrence rate of ulcers (%)	No. of death by perforation/No. of animals tested	Mortality by perforation (%)
Neusilin 1,000	5/20	25	0/20	0
Neusilin 500	14/20	70	0/20	0
Neusilin 250	18/20	90	4/20	20
Sodium bicarbonate 500	20/20	100	6/20	30
Control	20/20	100	8/20	40

The size of ulcer was divided into 5 steps and an index of occurrence of ulcer was created. The ulcerated area of less than 1mm in dia. was recorded as 1.0; 1 to 5 mm as 2.0; and more than 5 mm as 4.0 and the perforation as 16. The sum total per animal was calculated. When the sum total exceeded 32.0 among both animals died of perforation and the survived ones all was reckoned as 32.0

Photograph 3 - Appearance of stomach after the test (dosage: 500 mg each/kg)



Note: Dark black indicates hemorrhage

Table 4. Occurrence index of ulcer

Test substance (mg/kg)	Occurrence index of ulcer	S.E.
Neusilin 1000	1.75	± 0.67
Neusilin 500	11.0	± 2.37
Neusilin 250	23.3	±2.26
Sodium bicarbonate 500	24.4	±1.92
Control	24.0	±2.42

Test 2 - Stress-induced ulcer Test[15)]

Using the method of Takagi *et al*. (1968), Neusilin A was orally administered to Donryu rats to make an inhibitory test of water immersed stress ulcer. As a result, a marked antiulcer action was observed in the dose groups of 2,000 - 3,000 mg/kg as compared with the control group.

Table. 5 Inhibitory test of Neusilin A for water-immersed stress ulcer[15)]

Test substance (mg/kg)	No. of animals	Occurrence index of ulcer (av.± S.E)	Inhibitory rate (%)
Neusilin A 1,000	14	17.3 ± 2.05	25.4
Neusilin A 2,000	14	12.8 ± 2.36	44.8
Neusilin A 3,000	14	9.5 ± 1.42	59.1
Control group	16	23.2 ± 2.15	-

Length of erosion appeared at the corpus ventriculi were measured by a stereomicroscope (x 10) with lattice and the sum total of length per animal was considered as the index of ulcer.

Test 3 - Inhibitory test of histamine-induced ulcer[15)]

Using the method of Eagleton *et al*. (1971) Neusilin A was orally administered to Hartley albino guinea pigs to make the inhibitory test of histamine-induced ulcer. As a result a marked antiulcer action was observed in the dose group of 50 mg/kg as compared with the control group.

Table 6 - Inhibitory test of Neusilin A for histamine-induced ulcer

Test substance (mg/Kg)	No. of animals	Occurrence index of ulcer	Inhibitory rate (%)
Neusilin A 50	10	2.5 ± 0.22	34.2
Neusilin A 150	10	1.8 ± 0.29	52.6
Neusilin A 300	10	1.0 ± 0.30	73.7
Control group	12	3.8 ± 0.37	-

Ulcerated area on the gastric mucous membrane was measured by a stereomicroscope with lattice (x 10), and the sum total of ulcerated area per animal was divided into 5 stages, namely, 1 - 30, 31 - 60, 61 - 90, 91 – 120 and more than 120 mm^2 and the respective coefficient of the ulcer was calculated as 1, 2, 3, 4 and 5.

Introduction of the literature on the inhibitory action of the experimental ulcers

Inhibitory test of Shay's ulcer[16, 17, 19, 20, 21)]

Using the method of Shay *et al*. (1945) Neusilin was orally administered at the dose levels of 100 - 1,000 mg/kg to Wistar and Donryu rats. As a result Neusilin inhibits the appearance of ulcer dose-dependently and the dose groups given more than 300 mg/kg showed a significant difference from the control group.

Inhibitory test of histamine-induced ulcer[20)]

Using the method of Eagleton *et al*. (1971) Neusilin was administered at the dose levels of 30 - 300 mg/kg to Hartley albino guinea pigs and consequently, a significant difference in the dose group given more than 100 mg/kg was observed from the control group.

Inhibitory test of aspirin-induced ulcer[19)]

Using the method of Okabe *et al*, (1947) Neusilin was administered at the dose levels of 100 - 1,000 mg/kg to Donryu rats and consequently, Neusilin inhibits the appearance of ulcer dose-dependently and the dose group given 1,000 mg/kg inhibits almost completely.

Inhibitory test of stress-induced ulcer[16, 19, 20, 21)]

Using the method of Takagi *et al*, (1968) Neusilin was administered at the dose levels of 100 - 4,000 mg/kg to Wistar and Donryu rats and consequently, Neusilin inhibits the appearance of ulcer slightly or was effective at the dose levels of 1,000 - 3,000 mg/kg.

