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AN INVESTIGATION OF THE ROLE OF THE VAGUS NERVE IN THE GENESIS OF PEPTIC ULCER PRODUCED EXPERIMENTALLY BY CINCHOPHEN

BY

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A THESIS

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To Mary Anne, My Wife.
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CHAPTER I

HISTORICAL BACKGROUND OF THE DRUG
CINCHOPHEN

Though cinchophen was first synthesized in 1887 by Doebner and Giseke, it was not until 1908 that Nicolaier and Dohrn introduced it into medicine under the trade name of Atophan. For a great number of years, it was regarded as the drug of choice in the treatment of gout and, as a matter of fact, is still championed by some physicians (1).

Chemically, cinchophen or phenylcinchoninic acid is 2-phenyl-quinoline-4-carboxylic acid; structurally (see Figure 1). It occurs as small white or yellowish-white, needlelike crystals, or as a fine powder, and is stable in air. While nearly odorless, it has a very bitter taste. This drug is almost insoluble in cold water, but soluble in chloroform, ether, and alcohol as well as in dilute alkalies. No longer an official United States Pharmacopoeia (2) preparation, cinchophen appears in the National Formulary (3) but a similar preparation, neo-

Fig. 1.—Structural formula of cinchophen
cinchophen, appears in both.

Resembling the salicylates in all major actions, cinchophen naturally falls into the analgesic-antipyretic group of drugs (4). It increases uric acid excretion, almost doubling it at times, by direct action on the kidneys. At one time it was assumed that the main action of cinchophen in gout was to overcome the impermeability believed characteristically present in this metabolic disturbance (1). However, though gout is generally believed to be associated with faulty uric acid metabolism, the true pathogenesis remains unknown (4,5), and many believe the beneficial action of cinchophen here is due to its analgesic effect rather than to its uricosuric action (1).

Cinchophen is also a choleretic (1,4,6,7) but it is not used for this purpose therapeutically (1,4). Though recently shown to be as effective as dehydrocholic acid (decholin) or mixed ketocholanates (ketochol) (7), the bile produced by cinchophen is thin, watery, and high in bile pigments, but low in cholesterol and bile acids (1).

Ordinarily the drug is administered per ora, but experimentally it is effective when placed rectally (8), in isolated loops of intestine (8,9), subcutaneously (8,10), and intravenously (8,11). Its absorption by the intestine of the dog has been found to be practically a quantitative one (12).

The exact fate of cinchophen in the body is still
a matter of conjecture, but that it is destroyed is cer-
tain. Most probably it suffers the same fate as other
injurious agents absorbed from the intestinal tract.
i.e., destruction by the liver. The concensus is that
the liver protects the body from such agents by its abil-
ity to oxidize and/or conjugate them "... into rela-
tively non-toxic substances which are subsequently elimi-
nated in the bile and urine..." (13), and it is
only natural to assume that cinchophen is one of this
group. Lichtman (14) and Rotter (15) were unable to find
evidence of cinchophen oxidation by the dog liver. On
the other hand, Lichtman (14) occluded the circulation to
the liver in several rabbits and gave them cinchophen in-
travenously. In contrast to the control group, oxy-
cinchophen failed to appear in the urine in the function-
ally hepatectomized animals. Additional evidence favor-
ing the liver as the site of cinchophen oxidation is the
appearance of cinchophen in the bile of rabbits (16), dogs
(6,7), and humans (14). This cinchophen is not chemi-
cally intact as one might suppose but has been changed as
is supported by the work of Lichtman and Bradley. Licht-
man (14) of course, tests the bile for oxy-cinchophen,
and Bradley (6), though he ultimately determines chemi-
cally intact cinchophen, first adds concentrated hydro-
chloric acid and sodium hydroxide which Levine (17) be-
lieves is sufficient to de-conjugate cinchophen.

Regarding excretion, as just mentioned,
various men have demonstrated that some cinchophen is excreted in the bile, fifty per cent of the ingested drug having been recovered in a twenty-four hour period (6). It also appears in the urine in various forms, some known, some unknown. Several investigators (14, 18) have demonstrated the appearance of 2-(orthohydroxy)-phenyl-quinoline-4-carboxylic acid, or oxy-cinchophen, in the urine during the first few days of cinchophen administration. As a matter of interest, Lichtman (14) introduced a test for liver function on the appearance of excessive amounts of this compound in the urine when a certain amount of cinchophen was ingested. He assumed oxy-cinchophen to be an intermediate product in the oxidation of cinchophen by the liver and that the damaged hepatic cell could convert cinchophen to oxy-cinchophen but could not carry the catabolism any farther. Thus, there would be more than the normal seven to twenty-one per cent in the urine. The test has been abandoned because the results are not uniform (13). In addition to this product, five and one-half per cent of ingested cinchophen appears in the urine unchanged (19). Other oxidation products found here are still unidentified but for more detailed information the reader is referred to Böhm and Bournot (20) and Fürth and Kuh (21).

At any rate, if this circumstantial evidence is true, cinchophen, then, after absorption by the bloodstream, is brought to the liver. Here, part of it is con-
jugated and excreted in the bile. The remainder is broken down and is eventually excreted in the urine. Whether the pharmacological actions of this member of the analgesic-antipyretic group are due to the chemical nature of the drug per se or to its catabolic products, is not the objective of this treatise. As a matter of record, the preceding discussion regarding the fate of cinchophen being for most part hypothetical, should also have been disregarded; it was included at this point only because of the clarity it lends in understanding some of the points brought up later on.

The marked hepato-toxicity now associated with cinchophen did not become apparent, or rather was not recognized, until about 1925. Previously it had been regarded as no more toxic than the salicylates and was thought to have, relatively, the same symptomatology as "acute salicylism". In 1923, Worster—Drought (22) reported the first case of toxic manifestations presumably due to cinchophen. Slowly gaining momentum following the first report, others rapidly followed until in 1936, one hundred ninety-one cases had been reported with a forty-seven per cent mortality (4). The underlying pathology is a toxic cirrhosis, similar to that found with chloroform poisoning, which at times continues on to an acute, fulminating, yellow atrophy. Those, who do not develop the latter, recover, but very slowly (1).

In 1932, Reah (23) reporting numerous cases of
toxicity, included a fatality due to cinchophen in a male patient, who, at autopsy, was found to have a true peptic ulcer as well as liver damage. Not much significance was attached to this until a short time later when Van Wagoner and Churchill (24), while trying to determine liver damage in experimental cinchophen poisoning, accidentally discovered peptic ulcer in dogs. They found ulcer occurred in almost one hundred per cent of the animals in ten days or more after giving five to ten times the normal human dose of the drug.

Not long after this, Block and Rosenberg (25) tried to link cinchophen with ulcer in man. They cited Reah's case and presented a woman of their own who took cinchophen over a long period of time and at autopsy was found to have chronic gastric ulcers, early toxic cirrhosis of the liver, and marked cloudy swelling of both kidneys. Substantiating this supposition, several cases reported by Reah (23) had a history of epigastric pain, which may possibly have been due to ulcer. Unfortunately, autopsies were not obtained or, if they were, no report was made of the stomach. On the other hand, it should also be stressed that the case of Reah's believed due to cinchophen by Block and Rosenberg, occurred thirteen weeks following the removal of the etiologic agent. As regards their own case, one must draw his own conclusions.

A survey of the literature reveals that toxic
cinchophen manifestations vary somewhat according to the species (1,24,26,27). In humans (1,4,23) it appears they are chiefly of an hepatic nature while in dogs (24) the gastric symptoms predominate. With such indirect evidence on both sides, one can only say that if it is possible for cinchophen to produce peptic ulcer in man, it does so only in rare instances.

Be that what it may, the discovery of cinchophen as another means of producing peptic ulcer experimentally, opened an entire new approach to the problem of ulcer. This not only gave the physiologist an ulcer in a stomach anatomically intact, a thing unheard of before though often wished, but also a very easy method to produce that ulcer in almost one hundred per cent of dogs. Too, pathologically, cinchophen ulcer in dogs and peptic ulcers found in humans are histologically identical (8). Moreover, therapy which benefits one has, so far, had the same effect on the other and vice versa. Thus, one might call experimental cinchophen ulcer the "testing ground" for human ulcer therapy.

The role of cinchophen in producing experimental peptic ulcer has far surpassed its original one as a supposed "specific" for gout. The salicylates and colchicine have largely replaced it in treating acute and chronic arthritis (1,4). This has come about not only because of the hepatotoxicity of cinchophen but also because many clinicians believe they get better clinical results with
the other drugs (1). Consequently, current medical literature contains almost nothing on cinchophen therapeutically, whereas before, there was a veritable plethora of articles. One is aware of its existence only because of its role in the experimental field.
CHAPTER II

THE CHRONICLE OF CINCHOPHEN - ULCER

In 1931, Van Wagoner and Churchill (28) were giving toxic doses of cinchophen to dogs to determine whether or not the drug produced liver damage in these animals. While performing thorough routine autopsies, they noted some of these dogs had developed peptic ulcers. Experimenting a little farther (1932) (24), they were able to produce ulcers in eighty per cent of their dogs by using from 0.11 to 0.22 grams of cinchophen per kilogram daily. When the higher dosage was used, which is approximately ten times the human dose, ulcers occurred in almost one hundred per cent of the animals. The dogs had anorexia throughout, weight loss, occasionally nausea and vomiting, and, at intervals, tarry stools.

Glancing back through the literature previous to 1932, we see that numerous factors have been suggested as the cause of acute gastric erosions, and some of these have been used to produce chronic ulcer. Wolfer (29) produced ulcer by using x-rays; Cohnheim (30) used metallic salts intravenously; Ivy (31) confirmed Cohnheim but also found that inert materials did not produce ulcer; Decker (32) used heat; Ribbert (33) used intense cold; escharotics have been used locally (31); Ivy and Shapiro
(34) employed local anaphylaxis successfully, and, of course, exclusion of the duodenal contents, in whole or in part, as done by various men has also been employed (35,36,37,38,39,40,41,42,43).

Of all these, the Mann-Williamson operation (37) was the best means of producing a true peptic ulcer even though it destroyed the normal anatomy of the gastrointestinal tract. The procedure of Mann and Williamson, a rather difficult one technically, was accompanied by a fair-sized operative mortality; moreover, only eighty-five per cent of the survivors developed subacute or chronic ulcers. When the constant problem presented by the postoperative care of these animals is added to the drawbacks just mentioned, the value of Van Wagoner and Churchill's (2) discovery is readily seen. Cinchophen produces an ulcer, pathologically identical with that in man (8), in less time and in a greater percentage of animals than any previous method, without disturbing the normal physiology per se of the stomach.