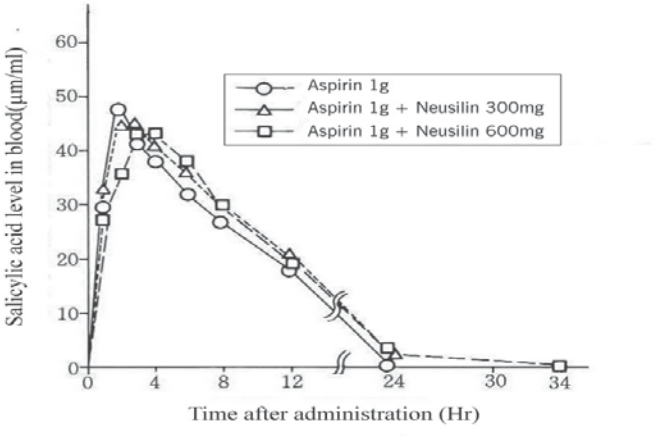
Influence on the absorption of other drugs

1. Influence on the absorption of Aspirin[22)]

Five young healthy men aged from 22 to 30 years were administered 1 g of Aspirin as a main active ingredient singly or in combination with 300 mg or 600 mg of Neusilin simultaneously by the cross-over design. The blood was collected at a given time after administration and the urine collected up to 34 hours after administration was all put together to perform the determination of the excreted amount into blood and urine respectively as salicylic acid.

In consequence, any influence was not observed on the blood level of Aspirin nor on its excretory amount into urine by the simultaneous administration of Neusilin.
Accordingly, it has become evident that Neusilin did not affect the absorption of Aspirin that is an acidic drug through the digestive tract.

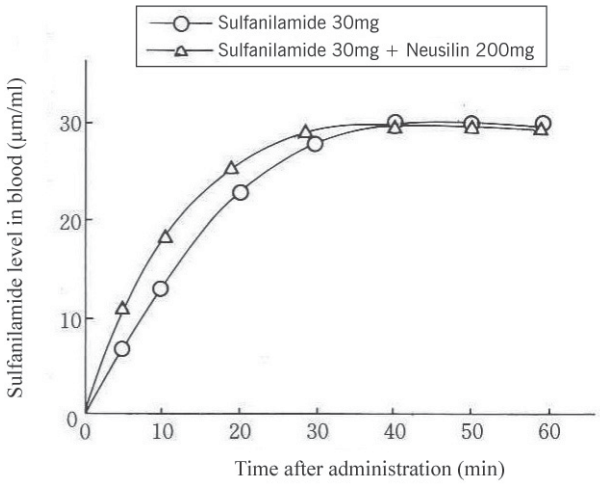
Fig.6. Influence on the absorption of aspirin



2. Influence on the absorption of sulfanilamide[23)]

Wistar male rats (body weight: 170 - 190 g) were used and 200 mg of Neusilin suspended in 5 ml of an aqueous solution of 0.6% sulfanilamide were orally administered by catheter. After administration, blood was collected from the tails at given intervals and the blood level of sulfanilamide was determined by an ordinary method.
As a result, the concentration of sulfanilamide reached its maximum in 20 to 30 minutes after administration. When comparing between the case where Neusilin was added and the case where Neusilin was not added no significant difference has been observed in any of max. concentration time required to attain the max. value and the rising curve of the blood level.

Fig. 7 Influence on the absorption of sulfanilamide



3. Influence on the absorption of tetracycline and others

There are literatures in which antacids containing sodium bicarbonate, aluminum, calcium and magnesium are reported to interfere with the absorption of tetracycline.[24, 55, 56)]
However, in such cases, it will be improved when administering Neusilin in 30 - 60 minutes after administration of tetracycline.[54)]

4. Influence on the digestion of starch, protein [4, 5, 13, 25, 26, 27, 28, 29, 30, 31)]

Using a simulated gastric fluid composing of soluble protein and degenerated hemoglobin by acid, the influence of antacid on starch-protein digesting activities of diastase, Taka-diastase and pancreatin was examined.[31)]

When adding Neusilin (named Neutran in the literature) starch digesting activity of diastase and protein digesting activity of pancreatin increased remarkably as compared to the control using enzymes singly, but it did not exert an effect on starch and protein digesting activities of Taka-diastase nor on starch digesting activity of pancreatin.

Measurement of enzymatic activity in case of combining enzymes with antacid [l0)]

Biodiastase 500, prozyme and lipase as enzyme and Neusilin as antacid were combined respectively in the ratio of 1 to 10 and the relative activity by pH when representing the activity of enzyme only as 100 was calculated.

Amylase (pH 5.0)
(Enzyme) Biodiastase

	Solution for Preparing T.S.	Potency (Per g of enzyme)	Relative activity (%)
Neusilin	Purified water	15.9	13.3
	pH 6.0, 0.1M Phos. Buffer	113.0	94.9
	pH 7.0, 0.1M Phos. Buffer	113.0	94.9
	pH 8.0, 0.1M Phos. Buffer	113.0	93.2
Neusilin A	Purified water	23.2	19.4
	pH 6.0, 0.1M Phos. Buffer	123.0	103.3
	pH 7.0, 0.1M Phos. Buffer	114.0	95.7
	pH 8.0, 0.1M Phos. Buffer	113.0	94.9
Biodiastase 500 only	Purified water	119.0	100

Protease (pH 8.0)
(Enzyme) Prozyme

	Solution for Preparing T.S.	Potency (Per g of enzyme)	Relative activity (%)
Neusilin	Purified water	19.6	63.6
	pH 6.0, 0.2M Phos. Buffer	29.6	96.1
	pH 7.0, 0.2M Phos. Buffer	29.8	96.7
	pH 8.0, 0.2M Phos. Buffer	28.0	90.9
Neusilin A	Purified water	27.1	87.9
	pH 6.0, 0.1M Phos. Buffer	28.8	93.5
	pH 7.0, 0.1M Phos. Buffer	31.0	100.6
	pH 8.0, 0.1M Phos. Buffer	31.0	100.6
Prozyme only	Purified water	30.8	100