Since 1932, other methods and factors have been advocated and employed to produce peptic ulcer; however, only one of them, the histamine in beeswax method introduced by Code, et al (44), has produced true peptic ulcer. This is the only procedure which compares favorably to that of cinchophen in all respects. Unfortunately, histamine evokes maximum secretory response from the parietal cells -- this phenomenon renders it of little value
in determining the efficacy of therapeutic agents proposed for the treatment of ulcer in man.

Roth and Ivy (45) have stated that caffeine produces ulcer experimentally in cats but recently it has been shown (46) that the method is not desirable since toxic doses must be employed and, even then, erosions, only, are found at autopsy.

Van Wagoner and Churchill (24), in their original work, were unable to determine the manner in which cinchophen produced ulcer. They believed, though, it had one of the following modes of action:

1. Cinchophen may have a direct toxic action on the gastric mucosa, combined with digestion by gastric secretions.
2. The drug may combine with the mucin of the stomach and thus remove the normal protection of the gastric mucosa.
3. It may act on the autonomic nervous system and induce erosions by its neurogenic effect.
4. Cinchophen may influence the secretion of gastric juice, either directly or through the endocrine system.
5. May have a general toxic action which affects the stomach directly or by causing metabolic disturbances as a result of its effect on the liver.
6. The nutritional disturbances resulting from the anorexia that follows the ingestion of cinchophen may be a factor in the production of ulcers.

Strangely enough, even now little can be added to these theories on causation as to other possible routes of action.

Myers and Goodman (26) noted in 1932 that ulcers failed to develop in rabbits and concluded that dogs were more susceptible to cinchophen than rabbits.
In 1933, Churchill and Manshardt (9) injected cinchophen into an isolated loop of jejunum and produced chronic gastric ulcers but the jejunum remained normal. From this they concluded that cinchophen does not have a local toxic effect. This conclusion was later confirmed by Hanke (10)(1934), who produced ulcers in cats by giving cinchophen subcutaneously.

Schwartz and Simmonds (27) (1935) confirmed the observation of Myers and Goodman (26) that cinchophen toxicity varied according to species, reporting that guinea pigs and rabbits were very resistant to cinchophen though cats developed cinchophen-ulcer very easily.

Reid and Ivy (47) (1936) advocated gastric mucin as a prophylactic against cinchophen ulcers in dogs and the "acute" toxicity resulting from cinchophen. After giving two groups of dogs cinchophen, one group also receiving one hundred milligrams per kilogram daily of mucin via stomach tube, ulcers were found in one hundred per cent of the control group but in only eighteen per cent of the dogs supplemented with mucin.

Stalker, Bollman and Mann (8), in 1937, gave cinchophen rectally, in intestinal fistulas, intravenously, and subcutaneously, producing gastric ulcers in each instance. In agreement with previous observers, they noted that no ulcer was present at the site of injection, and concluded that cinchophen acts not locally but after absorption. They wondered if cinchophen was excreted by the stomach after absorption but could find
no colorimetric evidence of the drug in samples from fundic pouches containing cinchophen ulcers. Therefore, they felt that cinchophen was not secreted by the gastric mucosa unless it was in very small quantities or in a chemically changed form.

In 1937, to determine the effect of cinchophen on the gastric secretory activity of dogs, Stalker, Bollman and Mann (48) observed two groups of animals. In the first group the stomachs were intact, the second consisted of fundic pouch dogs. In the dogs with intact stomachs, the secretory response to histamine was determined before, after, and during cinchophen administration. According to these investigators, hypersecretion was observed when the symptoms of gastritis appeared. In the second group, the fundic pouch animals, the only secretogogue used was normal diet. Checking gastric acidity and total volume of secretion for twenty-four hour periods, they noted an increase in total acidity and total volume during cinchophen ingestion. Ulcers developed in the pouches of all dogs. There was no increase in pH or pepsin. Thus, they established that during cinchophen administration, an hypersecretion occurs and that this increase in volume is due to an increased activity of the acid producing portion of the stomach, the parietal cells. It is interesting to note that hypersecretion appeared only when the signs of gastritis began and that hyposecretion replaced this shortly after the appearance of the ulcer.
Because of this, they suggested that cinchophen was a toxin of some type since toxins usually stimulate at first and later depress. During the same year, this group of workers (49) reported that coarse food hastened, milk delayed, and alkalies prevented cinchophen-ulcer.

In another publication of results in 1938, Bollman, Stalker and Mann (50) tabulated the effect of various factors in protecting the stomach from cinchophen ulcer: using cinchophen and milk produced acute or subacute ulcers but no chronic ones; cinchophen plus coarse food (bone) yielded one hundred per cent peptic ulcers; no ulcers were observed with cinchophen plus alkaline powders; gastric mucin plus cinchophen gave only fifty per cent ulcers; duodenal extract failed to protect though the lesions were not as severe as the control series; adding histidine gave a larger chronic peptic ulcer than any of the other groups; using gastrojejunostomy and cinchophen, they found lesions to be absent in the jejunum and only a few local mucosal erosions present in the fundus in the allotted time.

Further investigation regarding prevention was done by Winters, Peters and Crook (51), in 1939. Pectin had been used very successfully by these workers in treating the various intestinal upsets in children and when they found that pectin and mucin were quite similar, decided to see the effect of pectin on cinchophen-ulcer. So, pectin was used in addition to cinchophen in one
group of dogs and only eleven and one-tenth per cent developed peptic ulcer compared to one hundred per cent in the cinchophen-control group. Moreover, two dogs, who had demonstrable ulcer at operation, were taken from the control group and given pectin in addition to the cinchophen. They reported that the ulcers healed in these dogs. From these results it was concluded "... pectin has been shown to have prophylactic and curative properties for peptic ulcers produced experimentally with cinchophen ... ".

Neuwelt and Necheles (11) (1940) confirmed the original observation of Churchill and Manshardt, that the drug acts after absorption and not locally. However, administering cinchophen intravenously, so they said, to Heidenhain pouch dogs failed to give an increase in volume secretion following histamine stimulation. According to them this was contradictory to the findings of Stalker and his co-workers (48) on fundic pouch dogs for though the latter gave their cinchophen orally, this could not possibly explain the discrepancy between the findings of the two groups.

A method for determining cinchophen in bile was presented in 1940 by Bradley and Ivy (6), using chronic biliary fistula dogs prepared after Rous and McMaster (52). They estimated that about fifty-five per cent of the drug was eliminated daily in the bile and that it disappeared from the bile twenty-four hours after it was discontinued.
Therefore, they concluded that the liver excretes cinchophen. They also found that cholic acid formation was decreased though the volume of bile was increased. By using this method, Berman and Ivy (16) found very little cinchophen in rabbits' bile (six per cent) and that the sodium salt of the drug intravenously to these animals produced no choleresis.

Swan (53), endeavored to check the "protective influence" of the bile on cinchophen-ulcer (1940). In one group he gave cinchophen orally to dogs who had recovered from cholecystogastrostomy, ligation and division of the common duct. The control group had had no surgery and received only cinchophen. No difference was noted in the incidence of ulcer in the two groups but he observed an ulcerative enteritis in all the dogs, a fact which, heretofore, had never been reported. Considering that marked duodenal regurgitation occurs normally in dogs (54), it is difficult to understand how the short-circuiting of bile into the stomach would protect the mucosa from ulcer anymore than it does normally, since bile is regurgitated along with the other duodenal contents and comes to lie in the stomach.

Also during 1940, Davis, Bradley, Bachrach and Ivy (55) reported several observations regarding the drug. They found intravenous cinchophen increased pyloric sphincter activity in six out of fourteen dogs and that this increase was abolished by atropine but
bilateral section of the vagus in the neck had no effect on it. In view of this and the fact that the majority of cinchophen-ulcers occurred at or in contact with the pyloric ring, they theorized that if pylorospasm could be eliminated, enterogastric regurgitation and gastric evacuation would be facilitated and perhaps this would prevent ulcers from occurring at this point. Consequently, by employing the Rammstedt operation, the incidence of cinchophen-ulcer was reduced almost fifty per cent and gastritis was decreased. This, they believed, indicated that pylorospasm plays a significant role in the formation of cinchophen-ulcer but not an all inclusive one.

Using Pavlov- and Heidenhain-pouch dogs, no significant change was noted in the gastric secretory response of cinchophenized dogs to a test meal. This was not, however, over a twenty-four hour period. Testing liver function by the serum phosphatase and bilirubin clearance methods failed to reveal any damage to explain cinchophen-ulcer. They observed cinchophen to appear in gastric juice or pyloric secretion of their dogs at the rate of one and one-half milligrams per hour maximum, but failed to comment on the significance of this observation.

To investigate the various theories advanced in the literature to establish the relation of peptic ulcer and the endocrine glands, Slutzky, Wilhelmj and Stoner (56), in 1941, gave cinchophen-dogs Antuitrin-S and pos-
terior pituitary extract. All the dogs developed ulcer. After pointing out that cinchophen-ulcer responded to standard therapy, they concluded that these hormones had little effect on peptic ulcer and that clinically "... the percentage of cures obtained is apparently no better than the use of the more orthodox method of treatment. ..."

In 1942, Slutzky, Dietz, et al (57), investigated the effect of histaminase on cinchophen-ulcer in dogs and concluded that histaminase was of no value in prevention of peptic ulcer.

During this year, Annegers, Snapp, Atkinson and Ivy (58), reported that some animals are more susceptible than others to cinchophen as regards gastrointestinal symptoms and hepatitis. In addition, they tried to correlate a decrease of cholic synthesis by the liver with the amount of liver damage produced by cinchophen but failed.

Another report in 1942 by Berman, Snapp, Atkinson and Ivy (7), brings out the choleretic action of cinchophen. Using chronic biliary fistula-dogs, it was found that cinchophen was as potent a hydrocholeretic as dehydrocholic acid (decholin) or mixed ketocholanates (ketochol). They also reported recovering sixty to seventy-five per cent of cinchophen from the dogs via the bile daily.

Andersen and Hill (59), in the same year, sur-
gically altered the continuity of the gastro-intestinal tract by preparing seven gastrojejunostomies, with various sized stomas, and two Finney pyloroplasties. Sufficient cinchophen was then given to these dogs to produce peptic ulcers. The latter appeared in those animals where continuity had been modified the least. The animals with relatively large stomas at the gastro-intestinal junction developed no ulcers. They concluded that "... the better the opportunity for admixture of gastric and intestinal secretions, the greater is the inhibition of ulcer production due to cinchophen."

Two years later, in 1944, Annegers, Snapp, Atkinson and Ivy (60), concluded that when the various bile acids were used, an increase occurred in biliary cinchophen excretion.

In 1945 Nasio (61) reported that five milligrams of Calciferol or vitamin D₂ parenterally daily protected sixty per cent of his dogs from developing cinchophen ulcer in thirteen to nineteen days. His findings are presented in a modified form (see Table 1).
### TABLE I

**EFFECT OF CALCIFEROL ON CINCHOPHEN-ULCER**

<table>
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<tr>
<th>Dog Number</th>
<th>Days Given</th>
<th>Cinchophen and Calciferol</th>
<th>Results</th>
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<td>13</td>
<td></td>
<td>Erosion lesser curvature, gastritis, Ulcer, Ulcer, Healed antral lesions</td>
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<tr>
<td>3</td>
<td>14</td>
<td></td>
<td>Ulcerous erosion, Ulcerous erosion, Ulcer</td>
</tr>
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<td>2</td>
<td>15</td>
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<td>Simple antral erosion, Healed antral ulcerous lesion</td>
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<td>1</td>
<td>17</td>
<td></td>
<td>Gastritis</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td></td>
<td>Ulcer</td>
</tr>
</tbody>
</table>

*Modified chart of Nasio's (61) results*
EVALUATION OF THE WORK TO DATE
ON CINCHOPHEN-ULCER

The task of evaluating the accumulated evidence on experimental cinchophen-ulcer in terms of pathogenesis, is truly a difficult one. Unfortunately for this purpose, discrepancies exist in the data pertaining to several basic observations, as well as a paucity of corroborative evidence for other findings of fundamental importance. It follows then, that any considerations of etiology and the conclusions derived therefrom, are, with rare exceptions, wholly conjectural. A distinct effort has been made to judge the evidence fairly and to preserve a well-defined line of demarcation between fact and hypothesis. For the purposes of coherence and clarity, conjecture and actuality may have merged somewhat in several instances but the intent was not misrepresentation.

Summarizing the chronicle to establish a framework for the discussion, one is struck by the absence of correlation between the various known quantities in the literature. Aside from the early articles of Stalker, Bollman and Mann (8, 48, 49, 50), no attempt has been made
to piece together the saga of cinchophen-ulcer from the isolated bits of information which are available. It is clear, from the chronicle, that the following points have received corroboration and are, therefore, acceptable:

1. Cinchophen produces a true peptic ulcer (11, 24, 28, 48);
2. It has no local toxic effect but acts after absorption (8, 10, 11);
3. The drug is a choleretic (1, 6, 7) and is excreted by the liver in the bile (6, 14) and urine (14);
4. Mucin (42, 50), pectin (51), milk (49), alkaline powders (49), gastrojejunostomy (50, 59), and pyloroplasty (55, 59) prevent or retard cinchophen-ulcer formation;
5. The ulcer is hastened by coarse food (59);
6. Augmented by histidine (histamine) (50);
7. Cinchophen produces no increase in pH or pepsin of the gastric juice (48).

In contrast to these undisputed points, however, the validity of two basic observations is questioned by the evidence in the chronicle.

The first deals with the question of secretion of cinchophen by the stomach. Initially, Stalker, Bollman and Mann (8) were unable to find unchanged cinchophen in the secretion of fundic pouch dogs receiving the drug. Not long ago, Davis, et al (55), reported cinchophen was secreted at the maximum rate of one and one-half milligrams per hour by the stomach. The results of the two groups appear contradictory but are not for the second group uses a method (6) which probably determines a _chemically changed_ form of the drug (17). Regardless
of whether or not cinchophen is secreted by the stomach, the possibility that the drug produces an ulcer after re-secretion was eliminated by Stalker and his co-workers (50). These men fed normal dogs the secretions of fundic pouches containing cinchophen-ulcers but the normal animals did not develop an ulcer. Consequently, this avenue can be regarded as closed.

The second conflict concerns the effect of cinchophen on gastric secretion. Stalker's group (48) reported an hypersecretion while Neuwelt and Necheles (11) found no increase in gastric secretory activity. If one carefully considers both reports, it is clear the data of the two groups are incomparable when speaking of fundic pouch dogs. Neuwelt and Necheles reported results on fundic pouch dogs but employed the secretogogue and observation period used by Stalker and his group on their whole stomach animals. Therefore, the findings of Neuwelt and his partner apply to those of Stalker, Bollman and Mann on dogs with intact stomachs—not to the latter's findings on fundic pouch dogs! In contrast to the use of histamine as a secretogogue and an observation period of three hours as employed by Neuwelt and Necheles, Stalker and his colleagues gave their fundic pouch dogs food and observed gastric secretion for twenty-four hour periods. Thus, on the basis of the findings of Neuwelt and his co-worker there is no reason to disregard or hold in question the significant report of an
hyperacidity in fundic pouch animals by Stalker, Bollman and Mann. However, because the point is so important basically, it should be the object of further experimental effort.

Interestingly, the data of Neuwelt and Necheles (11) lend additional positive evidence to the assertion of Wilhelmj and his group (62) that the dilution factor must be corrected for when using subjects where dilution of gastric contents can occur. Manifestly, the hypersecretion reported in unoperated dogs by Stalker's group (48) could have been due, in whole or in part, to increased activity of the pyloric sphincter since dilution was unchecked and the recent work by Davis, et al (55), suggests such may have been the case. Had dilution of a known amount of phenol red solution by secretory activity of the stomach been determined in the unoperated dogs before, and during, cinchophen ingestion, the findings in this group could have been regarded as significant. As it stands now, the findings of Stalker's group on dogs with intact stomachs are valueless.

A third group (55) has reported an absence of gastric response to cinchophen fed to fundic pouch dogs but their observation period was much shorter than Stalker's group so the observations are not contradictory.

In the discussion, therefore, it is assumed that cinchophen produces an increase in the secretory activity of the stomach over the twenty-four hour period and that
this hypersecretion is chiefly due to an increase in the total volume of acid produced, or hyperacidity as defined by some (63). Even disregarding the findings of Stalker's group (48) completely, one would be justified in this assumption for there is a wealth of circumstantial evidence favoring the existence of an hyperacidity, be it relative or absolute, in peptic ulcer produced by cinchophen. To begin with, any procedure or form of prophylaxis, which prevents or retards cinchophen-ulcer formation, does so primarily be decreasing gastric acidity. Moreover, in examining all the known methods of producing a true peptic ulcer experimentally, it is impossible to find one which is not dependent on an absolute or relative increase in gastric acidity. By a relative increase in gastric acidity (Wilhelmj's Type II hyperacidity (63) ) is merely meant that acid is present in normal or even lowered amounts but is higher proportionately than one of the protective mechanisms, which is decreased or missing, e. g. Wolf and Wolff (64) continuously wiped mucus away from a portion of gastric mucosa exposing this area to a normal amount of acid and pepsin and gained a typical peptic ulcer--the term "relative hyperacidity" applies to this normal amount of acid. Consequently, it follows in all probability that cinchophen-ulcer has this common denominator.

Turning now to consideration of the possible modes of operation cinchophen may follow in producing peptic ulcer, the various modes suggested originally by
Van Wagoner and Churchill (24) will be used for discussion, with minor changes, for it is difficult to conceive of a possibility not included by them.

The first possibility suggested by these authors, the direct toxic action, has been eliminated beyond all doubt (8, 9, 11). Therefore, cinchophen acts after absorption into the blood stream.

The second hypothesis that "... it may combine with the mucin of the stomach and thus remove the normal protection of the gastric mucosa ...", is relatively unexplored. We have seen that gastric mucin given orally has a beneficial effect on cinchophen-ulcer, having prevented eighty-two per cent in one series (47), fifty per cent in another (48). The discrepancy in the efficacy of gastric mucin prophylactically is probably explained by the higher daily dosage of mucin in the first group (47) and also the small number of animals used in the second (four dogs) (49). Likewise, pectin (51) which has physical properties similar to mucin, has been shown to have marked curative and prophylactic properties when used on cinchophen-ulcer. In contrast to the alkalies which reduce gastric acidity by neutralization, mucin and pectin reduce acidity by absorption (51, 65). If it were not for their colloidal natures, little change would be noted in acidity for they are only slightly alkaline (66, 67). Consequently, these agents must have prevented cinchophen-ulcer in one of two ways: (1) by
replacing mucus, defectively combined with cinchophen, they restored normal protection to the gastric mucosa and prevented a normal amount of hydrochloric acid and pepsin from attacking the mucosa and forming an ulcer, or (2) in the event mucus was not defective, they nullified the increase in total volume of acid by the added effect of their absorptive powers.

Recently it has been shown that peptic ulcer can be produced in the presence of normal gastric juice merely by depriving the mucosa of its protective covering, gastric mucus (64). This corroborates earlier work demonstrating the protective role of mucus (68). It would be very easy for cinchophen to unite with mucus and render it incapable of clinging tenaciously to the mucosa, thus it would be swept aside by normal motility and the bolus of food. Or, by its union with mucus, cinchophen could destroy the absorptive powers of this colloid so that hydrochloric acid and pepsin would be free to attack the wall. Just what the sequence of events would be if cinchophen did combine with mucin is difficult to say. Whether cinchophen would pass directly from the blood stream into the mucus secreting cells, or whether it would first be changed by the liver and return from there to the cells or to the surface of the stomach, are possibilities which can be settled only after further experimentation. Additionally, one cannot forget the chemically changed cinchophen excreted by the
liver in the bile. Along with the other duodenal contents, this substance also comes to lie once more in the stomach and it would not be improbable that this chemically changed cinchophen could combine with mucin and produce the effects advanced above. The necessity for further investigation of the role of cinchophen contained in bile is obviated because cinchophen ulcers occur in pouches detached from the stomach, i.e. where it is impossible for duodenal contents to appear (48).

The second manner in which mucin and pectin could have been beneficial presupposes an hyperacidity. In that event, these colloids would augment normal mucus instead of replacing defective mucus.

The third modus operandi, the possible neurogenic action (24), presents a rather complex problem. To adequately consider this theory, one must recall the various ways in which a drug can act on the autonomic nervous system; centrally, by stimulation of the centers in the brain, and peripherally, by (1) stimulation of production of acetylcholine or some such substance, (2) by having the same action as this substance, or (3) by inhibiting production of the esterase responsible for destruction of this substance. Applying these concepts to our problem simplifies it somewhat. In the literature, there are only three factors which ally cinchophen directly to the autonomic nervous system: (a) histidine and cinchophen given concomitantly produce an ulcer lar-
ger than that created by cinchophen alone (50), (b) histaminase has no effect on cinchophen-ulcer (57), and (c) cinchophen given intravenously has an immediate autonomic-like action (8).