Lipase (pH 6.0)
(Enzyme) Lipase AP 6

	Solution for preparing T.S.	Potency (per g of enzyme)	Relative activity (%)
Neusilin	Purified water	48.4	80.6
Neusilin A	Purified water	49.4	82.2
Lipase AP6 only	Purified water	60.0	100

Influence of antacid on the enzymatic action[13)]

To find the relation between peptic action and acidity of gastric juice, add 0.1 g each of various antacids to 10 ml of gastric juice of healthy men, and pH and peptic activity obtained when warming at 40°C for 1 hour while occasionally mixing with shaking are measured by Gruetzner method. The results are shown in Table 7.

Table 7 - Acidity of gastric juice and peptic action by various antacids

Kinds of antacids	pH	Pepsin
Control (gastric juice)	1.3	5000x
Synthetic aluminum silicate	2.2	5000x
Neusilin	3.7	2500x
Sodium bicarbonate	6.8	1000x
Magnesium oxide	9.0	250x

Antipepsin:
Antacid exerts a neutralizing action on gastric juice and as the other important pharmacological action and the inhibition of proteolytic activity of protein by the adsorptive action of antacid can be quoted. When making *in vitro* test of Neusilin and Neusilin A based on K. Schaub method with clotting time as an index, they indicated strong inhibition of activity over a long time of 50 - 60 minutes and 60 - 70 minutes respectively.

Fig.8. Influence of Neusilin on pepsin activity

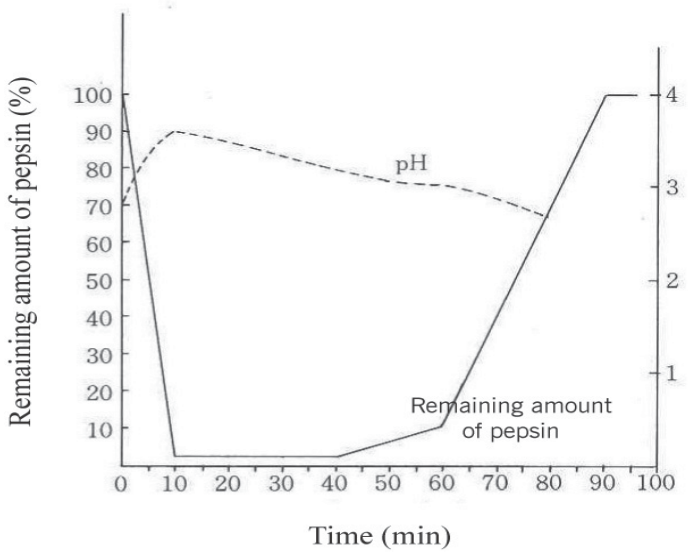
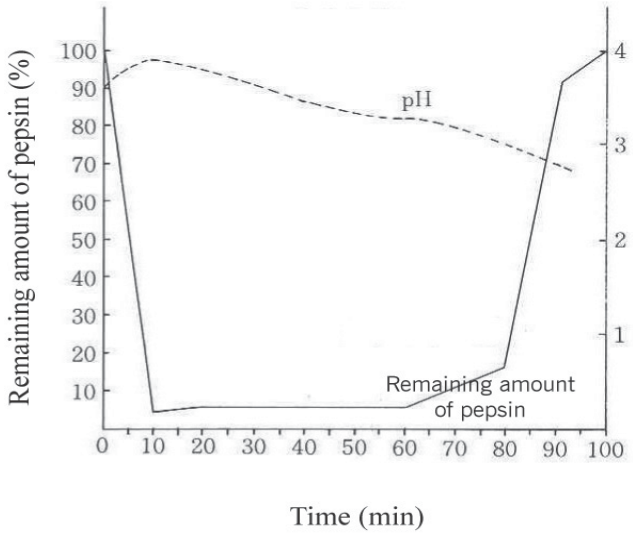


Fig.9. Influence of Neusilin A on pepsin activity



Influence on human body (*In vivo* tests of various antacids)

4 healthy men were administered 3 g each of various antacids and pH of blood and urine prior to and after administration were measured. The change of pH observed in case of sodium bicarbonate was not seen by the administration of Neusilin.

Clinical Study — Influence of various antacids on pH of blood and urine [13)]

4 healthy men were administered 3 g each of various antacids in empty stomach, before breakfast and the pH of blood and urine prior to and after administration were measured. As a result, the possibility of causing alkalosis associated with sodium bicarbonate, was not observed with an ordinary dosage of Neusilin.

Table. 8-Influence of various antacids on the pH of blood and urine

	Blood pH		Urine pH	
	prior to administration	1 hour after administration	prior to administration	2 hours after administration
Sodium bicarbonate	7.40	7.60	5.80	6.90
Magnesium oxide	7.35	7.35	6.25	6.70
Neusilin	7.30	7.30	5.65	5.80

SAFETY TEST OF NEUSILIN AND NEUSILIN A

Since Neusilin is non-absorbent, LD_{50} is over 5.0 g/kg (p.o.) in mice and rats, over 16 g/kg (p.o.) in mice (dd strain) and over 10g/kg (p.o.) in rabbits and dogs in the respective acute toxicity study and in this way there was no death case observed even with the maximum possible dosage of this drug.