From the fact that histidine and cinchophen augment one another, one can only conclude that they are not antagonistic and that perhaps cinchophen acts by producing histamine. This conclusion, of course, would be ruled out by the second factor except that the histaminase employed was not effective in vivo. Time and purpose do not permit indulgence in the subject of histaminase and anti-histamine substances. For our purpose suffice it to say that the preparations of histaminase available, thus far, have all been quickly inactivated when given orally or when given intravenously and intramuscularly, too impotent to appreciably antagonize histamine though potent in vitro (69). One group (70) tried to increase potency by increasing dosage of the preparation but was unable to because the protein containing the enzyme was toxic in large amounts. Unfortunately, none of the recent anti-histamine substances which are fairly effective on histamine induced gastric secretion (71,72,73), have been tried in the prophylaxis of cinchophen-ulcer, therefore, until such time as an effective anti-histamine substance is used concomitantly with cinchophen, the possibility remains that cinchophen may stimulate gastric secretion by the release of histamine. The autonomic-like action
of cinchophen intravenously cannot be localized or confirmed by the data gathered to date.

Actually, therefore, from the preceding trio
there is very little to gain, viz: (1) cinchophen might act by producing histamine, and (2) when administered intravenously, it has an autonomic-like action.

The fourth, and last, factor linking cinchophen with the nervous system, is an indirect one gained by inference. Let us accept for the moment, the conclusion that, there is, in dogs with intact stomachs, an increase in the total volume of acid during cinchophen administration (48). Then, if it is true that Heidenhain pouch-dogs are vagally denervated (74), in view of the findings of Neuwelt and Necheles (11) we could conclude that (1) cinchophen produces ulcer by the continuous secretion of hydrochloric acid (similar to histamine), and, (2) that it does so by centrally stimulating the autonomic nervous system, specifically, the vagus nerve. However, since Stalker, Bollman and Mann (48) found an increase in total volume in their Heidenhain pouch-dogs, and their findings on dogs with intact stomachs not significant, conclusions regarding the role of the vagus nerve or the autonomic nervous system in cinchophen-ulcer cannot be drawn without further study. The premise that an hyperacidity is produced by cinchophen, was taken up, in detail previously.
Returning for the moment to the evaluation of cinchophen's relation in the literature to the autonomic nervous system, it is self-evident that this hypothesis is still in the stage of antithesis, and that much work remains to be done to confirm or disprove it. That the hypothesis is feasible is undisputed.

In considering the fourth possibility it will be necessary to use some indirect evidence. Unless cinchophen has a neurogenic effect, it is difficult to see how the drug, unchanged, could stimulate the parietal cells directly except on a hormonal basis. That the drug, per se, is an hormone can only be assumed after every other possible modus operandi has been eliminated. That the drug might act by stimulating the endocrine system to produce such a hormone, or by destroying a hormone necessary for integrity of the gastric mucosa, are other possibilities. The last two will be dealt with indirectly, as stated above.

Fairly recently, evidence has been presented clinically and experimentally in an effort to link peptic ulcer with a faulty-functioning posterior lobe of the pituitary gland (75,76,77). Similarly, low sex hormone levels have been advanced as another etiology (78, 79,80). These assertions were based on premises gathered from clinical observations and the regression, in certain clinical cases, when these hormones were administered. Experimentally, however, all the cincho-
phen-dogs of Slutzky, Wilhelmj and Stoner (56) developed ulcer in spite of prophylactic Antuitrin-S and posterior pituitary extract. In an endeavor to produce achlorhydria, Atkinson and Ivy (31), employed theelin, pituitrin and pitressin, among other substances. Theelin was given to dogs and to a female ulcer patient who was undergoing menopause. In neither did it produce a decrease in gastric acidity. Moreover, one infers that the ulcer patient experienced no relief even after twenty-two days of therapy. Likewise, pituitrin and pitressin in their hands failed to produce an essential change in gastric secretion during a two week period.

After due consideration of the positive and negative findings, one can definitely conclude that, in rare instances, a defect of the posterior pituitary gland may produce peptic ulcer, but, generally speaking, it has absolutely no relation to ulcer formation or regression. Consequently, it follows that in all probability, cinchophen does not act by destroying one of the various hormones of the endocrine system. However, that it may produce or destroy a hormone arising in the liver or digestive tract is neither affirmed or denied. This approach, along with the others mentioned, deserves further investigation.

The fifth mode of operation (24) is barren of investigation. Although we know cinchophen affects the liver, whether this attack on liver function disrupts the
metabolism to the extent of peptic ulcer formation, or whether the drug itself is a general toxin and the pathology in the stomach merely a manifestation of this toxicity, has not been determined.

The sixth, and last, theory, regarding the nutritional disturbances from the anorexia as the factor in the production of peptic ulcer (24), is, to our way of thinking, impossible; however, to its role as a probable contributory factor, we agree. Thorough examination of Reid and Ivy's (47) data brings out the point that the dogs receiving gastric mucin had a good appetite and fair general condition rather than an anorexia. We remember, of course, that these dogs developed ulcer in only eighteen per cent of the cases. It could be argued from this that the beneficial effect produced by mucin is by means of returning the appetite to normal as well as by absorption of the hyperacidity. Nevertheless, determination of this role has yet to be done experimentally.

The significance of Nasio's report (61) on the efficacy of calciferol (vitamin D₂) in the prevention of cinchophen-ulcer remains to be seen. The relatively short period of observation, however, hardly warrants his conclusion that calciferol prevented ulcers in sixty per cent of animals fed cinchophen.

No further proof than this synopsis and evaluation is needed to bring out, conclusively, the great need
for further inquiry into the subject of the etiology of cinchophen-ulcer. The entire field is open to speculation and experimentation and a significant number of hypotheses remain to be ruled out before the subject will be raised above the stage of antithesis.
CHAPTER IV

PURPOSE OF THIS INVESTIGATION

The purpose of this treatise is to deal with the role of the vagus nerve in the genesis of peptic ulcer produced by cinchophen. In the previous consideration of the third modus operandi suggested by the discoverers (24), that the drug might have a neurogenic action, the three ways in which a substance could act on the autonomic nervous system were given. In the experiments which follow, disruption of the vagus nerves in the thorax was undertaken to determine if cinchophen stimulated the vagus centrally and produced ulcer by constant stimulation of the parietal cells to secrete acid.

A. Consideration of the Possible Neurogenic Action of Cinchophen

From the evaluation of the work on cinchophen in experimental peptic ulcer, very little doubt remains that cinchophen produces an increase in the total volume of acid over the twenty-four hour period (48). For the sake of simplicity this increase will be designated by the term hyperacidity throughout the remainder of the investigation. In brief, since alkalies (49), mucin (47,50), pectin (51), and increased admixture of gastric juice with
intestinal contents (50, 55, 59), prevent, to a marked degree, the formation of cinchophen ulcer, in all probability the drug causes its effect at least partially by producing the before-mentioned hyperacidity, for all these cinchophen-ulcer antagonists have a therapeutic common denominator, i.e. reduction of gastric acidity.

Assuming, therefore, that the intermediate-result of cinchophen is an hyperacidity, the end-result a peptic ulcer, only the primary-result or effect of the drug is the unknown in this theorem. Now, this hyperacidity is not due to an increase in pH of gastric juice but, as we have seen, is the result of prolonged gastric secretion (48). The typical fundic pouch curve of Stalker, Bollman and Mann (48) (see Figure 2) demonstrates the

![Fig. 2.—Gastric secretory curves of fundic pouch dogs before and during cinchophenization as redrawn from Stalker, Bollman and Mann (48).]
failure of the curve to drop to the level of the normal secretory curve. From comparison of the two curves, the prolongation in the cinchophenized pouch dogs is obviously due to one of two things, a prolonged intestinal phase, or an increased basal (resting) phase of gastric secretion.

The etiology or mechanism of the basal or resting phase of gastric activity in dogs has never been clearly explained. However, that it is not due to the vagus nerve has been proven a fact. We are not of the opinion that the hyperacidity is due to an increased basal secretion, as such, but rather that an additional phase has been superimposed on it to give the increase.

One of the most likely candidates for this role would be a cephalic phase, which is not to be confused with the psychic phase. Both have the same common path, the vagus, but the trigger mechanism or agent is not the same. The psychic phase has a sensual one, while the cephalic phase spoken of here would have cinchophen as the stimulant.

It has been shown that cinchophen is excreted continuously in the bile over a twenty-four hour period (6). Conversely, it follows that cinchophen is constantly being acted upon by the liver during this period and, therefore, a form of the drug if it were capable of producing such stimulation would be continually circulating in the bloodstream. Very easy, then, for
this substance to stimulate the vagal centers continuously and thus superimpose a cephalic phase on basal secretion.

The only objection to this rationalization is the belief that Heidenhain pouches are vagally free. Thus, to agree with this theory, the pouch-dogs in Stalker, Bollman and Mann’s series (48) should have demonstrated an absence of secretory response to cinchophen. Needless to say, they reported just the opposite. Pavlov (82) was the first to voice this imperfection of the Heidenhain pouch. The consensus among physiologists agrees with this belief (83). However, in view of the fact that a major portion of the posterior vagus goes to the coeliac plexus (84) and that many fibers from this plexus are intimate with gastric blood vessels, one seriously questions that such pouches are vagally free as long as they have a generous blood supply.

Pavlov believed that the Heidenhain pouch was vagally free for these reasons:

(1) According to Dr. Khizhin (85) the posterior vagus in the dog followed the greater curvature so that a Heidenhain pouch severed the vagal fibers completely.

(2) The effect of "sham feeding" is eliminated when the vagi are cut in the neck (86).

(3) The same holds true when the vagi are cut below the diaphragm (86).

(4) "Sham feeding" elicits no response in the
Heidenhain pouch (86).

However, we definitely know that it is impossible to destroy all vagal fibers subphrenically (87). This means that in number three above, the vagi were partially present anatomically and functionally. Why a few drops of gastric secretion did not form during prolonged "sham feeding" in this animal cannot be answered. Since the third proof is not valid, predication that the Heidenhain pouch is vagally denervated is unwarranted when based on this premise. One can only state that the vagal innervation of the Heidenhain pouch is decreased compared to the normal intact stomach.

In the original description of the operation, Stalker, et al (48), stated that each pouch retained its blood supply. Our experiments aided indirectly in this dilemma. If an ulcer failed to appear in this investigation, the pouches used by Stalker and his group were not vagally free, or if an ulcer appeared, the pouches were possibly vagally free, provided that the results of Stalker's group are correct. Thus, additional evidence would be added to the statement that central stimulation of the vagus nerves had no relation to the etiology of cinchophen-ulcer. The reasons just enumerated were felt to be sufficient justification for undertaking this investigation in spite of the objection voiced above.
B. The Vagus Nerve and Gastric Secretion Clinically

The vagus nerve has been associated with gastric secretion for a great number of years but the significance of this association was not grasped to any great extent until Pavlov (88) performed his classical experiments. Disruption of the vagus nerves as such is not by any means a new procedure since our knowledge of this nerve has been gained, for the most part, from unilateral or bilateral section at various levels in the body. However, fairly recently the procedure has again become prominent therapeutically and experimentally due principally to the efforts of Dragstedt (89,90). In spite of the fact that vagotomy was first performed in 1815 (91) and has been repeated many times since, the exact role played by the nerve in gastric secretion in man remains controversial. For instance, that section of the nerves before reaching the stomach produces a decrease in motility and gastric secretion cannot be denied. However, diversity of opinion has arisen over the permanency of these results in man.

Clinically vagotomy has been used to treat a number of disorders for instance, vagotonia (92), the gastric crises of Tabes dorsalis (93), spasm (94), and peptic ulcer (95,96). In some of these, the results were very favorable but around the value of the procedure in peptic ulcer there remains an aura of suspicion
and criticism mingled with intense enthusiasm. Latarjet (96) and Schiassi (95) were the foremost advocates and employers of vagotomy in the treatment of peptic ulcer. A composite of the diagrams showing Schiassi’s procedure is given (Plate I). Schiassi employed gastroenterostomy along with disrupting the nerves supplying the pyloroduodenal region and circumcision of the pyloric antrum to destroy vagal fibers in the treatment of intractable ulcer. These procedures he felt gave the ulcer bearing area a rest from the trauma of the bolus of food and the irritant action of gastric juice. A high incidence of success was reported in his patients.

Several years later, Pieri, Lapenna, and Tanferna (97,98) published their observations on patients in whom they had cut the vagi bilaterally above and below the diaphragm and followed two years postoperatively. They reported that the initial decrease in acidity and motility persisted for only a short period of time and then returned to the pre-operative level.

In 1942, Dragstedt (89) reviewed peptic ulcer and was convinced that ulcer in man was due to an excessive, continuous secretion of normal gastric juice. Moreover, believing that this hypersecretion was neurogenic in origin and that it could be due to stimulation of the secretory fibers of the gastric vagus to constant excessive activity, he devised a supra-diaphragmatic vagotomy and performed the same on certain intractable
Fig. a.—Distribution of the gastric vagi as described by Latarjet. a,b. The vagus nerves. c,c. Plexuses of Auerbach. d,d. Ganglia of Opechowski. e,e. Hepatic artery. f. Coronary artery. m. Hepatic plexus of the sympathetic (coeliac plexus). p,p. Pyloroduodenal sympathetic trunks (from the hepatic plexus).

Fig. b.—Sites of incision made by Latarjet and Schiassi to destroy the gastric vagi. A. Incision of the gastrohepatic ligament with resection of the pyloroduodenal sympathetic nerves; resection of the pyloric artery. B. Resection of the para-sympathetic group of nerve fibers (intraparietal division of the vagi branches). C. Incision of the gastrocolic ligament to give access to the posterior cavity of the epiploon.
PLATE I

Fig. a.*

Fig. b.*

*Photographed from Schiassi (95)
ulcer patients with success (90). Subsequently, he has accumulated quite a series, the majority all favorable to this procedure (99, 100, 101, 102). Other men have also reported results using this operation, some favorable (103, 104, 105), some not so enthusiastic (106).

The hypothesis of Dragstedt was based on the presence of an excessive nocturnal secretion in the peptic ulcer patient. A short time ago, Sandweiss, et al (107), contradicted this bit of evidence for these workers found that compared to the normal individual, the ulcer patient does not have a greater total volume of nocturnal secretion but rather a longer emptying time, due perhaps to pylorospasm, which accounts for the increased recovery of gastric contents. In brief, the ulcer patient does not secrete more, just holds it longer, according to Sandweiss.

Initially of course, Dragstedt employed supra-diaphragmatic section of the vagi exclusively for he felt it was not possible to cut all the fibers subphrenically. Recently, his group (102, 108) has modified the procedure so that now the vagus nerves are cut below the diaphragm and a gastroenterostomy performed simultaneously. Colp and his colleagues (109) employ subtotal gastric resection along with subphrenic vagotomy believing this to be a better procedure than vagotomy alone.

At any rate, several years must pass before any
conclusions can be reached regarding the advisability and value of these procedures in the management of peptic ulcer in man. The purpose, here, is not to indulge in this debate but to deal with the effect of vagotomy in the dog and its value in the prevention of cinchophen-ulcer.

C. The Vagus Nerve and Gastric Secretion in the Dog

In contrast to the confusion surrounding the effect of bilateral section of the vagus nerves at different levels in the body of man, the knowledge of this procedure in the dog appears clear-cut. Undoubtedly the major portion of the credit for this clarity belongs to Hartzell (87). Pavlov (86,88), in his experiments, had demonstrated conclusively that the vagus nerve was responsible for the psychic phase of gastric secretion by "sham feeding" dogs in whom the vagi had been sectioned in the neck (38a). He showed that this reduced greatly the amount of gastric juice secreted and in several dogs who survived this procedure, noted an increase in emptying time. Unfortunately, the experiments of Pavlov were not conducted with an eye to determining how long the vagus would remain functionless.

Hartzell (87) (1929) after reviewing the literature, realized conclusions regarding the effects of vagotomy could not be drawn clinically or experimentally,
clinically because the observations were incomplete, experimentally because pre-operative normal values were often incorrect, the animals frequently had had previous surgery on the stomach, and the postoperative observation period was usually too brief. Correcting for these sources of error, he de-vagotized a number of dogs, recording his observations over a period of five and one-half months. Establishing normal pre-operative secretory values for each animal, the vagi were cut above the diaphragm or below the diaphragm and the resultant secretory values recorded. To insure cutting all the vagal fibers below the diaphragm, Hartzell severed the pyloro-duodenal nerves and circumcised the stomach at the junction between cardia and esophagus, down to the mucosa, and closed the incision by inverting the serosa. There was a marked decrease in free and total acid in those dogs sectioned intrathoracically which persisted throughout the period of observation. Those animals sectioned abdominally had, for all practical purposes, the same type of secretory curve exhibited pre-operatively except that the curves were of shorter duration.

From this work two points are gained: (1) in dogs, it is almost impossible to section all fibers of the vagi subphrenically, and (2) transthoracic vagotomy produces a decrease in gastric acidity which persists for at least five and one-half months.

Two and one-half years later, Vanzant (110) ex-
amined the dogs used by Hartzell (87) and reported that gastric secretion and motility had, for all practical purposes, returned to normal. She demonstrated that this return was due to the parasympathetic system, since atropine abolished secretory response as it had before, even though no regeneration of the vagi was present. Therefore, the vagus had re-established itself functionally but not anatomically. Whether the return was accomplished by means of a shunt over fibers which were missed, such as the intrinsic plexuses of Auerbach and Meisner, or an hormonal basis, no one knows; however, according to Vanzant's findings, that it did not do so by regeneration is certain.

Shapiro and Berg (111) (1932) performed gastric resections (Polya type) and vagotomies, abdominally, locating the vagi anatomically after the description of McCrea (84). In a few weeks the initial decrease in acidity disappeared.

Sectioning the vagus bilaterally in the chest, Wilhelmj, McCarthy and Hill (112) (1937) repeated this work on dogs for previously they had found that subtotal gasterectomy (Polya type) reduced gastric acidity (113). These workers reported that combination of the two procedures produced an acidity which was lower than that following gasterectomy alone and, in contradistinction to the results of Shapiro and Berg (111), these changes persisted for at least three months without the slightest
indication of a return to normal at that time.

D. Means Available to Study the Role of the Vagus in Cinchophen-Ulcer

To adequately observe the effect of the vagus on cinchophen-ulcer, two things were necessary: (1) a stomach vagally free, and (2) an animal that lived a sufficient period of time after disruption of the vagi to observe if a cinchophen-ulcer would develop. By sectioning the vagi in the neck, the stomach would be vagally denervated but chances are the animal would die (114,115), an undesirable possibility. Thus, two alternatives remained: to cut the vagi immediately above the diaphragm or just below it. With the wealth of evidence advanced above favoring the transthoracic, supradiaphragmatic procedure for successful elimination of the gastric vagi of the dog, there can be no question that this procedure is the one of choice. Therefore, intrathoracic vagotomy was the procedure used exclusively in all experiments.

Nothing was done to disrupt the third neuron in vagal transmission, in myenteric plexuses of Auerbach and Meisner (116). Whether the second neuron in transmission of the vagal impulse, the nerve itself, is destroyed high enough intrathoracically to obviate an ultimate shunt of vagal impulses over the tertiary neuron is not within the scope of this investigation. Suffice it to say, the vagi were destroyed as completely as pos-
sible and still have live animals for chronic experiments, and that it was previously shown that the effects of trans-thoracic vagotomy persisted for certain three and one-half months in one series (112), five and one-half months in another (87).
CHAPTER V

EXPERIMENTAL DATA AND PROCEDURE

Despite a rather extensive search through the literature, it was impossible to find an adequate description of the procedure for cutting the vagus nerve transthoracically (87,112,117). In addition, the course of this nerve in the thorax as given by various authors (83,84,118) was not as detailed as was deemed necessary. Consequently, in order to successfully resect the vagi and guarantee a stomach that was vagally free, it was necessary to observe the course of the vagus nerves in the thorax of a significant number of dogs and, from these observations, to devise an operative procedure, which would be applicable to any dog used.

A. Anatomical Course of the Vagus Nerve in the Thorax of the Dog

After observing the course of the vagus nerves in the thorax of forty-two dogs, who came to autopsy for various reasons, it was apparent, in contrast to man (119, 120), that both nerves pursued a constant course (see Figure 3) deviating from the normal only in diameter of the branches. The typical description, which follows, was taken from the autopsy protocol of one of the animals
Fig. 3.—Schema of the vagi in the thorax and abdomen of the dog.
photographed to demonstrate the course of the vagi in the thorax.

In this dog the course of the vagus nerve was easily demonstrated in the thorax and neck. The ribs were cut away, the nerves dissected, black India ink applied to the vagi along with the phrenic nerves, and pictures taken to show the course and relations of the phrenic and vagus nerve on each side (Plates II, III, IV, V).