Further, as a result of the sub acute and chronic toxicity studies in mice, rats, rabbits, dogs and monkeys any abnormality that was considered attributable to this drug was not observed. Also, judging from the result of teratogenic study in mice no significant influence on mother body, birth of fetus and its growth after birth was observed as compared with the control group.

Acute Toxicity

Neusilin was orally administered to mice (dd strain) up to 16 g/kg[32], up to 5.0 g/kg to mice and rats[33], up to 6 g/kg to mice[35] but no remarkable abnormalities were found in all cases.

Acute toxicity study 1[32]

The test substance was suspended in 80% propylene glycol, orally administered to mice using metal gavage tube (dd strain, males, body weight: 18 - 20 g) at a dose of 0.2 mL/20g for Group 3, 0.3 mL/20g for Group 2, and 0.45 mL/20 g (0.25 and 0.20 mL/20g with a 10 min interval) for Group 1 and the development was observed for a week. The result is shown in Table 9.

[Ratio of dosage level] 1:2; No. of animals per level: 8

Table 9. Acute toxicity test in mice

Level No.	Dosage (g/kg)	No. of animals that died on each day of the study period 1 2 3 4 5 6 7	Mortality (%)
1	16.00	0/8 → 0/8	0
2	8.00	0/8 → 0/8	0
3	4.00	0/8 → 0/8	0

Neusilin was orally and intraperitoneally administered to 10 male mice dd strain and to 10 male albino rats up to 5 g/kg for 1 week. There was no death of mice or rats and the animals did not show any symptom of toxicity [33)].

In another research from laboratory of Diamant[34)], Magnesium aluminosilicate tetrahydrate chemically equivalent to Neusilin, in a suspension of 10% aqueous solution of gomme syrup was orally administered to 50 mice up to 5 g/kg, 30 rats up to 5 g/kg, 10 rabbits up to 10 g/kg and 4 dogs up to 10 g/kg during a period of 15 days to 1 month. No animal showed any visible problem.

Acute toxicity study 2[35)]

ICR-JCL matured female mice were given aqueous suspension of 6,000, 3,000 and 600 mg/kg of Neusilin respectively suspended in 10 ml/kg of water which were considered excessively larger dosage than estimated usual dosage for human body once a day and for consecutive 2 weeks. One group consisted of 5 mice each and the control group was given distilled water.

Higher dose group: general symptomatic signs such as decreasing tendency of body weight, decrease of spontaneous movement, general coarse fur, etc. were observed from the 3rd day after administration, but those were recovered from about the 10th day.

Medium and small dose groups: a slight decrease of body weight was only observed after the start of administration.

There was no death case in all, groups. Animals were sacrificed after two-week consecutive administration for necropsy and no abnormality was found in all visceral organs. Also, there was no marked difference observed among all groups in body weight gain as well as in intake of food and water during the administrative period.

Sub-acute Toxicity

Neusilin was orally administered to persons up to 4.5 g/day for 1 month, and to Rhesus monkeys up to 2.4 g/kg/day for 1 month, Neusilin in Nilocid gel formulation was orally administered to Sprague Dawley rats up to 1,200 mg/kg/day (10 mL of Nilocid gel) for 1 month, and finally Neusilin was mixed with food of dogs at the level of 5g/kg/day for 2 months. All the results showed no remarkable toxic effects.

Sub-acute toxicity study 1[36)]

Neusilin in Nilocid gel formulation was orally administered to Sprague Dawley rats up to 1,200 mg/kg/day (10 mL of Nilocid gel) for 30 days. There were no toxic effects as determined by clinical observation, food consumption, body weight gain, hematology, gross, and microscopic necropsy examination, and relative organ weights.

In another research from laboratory of Diamant[34)], five healthy dogs were given food which was mixed with Magnesium aluminosilicate tetrahydrate chemically equivalent to Neusilin at the level of 5,000 mg/kg/day for 2 months. The results showed no abnormalities in general behavior, feces, and the body weight.

Table 10 - Body weight change in dogs

Dogs	1	2	3	4	5
Before test (g)	6,220	6,480	7,810	8,320	13,150
After test (g)	7,450	7,660	9,110	9,020	13,720

Necropsy revealed no abnormality in digestive organs and mucosa and no side effects ascribed to the administration were seen at all.

Sub-acute toxicity study 2[38)]

In another research Neusilin was orally administered to 7 Rhesus monkeys with dosage range from 0.05 to 2.4 g/kg/day for 1 month. The results showed that clinical appearance and body weight were not materially affected. Clinical laboratory determinations (hematologic, clinical chemistry and urinalysis) and gross necropsy findings were not remarkable. Histopathology study of the kidneys did not reveal any alterations.

Sub-acute toxicity study 3[51)]

Neusilin was orally administered from 0.5 to 4.5 g/day to ninety persons for 1 month. The results of urine tests, blood tests, electro-cardiogram, and physical examination showed no problem except some minimal side effects such as constipation happened to 2 patients, nausea and diarrhea happened to 1 patient. No side effects referred to kidney.