As the vagus nerves parted company with their respective carotid sheaths, each on entering the thorax gave off showers of nerve fibers, which ran to the base of the heart. Shortly thereafter, each vagus gave off a recurrent laryngeal nerve, the left as it crossed the aortic arch anteriorly, medial to the left subclavian artery, and the right as it crossed anterior to the brachiocephalic artery. Then, running in the mediastinal pleura along the lateral walls of the trachea, the right passing under the azygos vein, the left having crossed the ascending aorta diagonally, both nerves passed the hilus of the respective lungs posteriorly. As they did so, numerous fibers were given off to each hilus, where the fibers united to form the pulmonary plexus on each side, while the main trunk of each vagus continued caudad.

Below the level of the tracheal bifurcation, the nerves came to lie on the lateral walls of the esophagus, still invested in mediastinal pleura. Immediately below this level, the right vagus divided into an anterior and
RELATIONS OF THE RIGHT PHRENIC NERVE IN THE DOG

RIGHT LATERAL VIEW

- Heart
- Right Phrenic Nerve
- Pleura
- Trachea
- Right Vagus Nerve
- Amygos Vein
- Esophagus
- Lung
- Posterior Vagus Nerve
PLATE III

Relations of the Right Vagus Nerve in the Dog
PLATE IV

Relations of the Left Phrenic Nerve in the Dog
Relations of the Left Vagus Nerve in the Dog
a posterior branch. The left vagus divided into an anterior and a posterior branch a little farther caudad. As soon as the anterior branch of the right vagus was off, it crossed the esophagus anteriorly and united with the corresponding branch of the left vagus in the anterolateral plane of the esophagus, approximately halfway between the level of the hilus of the lung and the diaphragm. The nerve thus formed, the anterior vagus, continued caudad with the esophagus and pierced the diaphragm a little to the left of the anterior plane of the esophagus. The nerve remained covered by, and invested with, mediastinal pleura during its entire progress through the thorax.

The posterior branch of the right vagus continued to run caudad but traversed the length of the esophagus on the right beginning anteriorly and gradually sloping posteriorly. A short distance before piercing the diaphragm, it was joined by the posterior branch of the left vagus to form the posterior vagus. This nerve then accompanied the esophagus through the diaphragm in the postero-lateral plane. The course of the left posterior vagus was a gradual sloping one behind the esophagus, passing almost the entire distance between hilus and diaphragm before coming to lie on the right postero-lateral wall of the esophagus where it joined the posterior branch of the right vagus.

Esophageal fibers were constantly given off by both vagus nerves on the journey through the chest.
The course pursued by the right and left vagus nerves in the thorax as observed at the autopsy table agrees with that described by Jemerin and Hollander (83); however, in contrast to the report of McCrea (84), the right and left vagus nerves divided, below the level of the lung roots, usually into one anterior and one posterior branch. In only two dogs was it found that the left vagus divided into three branches, one going anterior and the other two coursing posterior. The supernumerary third branch was insignificant in comparison to the other two; it also joined the right posterior vagus about five millimeters from the junction of the other left posterior vagus with the right. Plexus formation about the esophagus was observed in none.

B. Anatomical Distribution of the Abdominal Vagus in the Dog

The distribution of the vagi in the animals that came to autopsy corresponded to the descriptions of McCrea (84) and Jemerin and Hollander (83). This lends additional proof to the assertion of the latter that Pavlov and Khizhin (85) were in error in their belief that the posterior vagus follows the greater curvature of the stomach.

In discussing the posterior vagus, one point must be made clear: McCrea (84) says the major portion of this nerve after entering the abdomen does not go to the lesser curvature of the stomach but to the coeliac plexus, the
pancreas, the spleen, the superior mesenteric artery and hepatic artery, and to the renal and suprarenal plexuses. This was observed to occur in our animals. McSwiney (121) states that McCrea's work confirmed the previous findings of Perman (122), Latarjet (96), and Kollman (123). In view of the generous supply of left vagal fibers to the coeliac plexus, that fibers from the coeliac plexus are intimate with blood vessels, that the Heidenhain pouch has a generous blood supply, that the myenteric plexuses have not been destroyed, it seems improbable that a fundic pouch with a good gastric blood supply would be completely denervated. Moreover, it follows from this that though a Pavlov pouch has an interrupted vagal supply (83), the interruption is only a partial one since the pouch has an uninterrupted gastric blood supply. Furthermore, in the Pavlov pouch the myenteric plexuses are undisturbed in the flap of the pouch. Since the vagus ends in these plexuses (124) and it has been demonstrated that the tertiary neuron in the transmission of the vagal impulse is located in the myenteric plexuses (125,126), the free passage of the plexuses through the isthmus of the Pavlov pouch means that the vagal impulse is uninterrupted.

With such evidence, both pouches should be regarded as being supplied by the vagus nerve. However, it is agreed that they do not have all the vagal fibers originally supplied them, the Pavlov pouch having more
vagal fibers though than the Heidenhain pouch. This might explain the differences in their response to Pavlov's "sham feeding" experiments (86). As pointed out by Jemerin and Hollander (83), previous criteria did not distinguish "... a partial vagal response from a complete one. ... " In the absence of further data, it is useless to try and determine the degree of vagal integrity of these pouches for the discussion would be hypothetical. Obviously there is a great need for a method and standards for "... determining the exact functional capacity of a pouch. ... "(83)

C. Technique for Intrathoracic Vagotomy in Dogs

From observations made at the autopsy table and benefiting from mistakes made during several operations, the following procedure was derived:

After clipping and shaving the right chest, the dog was placed on the table on the left side to expose the right chest. The area was scrubbed with Linimentum Saponis Mollis (Tincture of Green Soap) and water, swabbed twice with an antiseptic solution of iodine and alcohol, and the skin allowed to dry between each procedure. Finally, Tincture Merthiolate, one to one-thousand (1:1000), was poured over the area. Although iodine and merthiolate theoretically should not be used together, in these experiments fewer wound infections occurred using these together than when iodine and alcohol
solution was used alone, nor was any undesirable skin reaction noted. These elaborate precautions were taken to minimize the chance of infection which so frequently follows thoracotomy in the dog.

Employing standard aseptic surgical technique throughout, the thorax was draped and an incision about four inches long was made over the seventh or eighth interspace, the center of the incision lying in about the mid-axillary line. Wound towels were attached, and the right thorax opened taking care to avoid the intercostal artery, vein and nerve, superiorly. A self-retaining retractor was inserted between the ribs and spread. The anesthetist began positive intratracheal pressure at this point.

Using a wet gauze sponge, the lower lobe of the right lung was grasped gently and pulled superior and anterior. This placed the mediastinal pleura on the stretch for it is a continuation of the visceral pleura reflected off the lung. Thus, the mediastinum was exposed from the hilus of the lung to the diaphragm and the right vagus was easily identified running in the mediastinal pleura, posterior to the hilus of the right lung. This was in contrast to the right phrenic nerve, which passed anterior to the hilus, intimate with the pericardium. The mediastinal pleura was then incised with a long-handled knife just anterior to the right vagus about half-way between hilus and diaphragm. As a
matter of fact, due to the long chest of the dog and the relatively high dome of the diaphragm, it is difficult to open the pleura at a lower level.

The right vagus was then hooked and a hemostat applied. Tracing the vagus cephalad by pulling caudad on the hemostat, the division of the right vagus was found slightly inferior to the level of the hilus of the right lung. Consequently, the hemostat was on the posterior branch of the right vagus. By pulling cephalad on the posterior right vagus and following it along the lateral wall of the esophagus, the junction of this branch with the posterior branch of the left vagus was easily located slightly above the diaphragm. Here, the left vagus had just emerged from behind the esophagus. Maintaining cephalad traction on the hemostat, two more hemostats were applied distal to this union and approximately one and one-half to three and one-half centimeters of the posterior vagus, formed by this union, resected. The cut ends were tied with white cotton number forty and hemostats removed.

Keeping in the mediastinum and crossing the esophagus anteriorly, the left vagus was easily identified running parallel to this structure invested with mediastinal pleura. After hooking the nerve, it was dissected partially free and a hemostat applied. By creating caudad
traction on the hemostat, the junction of the anterior branches of the vagus nerves was brought into view. This union was below the bifurcation of the left vagus. The hemostat, therefore, was on the anterior vagus. Another hemostat was applied and one and one-half to three and one-half centimeters or more of the nerve removed, the cut ends being ligated also with white cotton number forty.

Thus, both vagus nerves were disrupted in the thorax. Removing the instrument, the thorax was closed with number eight white cotton after Markowitz (127). A sterile piece of gauze was then placed on the wound and overlaid with flexible collodion in several animals but this procedure was abandoned eventually and the wound left open to the air after being swabbed with merthiolate for we found that the incidence of wound infection decreased slightly using the latter technique. Operation complete.

D. Anesthesia

Four vagotomies were performed using ether administered via intratracheal catheter. As a pre-operative medicant, three milligrams of Morphinae Sulfas was given intraperitoneally per kilogram of body weight at least thirty minutes before surgery. Upon opening the thorax, the anesthetist attached a positive pressure machine to the intratracheal catheter in order to maintain the constant interchange of gases in the lungs. Follow-
ing the fourth vagotomy, ether was abandoned as the anesthetic agent since it was felt to be irritating to the lung and, in this procedure, stimulation of mucus added to the post-operative respiratory distress concomitant with thoracotomy. Consequently, on the remainder of the cases a barbiturate, Pentobarbital Sodicum, was used as the anesthetic agent. Ten milligrams of this substance per pound of body weight was given intraperitoneally or intravenously, Morphinae Sulfas, three milligrams per kilogram of body weight, having been injected into the peritoneal cavity at least one-half hour before (128).

Pentobarbitalum Sodicum, intravenously, acted almost immediately but required about five minutes to produce its effect when given intraperitoneally. Positive pressure was employed, of course, in conjunction with the morphine and pentobarbital while the thorax was open. Only rarely did the anesthetic have to be supplemented with additional pentobarbital.

For the purpose, this anesthesia proved to be the more satisfactory. Since the system used employed continuous positive pressure, the carbon-dioxide content of residual air is lower than normal because there is no such thing as dead space air in this case. The constant influx of air through the intratracheal catheter washes out, so to speak, the dead space air and residual air. Thus, the carbon-dioxide content of the blood became lower
than normal and the rate of respiration was cut down reflexly. The majority of the dogs, therefore, had a number of apneic periods when the intratracheal flow of air ceased. As a matter of fact, artificial respiration was introduced in several because of this but normal ventilation soon recurred when the carbon-dioxide content of the blood was returned to normal by these periods of apnea.

As the thorax was being closed in one operation, the heart stopped beating so the thorax was reopened, the heart massaged, and normal rhythm reinstated. The thorax was closed and the dog recovered marvelously, dying, unfortunately, several days later of empyema.

In the case of intratracheal ether anesthesia, the animal to be operated was placed in an ether box, designed in this laboratory, thirty to sixty minutes following morphine administration. Watching the subject through a glass window provided for that purpose, the animal was removed just as the anesthesia entered the third-stage. Just when to remove the subject so as not to have a dead dog or one that begins struggling a few minutes after removal, depends largely on the length of experience of the observer. Ordinarily if one waits about one minute after the struggles have ceased and if the animal cannot be roused by a loud noise, removal to the operating room and insertion of the tracheal catheter can be accomplished without the dog rousing.
To insert the metal tracheal cannula, the dog is placed on its back, mouth opened, the tongue grasped with a towel clip and pulled forward. Using a pencil-flashlight, the epiglottis, which was pulled up by the tongue, is identified and the metal cannula inserted through the black-V formed by the space between the vocal cords. The tube is pushed very gently along the trachea until an obstruction is met—the tracheal bifurcation. When this occurs the tube is withdrawn an inch or so, the dog's mouth closed and a piece of cord wrapped around the nose and lower jaw to keep the tube from slipping out. Air can be felt coming out of the tube. The cannula can be connected to the pressure machine whenever desired.

The metal cannulas or catheters were all members of a set graded to size according to caliber and each was eighteen inches long. A cannula approximately one size smaller than the diameter of the tracheal opening was used so as to permit a flow of air around the tube.

In two operations, the metal cannula was pushed through the tracheal wall and air forced into the mediastinum—the animals died on the table. During several other operations, alveoli were ruptured, the lungs partially collapsed, and air could be felt flowing from the thoracic cavity. This accident occurred as the chest was being closed—when the lung was being inflated to
drive all the air from the thorax and establish the normal vacuum present between lung and chest wall.

To avoid pushing the cannula through the tracheal wall use gentleness! So as not to rupture an alveolus in later operations, a rubber balloon was placed in the pressure system (Figure 4). When it was desired to inflate the lung, the balloon was filled first, the system closed, and the air flowing from the balloon allowed to blow up the lung. Thus, not too much pressure was placed on the alveoli. In the last three or four experiments, the balloon was removed from the system because of wasted time involved in inflating it. To take the place of this safety factor, the anesthetist's thumb was placed over the stem of the Y, where the balloon had been attached, when the lung was to be inflated. The thumb could be removed when the anesthetist felt a too great increase in pressure or when he saw the lung to be inflated to the desired degree (Figure 5). Pressure from the pump could be cut off anytime merely by kinking the tube with the free hand.

When morphine-pentobarbital anesthesia was used, the tracheal tube was inserted as soon as the animal was anesthetized following injection pentobarbital.

Pressure was employed only when the thorax was open. Following closure of the thorax it was immediately discontinued but the tracheal catheter was not removed until the anesthetist made sure the dog was breathing.
Fig. 4.—Diagram of Pressure System Used During Thoracotomy

Fig. 5.—Diagram of Pressure System Without Ballon

CLAMP HERE TO STOP PUMP PRESSURE

THUMB IS A SAFETY VALVE
In intratracheal ether anesthesia, as described in any textbook of experimental procedure, air from the pump first passed over ether in a bottle before going to the lung.

E. Insulin Test for Vagal Intactness

It was planned to determine the integrity of gastric vagi postoperatively by subjecting the animals to the insulin test; however, after several attempts, the test was abandoned.

The insulin test, recently proposed by Hollander (129), is based on the fact that stimulation of the vagal centers to provoke gastric secretion and motility has been observed in the presence of hyperinsulinism and hypoglycemia. According to him, no secretion or motility is evoked in spite of the hypoglycemia and hyperinsulinism if the nerve pathway be destroyed. The test consists of giving approximately fifteen units of regular insulin in the vein of a fasting subject, attempting to withdraw gastric specimens every fifteen minutes by means of a stomach tube, and determination of the blood glucose level every one-half hour. These procedures are carried out for at least two hours following insulin injection.

This test was abandoned because it is not practical for use in the dog. In contrast to man, before gastric studies can be conducted in the dog, the stomach must be washed out to remove hair-balls, worms, food
particles, the accumulations of basal (continuous) secretion, and the like. Anyone, who has washed the dog's stomach with one hundred to five hundred milliliters of water, knows that but rarely is the original volume regained even when withdrawn immediately. This means that a certain amount of wash water must have entered the duodenum or remained behind in the folds of the stomach.

No means of checking for dilution of gastric secretion with this wash water is provided in the test. That such a correction must be made is clear considering the frequency of duodenal regurgitation in the dog, and, of course, the reappearance of wash water during rearrangement of stomach folds. Further justification of this decision is furnished by the speed of gastric evacuation at times in the dog which would make it impossible to obtain a gastric sample even though secretion was occurring.

The desired blood sugar level of below fifty milligrams per cent was obtained in two fasting animals by injecting sixteen units of regular insulin intravenously. No secretion was observed over a two hour period. Later, at autopsy, the vagi were found disrupted in these animals ("Dickie" and "Snowball").

In a third animal, "Old Shep", it was felt that the desired blood sugar was attained (the blood sugar determination was faulty) following sixteen units of insulin intravenously, for marked sluggishness, retching,
salivation, and muscular weakness were observed. However, a gastric specimen was obtained only at the end of an hour and one-half. Bile, four-plus, was present, no free acidity, and a negligible amount of total acidity. At the time it was felt that this did not represent vagal activity for one would expect secretory stimulation within an hour following insulin injection. Certainly by the end of ninety minutes the effect of insulin should have disappeared since by that time the blood sugar, at least in the two cases observed here, is well above fifty milligrams per cent. This is an instance where some measurement of dilution from wash water would have been invaluable. At autopsy, the left posterior vagus was found to be intact.

When cleaning out the stomachs preparatory to running the tests, putrefied food particles were aspirated even after a twenty-four hour fast. This was evidence of a marked increase in emptying time of the stomach.

F. Method

Following vagotomy, the dogs were aided as much as possible towards recovery being given sulfathiazole tablets and some form of combined vitamins daily by mouth. Some had uneventful courses, others were not so fortunate. Finally, after recovery was complete, each dog was placed on either a cinchophen regime advocated by Bollman, Stalker and Mann (50), or one employed previously with success in this laboratory.
Four dogs were placed on a bone-free, meat-scrap, oatmeal and biscuit diet, and each was given approximately two grams of cinchophen daily in capsules per os. Cinchophen was given for four consecutive days, then a three-day rest, then four more days, then a three-day rest. This cycle was repeated throughout the experiment. This particular regime was used since with it the incidence of chronic cinchophen ulcer is the greatest. Then, after sufficient time had passed for an ulcer to form, the drug was given every day in an attempt to cause the ulcer to perforate. Thus, the gastric mucosa was subjected to terrific abuse over a fairly long period of time. If an ulcer failed to appear during this period, there would be no doubt of the value of vagotomy. On the other hand, if the reverse occurred, the conclusion would be an obvious one.

The second regime, as mentioned, had been used successfully, here, to determine the efficacy of Antuitrin-S (56), posterior pituitary extract (56), histaminase (57), and various surgical procedures (59) on cinchophen-ulcer. The remainder of the vagotomized dogs were placed on this schedule to compare vagotomy to the other agents since their value was determined over a relatively short period. These animals were given approximately two grams of cinchophen in capsules orally each day, six days a week, and received the bone-free diet outlined above.
G. Protocols

1. Cinchophen Control Group

(Two Dogs)

"Little Wire" Male.

Weight 12.5 pounds.

To test the integrity of a new batch of cinchophen this animal was given two grams of cinchophen six times a week from 6/30/47 to 7/10/47 when he was found dead. Thus, the dog had eighteen grams of cinchophen in ten days being found dead on the eleventh. Two pound weight loss.

Autopsy findings: There was an ulcer at the pylorus on the superior edge one-fourth centimeter in diameter. Two more ulcers this size were found on the inferior edge of the pylorus posteriorly.

Cause of death: cinchophen toxicity.

"Colonel Brown" Female mongrel.

Weight 13 pounds.

This animal was another control to test the new batch of cinchophen. She received two grams of cinchophen daily for six days being found dead on the seventh, 6/30/47 to 7/6/47. On 7/4/47 she had a poor appetite and was listless continuing this way until death.

Autopsy findings: The lungs showed typical findings of distemper. A small punched-out ulcer three millimeters in diameter was observed on the lesser curva-
ture of the pyloric sphincter.

Cause of death: distemper.

2. Vagotimized Dogs That Died Before Receiving Cinchophen

(Four Dogs)

Dog #87 Brown and white long-tail short hair mongrel; male.

Weight 12.5 pounds.

On 12/23/46 the vagus nerves were cut in the thorax under intratracheal ether anesthesia and positive pressure employing asepsis throughout. The thorax was closed with cotton.

The dog was found dead four days later but an autopsy was not obtainable.

Dog #90 Brown and white long-tail, medium hair, brindle mongrel; male.

Weight 21 pounds.

The vagus nerves were resected in the chest 4/15/47 under morphine and pentobarbital anesthesia employing asepsis throughout and positive pressure.

Immediate postoperative recovery was uncomplicated except that palpation caudad to the incision in the thorax revealed marked crepitus. Eventually a large portion of the chest wall surrounding the incision became black, gangrenous, and sloughed 4/24/47. Two grams of sulfathiazole was instituted daily by mouth 4/21/47.
as well as three per cent hydrogen peroxide washes to
the wound. Vitamin B complex was given in the muscle
four times a week. On 5/2/47 all treatment was stopped
and the wound which was about one-half its former size
continued to heal.

On 5/18/47 the dog was found dead in the cage. He
had been killed and partially devoured by another animal.

Cinchophen was to have been started this date.

Dog #4  Brown and white bird dog; female.
Weight 30 pounds.