Chronic Toxicity

Neusilin was orally administered to rats and rabbits at dose levels of 200 mg/kg and 50 mg/kg, respectively, for 27 months[37)], and to Rhesus monkeys at the dose levels of 0, 50, 300 and 1,200 mg/kg/day respectively for 3 - 6 months[38)]. Neusilin was also mixed with food at concentrations of 0, 0.2, 1, 5, and 7% and given to mice (dd strain) and rats for 1 year[57)]. Clinical observations and pathologic findings did not reveal any significant toxic effects.

Chronic toxicity study 1[37)]

20 rats and 10 rabbits were used. Neusilin was administered at the dose levels of 50 - 200 mg/kg for 27 consecutive months. Body weight, hematological finding, general clinical signs, autoptic findings and histological findings were examined. As a result, any abnormal lesion considered ascribed to the drug was not observed in all items for inspection.

Chronic toxicity study 2[58)]

Twenty four Rhesus monkeys were divided into 4 groups, each consisting of 6 monkeys and were orally administered Neusilin suspension at the dose levels of 0, 50, 300 and 1,200 mg/kg/day respectively for 3 - 6 months. Clinical observations, clinical laboratory findings, necropsy, organ weights, and histopathologic findings were examined. Clinicopathologic

abnormalities considered ascribed to the administration of the drug were not observed in all groups.

Chronic toxicity study 3[57)]

Neusilin was mixed with food at concentrations of 0, 0.2, 1, 5, and 7% and given to mice (dd strain) and rats for 1 year. Clinical observations and pathologic findings did not reveal any significant effects. Administration of Neusilin did not cause any deposition of Aluminum in liver, kidney, heart, spleen, and testicles.

Teratology

Teratogenetic study[35)]

ICR-JCL primiparous female mice of 12 - 18 weeks old were mated with male mice to obtain pregnant mice. Neusilin was suspended in water and orally administered at the dose levels of 6,000, 3,000 and 600 mg/kg once a day for 6 days from the 7th to 12th day of pregnancy. Fifteen mice of 20 per each group were sacrificed on the 18th day of pregnancy and their abdomens were opened for making observation of mother-body and fetuses. The remaining 5 mice were spontaneously delivered and the observation was made. Further, 3 weeks after the birth, both mothers and fetuses were sacrificed and their abdomens were opened to perform the observation.

Influence on the mother-body: Regarding body weight gain there was no significant difference between dose groups and control group ($P < 0.01$). When opening the abdomens a mild pneumonia was detected only in high dose groups and in all other cases, no abnormality in body weight and various thoracic and abdominal organs were observed nor was any significant difference found.

Influence on the fetuses: There was no significant difference in the mean number of implantation per dam as well as in the number of born fetuses. Also, there was no significant difference in the average body weight of born fetuses although the average body weight of the medium and high dose groups was a little lower ($P < 0.0l$), and no inhibitory action of growth of fetuses was observed. In regard to the external abnormality, the occurrence rate of the treated groups equaled that of the control group.

As for hematoma, 2 cases were observed in the control group and 1 case each in the medium and high dose groups, but there was no significant difference among them ($P < 0.0l$). No skeletal malformations were observed, however skeletal variations of cervical rib and asymmetry of stern brae were significant difference from the control group ($P < 0.0l$). As for degree of ossification, a significant difference was observed in the high dose group in respect of the number of ossified talus of both the fore- and hind paws($P < 0.05$). Besides the above, there were remarkable differences in any other incidences compared to the control groups.

Influence on the growth of born fetuses: Marked difference was not observed in the number of implantation, delivery rate, and sex ratio of newborns. The death during perinatal period (prior to and after delivery) was none and the average body weight of born fetuses showed a satisfactory gain ($P < 0.01$). As for differentiation status at time of weaning no abnormality was observed in

external appearance, general behavior and hearing function. Abnormality of thoracic and abdominal organs was not detected nor was any abnormality observed by examination of skeletal specimen of offspring

Table 11 - Influence of Neusilin on body weight of mothers giving spontaneous delivery
(Unit: gram)

Group (mg/kg)	No. of mothers	Gestation					Development per week after delivery		
		0 day vaginal plug confirmed	7th day start of administering	12th day finish of administering	18th day before delivery	19th day delivery	1st week	2nd week	3rd week
Control group (distilled water)	5	36.4 ± 1.31	41.2 ± 1.16	47.6 ±1.89	67.2±3.64	43.2±1.89	51.8 ± 3.09	51.8 ± 1.42	46.1 ± 2.01
600	5	36.4 ± 1.97	40.9 ± 2.19	47.9 ± 1.86	65.3±1.72	43.4±1.60	48.2 ± 2.29	51.6 ± 1.98	46.1 ± 1.98
3,000	5	36.0 ± 0.66	40.5 ± 0.89	145.2 ± 1.12	62.5±6.28	41.3±0.79	51.0 ± 1.38	52.8 ± 1.69	44.1 ± 1.00
6,000	5	35.2 ± 2.71	39.6 ± 2.73	41.6 ± 3.11	63.1±4.50	41.4±1.90	47.4 ± 2.78	52.4 ± 1.60	45.0 ± 1.56

Table 12 - Influence of Neusilin on mice fetuses

Group (mg/kg)			Control (dist water)	600	3,000	5,000
No. of mothers			15	35	15	15
Fetuses	No. of total implantation (Mean ± S.E.)		203 (13.5±0.80)	210 (14.0±0.39)	222 (14.8±0.43)	221 (14.7±0.58)
	No. of resorbed or dead fetuses (%)		35 (7.4)	21 (10.0)	23 (10.4)	25 (11.3)
	No. of lived fetuses (Mean ± S.E.)		188 (12.5±0.75)	189 (12.6±0.47)	199 (l3.3±0.38)	195 (13.1±0.56)
	Sex ratio		100/91	103/85	103/96	95/l01
	Mean body weight ±S.E.	♂	1.40±0.033	1.44±0022	2.37±0.035	1.36±0.032
		♀	1.34±0.036	1.39±0.030	1.23±0.032	1.30±0.033
	External malformation Type No. Cleft palate Open eye Club foot Twisted tail Malformed fetuses/observed fetuses (%)		 1 0 1 1 3/188 (1.6)	 0 0 2 1 3/139 (1.6)	 1 1 2 0 4/199 (2.0)	 3 0 1 0 4/396 (2.0)
	Visceral malformation Type No (%) Hydronephrosis Malformed fetuses/observed fetuses (%)		 0	 1(1.1) 1/91(1.1)	 0	 1(1.1) 1/94(1.1)
	Hematoma (%)		2(2.2)	0(0)	1(1.0)	1(1.1)
	Edema (%)		0(0)	0(0)	1(1.0)	0(0)

S.E.: Standard Error

Table.13- Influence of Neusilin on new born fetuses of mice

Group (mg/kg)			Control (dist, water)	600	3,000	6,000
No. of mothers			5	5	5	5
Total implantation (Mean ± S. E.)			70 (34.0±0.71)	70 (14.0±1.18)	68 (13.6±0.40)	69 (13.8±1.50)
Delivery rate (%)			66/70 (91.3)	60/70(85.7)	60/68(88.2)	57/69(82.6)
Sex ratio of newborn			32/34 (0.91)	29/31(0.91)	31/29 (1.07)	32/25 (1.28)
Newborn Baby weights	At birth (Mean ± S.E.)	♂	3.74±0.078	1.70±0.022	1.68±0.050	1.79±0.092
		♀	1.67±0.061	1.65±0.061	1.59±0.059	1.71±0.072
	1 week alter birth (Mean ± S.E.)	♂	4.36±0.348	4.40±0.303	4.11±0.093	4.71±0.294
		♀	4.27±0.336	4.30±0.303	4.10±0.204	4.49±0.322
	2 weeks after birth (Mean ±S.E.)	♂	7.58±0.586	8.00±0.663	7.65±0.331	8.05±0.621
		♀	7.25±0.616	7.37±0.736	7.45±0.503	7.88±0.702
	3 weeks after birth (Mean ± SE.)	♂	12.61±1.049	13.63±0.955	12.71±0.484	13.75±1.188
		♀	12.22±0.975	12.91±1.089	11.92±0.624	13.23±1.203
Weaning rate (%)		♂	32/32 (100)	29/29 (300)	31/31 (100)	31/32 (96.9)
		♀	34/34 (100)	30/31 (96.8)	29/29 (100)	24/25 (96.0)
External and visceral anomalies			0	0	0	0
Behavioral and auditorial abnormalities			0	0	0	0
Skeletal anomalies			0	0	0	0

S.E.: Standard Error

CLINICAL STUDIES OF NEUSILIN AND NEUSILIN A

Regarding the clinical results produced by a single administration of Neusilin and Neusilin A, a high effect of improvement on the diseases such as gastric ulcer, duodenal ulcer, gastro-duodenal ulcer, acute and chronic gastritis, hyperacidity and so on was observed. Further, a very good result has been obtained for the prevention of gastrointestinal disturbances induced by other drugs such as adrenocortical hormone, aspirin, phenylbutazone, PAS and others.

As for the side effects, constipation, diarrhea, slight thirst are rarely seen, but all of them are mild and nothing to specially mention is observed.

Effect on the subjective symptoms

In case of administering Neusilin and Neusilin A to 160 cases who showed the pains such as stomach ache, epigastric pain, abdominal pain, and pain after meals and so on, the improvement such as disappearance or remission of the subjective symptoms was seen in 144 cases (90.0%). Among them, the improvement of symptoms was seen in 63 cases out of 68 (92.6%) regarding the pains associated with the ulcerous diseases of stomach and duodenum. In regard to 90 cases that showed the subjective symptoms such as acid indigestion, heartburn, etc. the improvement was seen in 83 cases (92.27.), out of which the improvement of symptoms was seen in 18 cases of 19 who showed the symptoms associated with ulcerous diseases of stomach and duodenum (94.7%). Some of these subjective symptoms disappeared by a single dose in the earliest case[38)] and in most cases the symptoms were improved by the administration of from two or three days to about fifteen days.[7, 40, 41, 42, 43, 44).]

Table 14 - Effect on the subjective symptoms

( ) shows percentage

Item		No. of cases	Improvement	No change	Literature
Pain*	Associated with ulcerous diseases of stomach and duodenum	68	63 (92.6)	5 (7.4)	6,7,10,11,39, 40, 44, 45, 46, 47
	Others and unknown cases	92	81 (88.0)	11 (11.9)	6,7,11,40, 41, 42, 43,44,45,46,47, 48, 49
	Total	160	144 (90.0)	16 (10.0)	
Heartburn indigestion	Associated with ulcerous diseases of stomach and duodenum	19	18 (94.7)	1 (5.3)	8, 10, 42
	Others and unknown cases	71	65 (91.6)	6 (8.4)	6,7,8,40,41,42,45, 47,49,50
	Total	90	83 (92.2)	7 (7.8)	
Belching	Associated with ulcerous diseases of stomach and duodenum	18	18 (100.0)		7,8,10,42
	Others and unknown cases	3	3 (100.0)		40
	Total	21	21(100.0)		
Nausea, vomiting	Associated with ulcerous diseases of stomach and duodenum	11	11 (100.0)		7,8,10,42,45
	Others and unknown cases	41	39 (93.1)	2 (4.9)	6,7,8,10,41,43,45
	Total	52	50 (96.2)	2 (3.8)	

* includes epigastric pain, stomach ache, abdominal pain, hypochondriac pain, ache.

Effect on the objective symptoms

When administering Neusilin or Neusilin A to 75 cases showing hyperacidity, the lowering of acidity of gastric juice was observed in 64 cases (85.3%). Among them there were 42 cases suffering from ulcerous diseases of stomach or duodenum, out of which the lowering of acidity of gastric juice was seen in 36 cases (85.7%). The occult blood test was made on 29 cases and the result was found negative in 24 cases by the administration of Neusilin (82.7%). Among them, the result was also negative in 20 cases out of 24 of ulcerous diseases of the digestive organs (83.3%). (Table15).

For reported examples, where Neusilin was administered to 10 cases of gastric or duodenal ulcer (7 for hyper acidity, 2 for normal acidity, 1 for hypo acidity) the lowering of acidity was observed in 7 cases, 1 case of hypo acidity remained unchanged and the result was unknown in other 2 cases.[42)] Furthermore, when administering Neusilin A to 21 cases of gastric or duodenal ulcer (13 for hyper acidity, 6 for normal acidity, 2 for hypo acidity) Neusilin A was either excellently effective or effective for 12 cases of hyper acidity, 5 cases of normal acidity and 1 case of hypo acidity totaling to 18 cases. [41)]

Table15. Effect on the objective symptoms
( ) shows percentage

Item		No. of cases	Improvement	No change	unknown	Literature
Lowering of acidity of gastric juice	Associated with ulcerous diseases of stomach and duodenum	42	36 (85.7)	5 (11.9)	1 (2.4)	7,9,1.0,40, 41,42,46
	Others and unknown cases	33	28 (84.9)	5 (15.2)		9, 40, 41, 42,45,47
	Total	75	64 (85.3)	10 (13.3)	1 (1.3)	
Negative results for occult blood test	Associated with ulcerous diseases of stomach and duodenum	24	20 (83.3)	3 (12.5)	1 (4.1)	7,8,10,42, 45,46
	Others and unknown cases	5	4 (80.0)	0	1(20.0)	7,45
	Total	29	24 (82.7)	3 (10.3)	2 (6.9)	

Effect for individual diseases

The cases of gastric- ulcer numbered 58. Among them the cases judged excellently effective, effective and moderately effective were 22 cases (37.9%), in 16 cases (27.6%) disappearance or remission of subjective or objective symptoms was seen and the improvement of subjective or objective symptoms was observed in 11 cases (19.0%). As mentioned above, all the improved cases came to 49 cases (84.5%) when summing them up and the rest were 5 cases of no change (8.6%) and 4 cases of the unknown cases (6.9%). The cases of duodenal ulcer numbered 31, out of which all the effective cases observing the improvement were 25 cases (80.6%), 3 cases were the cases of no change (9.7%) and another 3 cases were the cases of the unknown cases (9.7%).

The cases of gastritis including acuteness and chronicity totaled to 99 cases and the cases judged excellently effective, effective and moderately effective were 63 cases (63.7%). The cases in which both or either of subjective or objective symptoms disappeared or were remitted numbered 20 cases (20.2%) and when summing up those improved cases, 83 cases were effective cases (83.9%), 12 cases were those of no change (12.1%) and the unknown cases numbered 4 (4.0%).

The cases of hyperacidity numbered to 27 cases and all the cases in which improvement was observed were 19 cases (70.4%). As for abnormal intestinal fermentation it was considered fermentative colitis and the effect was observed in 12 cases out of 13 cases (92.3%). Further, an abdominal, distention was also mentioned, but it was not ascertained whether or not this was actually the case (Table 16).

Giving a few reports as example, when administering 4 - 6 g of Neusilin daily for 10 - 20 days to 7 cases of gastric ulcer and 3 cases of duodenal ulcer, disappearance or remission of pains was seen in all the cases except 1 case of duodenal ulcer on the 8th to 10th day. Among 6 cases of gastric ulcer with niche, the reduction of niche was observed in 2 cases and remission in 4 cases. Reduction of niche was found averagely 15 days after and its disappearance was found 20 to 30 days after. [42)]

To 9 cases of gastric ulcer and 2 cases of duodenal ulcer 3 g of Neusilin was administered daily for 30 days and disappearance or remission of the subjective symptoms was observed in all cases. 4 cases with occult blood became negative in 5 to 7 days and niche partly disappeared in one case out of 2 of gastric ulcer with niche and another case died of copious hemorrhage.[11)] Further, Neusilin was administered to 6 cases of gastritis and chronic gastritis and improvement of subjective symptoms as well as gastric juice, X-ray findings, etc. was observed in all cases. [45)]

In addition, when administering 3 - 4 g of Neusilin daily for 4 - 21 days to 11 cases of acute and chronic gastritis there were 2 cases of excellent efficacy and 5 cases of efficacy. [50)]

The abovementioned cases received the treatment of diseases by the administration of Neusilin or Neusilin A totaled to 345 cases.

Table 16 — Effect for individual diseases
( ) shows percentage

Diseases	No. of cases	Excellently effective	Effective*	Improvement of subjective and objective symptoms	Improvement of subjective or objective symptoms	No change	Unknown	Literature
Gastric ulcer	58	7 (12.0)	15 (25.9)	16 (27.6)	11 (19.0)	5 (8.6)	4 (6.9)	6,7,8,9,10, 11, 38, 39, 40, 41, 44, 45
	Total	49 (84.5)						
Duodenal ulcer	31	8 (25.8)	8 (25.8)	1 (3.2)	8 (25.8)	3 (9.7)	3 (9.7)	8, 9, 10, 11, 38, 39, 41, 41, 44
	Total	25 (80.6)						
Gastro-duodenal ulcer	24	1 (4.2)	3 (12.5)	1 (4.2)	16 (66.7)	3 (12.5)		8, 39, 44, 47, 48
	Total	21 (87.5)						
Acute chronic gastritis	99	27 (27.3)	36 (36.4)	10 (10.1)	10 (10.1)	12 (12.1)	4 (4.0)	6, 7, 8, 9, 10, 11, 39, 40, 42, 43, 44, 49
	Total	83 (83.9)						
Hyperacidity	27	6 (22.2)	9 (33.3)	3 (11.1)	1 (3.7)	8 (29.6)		7, 39, 41, 44, 45, 46, 50
	Total	19 (70.4)						
Fermentative colitis	13	5 (38.5)	7 (53.8)			1 (7.7)		48
	Total	12 (92.3)						

*includes moderate effectiveness.

All the effective cases including the cases judged excellently effective, effective and moderately effective by the synthetic judgment as well as by the improvement of subjective or objective symptoms were 297 cases (86.1%), the cases of no improvement numbered 42 cases (12.2%) and the cases of unknown result were 6 cases (1.7%).

Efficacy of Neusilin in combination with other drugs

The cases in which the treatment of diseases was aimed in combination with other drugs were 83 cases, and among them the improvement of symptoms was observed in 21 cases out of 22 cases of gastric ulcer (95.5%) [39, 43, 48)] in 34 cases out of 38 cases of duodenal ulcer (89.4%) [43,44,48 ,49)] and in 8 cases of 8 of gastro duodenal ulcer (100%).[44)] In total, Neusilin was effective for 78 cases out of 85 cases in all (91.8%). The drugs used in combination were anticholinegic agents such as atropine and other antiulcer agents.

Protective effect of gastrointestinal disturbances due to the other drugs

There were 89 cases in which the prevention of side effects due to the administration of adrenocortical hormone preparations, aspirin, phenylbutazone, PAS, etc. was aimed and disappearance or remission of the gastrointestinal symptoms such as hyperacidity, heartburn, epigastric pyrosis, nausea, stomachache, etc. was observed in 80 cases of them (89.9%) [39, 40, 43, 44, 48, 52)]

For instance, Neusilin was jointly administered to 14 cases given aspirin and 16 cases given corticoid, and as a result it was possible to continue to administer to 26 cases (86.7%) except 4 cases with hemorrhage without causing any disorders of the digestive organs.[44)] Further, to 30 cases given corticoid, phenylbutazone, salicylate, etc. Neusilin was jointly administered and an entire disappearance or marked improvement of disorders of the digestive organs was seen in 28 cases (93.3%). [55)]

Side effects

The side effects occurred were mostly slight and all of them took place when administering Neusilin singly. Most of them were constipation, which was considered to be due to aluminum contained in the composition[53)] and as the constipation occurred in the patients who were confined to bed regarding 10 cases out of 14 cases, the dosage has to be decreased.[47)] Further, in another case the constipation occurred by an administration of 9 g per day, but it disappeared by decreasing the dosage to 3 g per day.[46)] Likewise, diarrhea as considered to be due to magnesium contained in the composition.[53)] Slight thirst occurred in 2 cases, but it was not distinct about whether or not it was ascribed to the, use of Neusilin.[7)] Vomiting occurred in the case of pyloric stenosis given 1 g of Neusilin only once.[39)] Moreover, Neusilin was administered to 30 cases of

healthy volunteers for 30 days and when making the inspection of urine, blood and others prior to and after administration no disturbances were found. [51)]

Table 17 - Side effects

No. of cases	Symptoms	No. of occurrence	Literature
596	constipation	14 (2.34)	10, 41, 45, 46, 51
	Diarrhea	2 (0.34)	40, 51
	Slight thirst	2 (0.34)	7
	Slight vomiting	1 (0.17)	10
	Vomiting	1 (0.17)	39
	Itch	1 (0.17)	51
Total		21 (3.52)	

( ) shows percentage

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