On 3/27/47 the thorax was entered on the right
in the seventh interspace under morphine and pentobar­
bital anesthesia and positive intratracheal pressure,
aseptic technique being used throughout. The exposure
was fair though it would have been much better had the
eighth interspace been used. The right lower lobe was
pushed anterior and superior by the assistant. The medi­
astinal pleura was opened in an avascular area with a
long handled knife. The esophagus was identified and the
posterior branch of the right vagus was seen coursing in
the pleura parallel to this structure. The nerve was
hooked, elevated, and traced down several centimeters to
its junction with the posterior branch of the left vagus
which had crossed ventral to the esophagus. This junc­
tion was about one inch above the diaphragm. A two cen­
timeter section was removed below the junction and the
ends tied with black cotton. Then, passing anterior to
the esophagus, the anterior vagus was seen in its pleural bed running parallel to the esophagus and it also was cut, ligated and a two centimeter section removed. The anterior branch of the right vagus had previously joined this anterior branch of the left vagus just beneath the base of the heart. While closing the heart stopped beating. The sutures holding the ribs together were cut and massage of the heart was begun. The irregular contractions thus stimulated became regular in about three minutes and closure was performed without any further difficulty using white cotton.

The dog seemed to be doing fine for several days, eating well and evidently experiencing no respiratory difficulty. Unfortunately she died of an empyema and wound infection 4/7/47.

At autopsy the vagus nerves were found to have been sectioned.

Dog #29 Spotted brown, black and white mongrel; male.
Weight 15 pounds.

The right thorax was opened aseptically under positive pressure and morphine and pentobarbital anesthesia 3/17/47. Approximately one and one-half centimeters of both vagus nerves were removed below the junction of their respective branches. The chest was closed with cotton and wound cleansed with iodine and alcohol solution.

The immediate recovery was fair but the dog
dragged around and on 3/21/47 was found dead.

Autopsy findings: purulent fluid in both lung cavities. The pleura was thickened and covered with fibrinous exudate. The vagus nerves had been successfully resected.

Cause of death: empyema.

3. Cinchophen Administration To Partially Vagotomized Animals

(Two Dogs)

Dog #82 "Collie" Brown and white mongrel collie; female.

Weight 20.5 pounds.

The vagus nerves were cut in the thorax 2/5/47 through an incision in the fifth interspace above the pulmonary plexus bilaterally. Intratracheal ether and pressure anesthesia were used. The wound was closed with cotton.

The immediate postoperative recovery was uneventful.

The dog was in excellent condition 2/10/47 so cinchophen, two grams, was given daily from then until 3/3/47 with the exception of 2/20/47 and 3/2/47. From 3/3/47 on, two grams were given four times a week. The dog gradually lost weight and appetite being sacrificed because of cachexia 3/19/47, thirty-nine days after institution of this regime. Weight, fourteen pounds.

This dog received a total of sixty grams of cinchophen in thirty-nine days.
Autopsy findings: The right lung was plastered against the mediastinal pleura and when stripped away, revealed the vagus had been cut above the pulmonary plexus on the right. Dissection of the left vagus nerve revealed it to be intact. The gallbladder was four times its normal size and was filled with thick, brown, gravy-like bile. The mucosal surface looked like a honeycomb. The stomach was filled with a hair ball and regurgitated duodenal contents plus many worms. The pyloric antrum contained four ulcers with indurated edges and fibrotic bases, one large oval shaped ulcer two and one-half centimeters by thirteen millimeters, and one small circular ulcer five millimeters in diameter. Both were on the lesser curvature. On the greater curvature there were two ulcers, one eight millimeters in diameter and the other seven millimeters in diameter. Duodenum normal.

Cause of death: cinchophen toxicity.

Dog #100 "Old Shep" Black and brown long-tail shepherd; male.

Weight 20 pounds.

The vagus nerves were cut in the thorax above the diaphragm through an incision in the seventh interspace 2/4/47. Asepsis was employed throughout and ether intratracheally was used under pressure as the anesthesia. The chest was closed with cotton.

The dog recovered uneventfully and was placed
on cinchophen by mouth 2/11/47. Two grams of the drug were given daily until 3/7/47 when the dog was found dead. However, cinchophen was not given on these days: 2/20/47 and 3/2/47.

This dog received a total of sixty-four grams of cinchophen in thirty-two days.

Autopsy findings: The right lung could be seen from the outside through a portion of the broken down operative wound. The upper and middle lobes of the right lung were adherent to the parietal pleura around the incision. The lower lobe was adherent to the diaphragm and lower mediastinum. The left pleural cavity was filled with straw colored murky fluid. The entire right pleura, pericardial, visceral and parietal, was thickened. The pyloric antrum contained an area of gastritis, hemorrhagic, two and one-half centimeters in diameter in its upper limits on the posterior wall. There was also a punched out ulcer eight by eighteen millimeters with indurated edges on the anterior wall about two centimeters from the pyloric ring. There is also a smaller ulcer three by three millimeters on the lesser curvature about one and one-half centimeters from the pylorus. A third ulcer, seven by nine millimeters, was present on the posterior wall of the pyloric ring. Inspection of the vagus nerves in the chest showed that left posterior vagus was still intact for the right posterior vagus had been cut mistakenly for the posterior vagus.
4. Cinchophen Administration to Vagotomized Animals for a very short period of time

(Two dogs)

"Bulldog" Black and white long tail mongrel bulldog; male.

Weight 18 pounds.

Transthoracic, supradiaphragmatic vagotomy was performed 6/12/47 through the seventh interspace using aseptic technique and positive intratracheal pressure. The morphine-pentobarbital anesthesia was satisfactory. The vagus nerves were identified, resected as usual and the chest closed with interrupted cotton.

Sulfathiazole and vitamins were given daily until 6/19/47. The next day cinchophen was given orally, two grams, and repeated 6/21/47. The dog was found dead 6/23/47.

This dog had four grams of cinchophen in three days.

Autopsy findings: The findings in the lungs were typically distemper. There was no sign of ulcer in the stomach or duodenum but the vagus nerves were found cut in the thorax.

Cause of death: distemper.

Dog #21 Black, long-haired dog with white chest and long-tail; male

Weight 20 pounds.

On 4/15/47 the thorax was entered in the eighth interspace uneventfully and the anterior and posterior
vagus nerves resected. Asepsis was employed throughout along with positive intratracheal pressure and morphine-pentobarbital anesthesia. The chest was closed, cleaned with iodine and alcohol and overlaid with a piece of sterile gauze soaked in collodion.

On 4/19/47 the wound was draining pus so the skin suture was removed and pus literally poured from the wound. Sulfathiazole therapy, hydrogen peroxide washes and vitamins were instituted and continued until 5/2/47. A long piece of cotton was removed from the wound at this time and healing progressed very rapidly without aid. 5/19/47 cinchophen two grams per day was begun and continued until 5/23/47. On this day sulfathiazole therapy was again instituted and continued until 6/5/47 because of a chronic draining fistula of the right chest. Penicillin one hundred thousand units, was given daily in beeswax from 5/30/47 to 6/4/47.

The dog was in fair condition 6/6/47 though very thin so cinchophen administration was again begun. The drug was given in two gram doses for nine doses, 6/6/47 to 6/14/47. On 6/15/47 the animal was found dead.

Thus, the dog received eighteen grams of cinchophen in nine days time.

Autopsy findings: The left chest was filled with about ten centimeters of clear fluid. There was a walled off pleural fistula beneath the old incision in the right thorax containing pus. The vagus nerves were verified as
having been cut. There were no areas of gastritis or ulceration in the stomach or duodenum.

Cause of death: chronic empyema with debilitation.

5. Vagotomy And Cinchophen (Stalker Regime)
(Four Dogs)

"Shep" Brown and white mongrel collie; male.
Weight 27 pounds.

On 3/25/47 the thorax was aseptically opened in the seventh interspace, right side, using positive intratracheal pressure and morphine-pentobarbital anesthesia. The mediastinal pleura was opened following retraction of the lower lobe anterior and superior. The right vagus was identified and a two centimeter section removed distal to the junction with the posterior branch of the left vagus. The cut ends were ligated. The anterior vagus was located in the pleura lateral to the esophagus and a section removed. During this time trouble was encountered with our pump as well as difficulty in ascertaining whether or not the metal tube was in the trachea. A tracheotomy was done and the cannula inserted. The lungs could not be inflated fully so as to drive all air out of the thorax (most probably because of a ruptured alveolus) so the thorax was closed with white cotton and aspirated with a fifty cubic centimeter syringe. The dog was alive when placed in its cage.
The postoperative recovery was uneventful though the thoracic wound healed slowly necessitating daily washes with hydrogen peroxide solution (three per cent). A stomal ulcer was cleared by the use of vitamin B complex intramuscularly several times a week. Following operation though, the dog did not regain his former weight in spite of good care.

On 2/41/47 cinchophen therapy was instituted orally, at least two grams being given in capsules at each administration. Nothing was given 4/22/47. From 4/23/47 to 4/26/47, the drug was given daily; a rest on 4/27/47. Beginning 4/28/47 and ending 6/1/47, cinchophen was given for four days, withheld for three, and the sequence repeated. From 6/2/47 until 6/18/47, the animal received two grams of cinchophen every day except from 6/2/47 to 6/4/47 when three grams were given daily.

On 6/19/47 the dog was found dead in the cage and signs of violence indicated that he may have been killed in a fight with another dog.

Up until the last few days the dog was active and had a ravenous appetite but never gained any weight. Thus, in a period of sixty days two grams were given for forty days and three grams for three days—a total of ninety-two grams of cinchophen in the sixty day period and seventeen days of continuous cinchophen therapy.

Autopsy findings: pneumonic process in the right lung, which was plastered against parietal pleura and low-
er mediastinal pleura. The gallbladder was very pale and larger than normal. The bile ducts were also pale but bile was found in the duodenum. The dog was very emaci­ated and had a stomal ulcer orally. In the stomach there was an annular ulcer, one centimeter wide in the pyloric antrum, one centimeter above the pyloric ring, which was rather shallow but indurated with crater edges. There was also a circular punched out ulcer four centimeters above the pyloric ring five millimeters in diameter with the mucosa "puckered" around it. Exploration of the chest showed the vagus nerves had been cut.

Cause of death: chronic pneumonitis of some type or violence.

"Boxer" Brown boxer; male.

Weight 24 pounds.

The right thorax was entered in the seventh in­terspace aseptically 4/10/47 and the posterior and an­terior vagus nerves resected under morphine-pentobarbital anesthesia and positive intratracheal pressure. The chest was closed with cotton and the dog placed in a cage. It is possible that an alveolus was ruptured for when inflat­ting the lung preparatory to tying the last sutures around the ribs, a steady current of air was felt coming from the pleural cavity.

The wound healed promptly and the dog returned to normal in a short time. The appetite was excellent.

Cinchophen administration was begun 4/28/47, two
grams being given at each administration. From 4/28/47 the drug was given four days and then withheld three, and then this regime repeated until 6/1/47. On 6/2/47 three grams were given and repeated daily until 6/5/47. From 6/6/47 until 7/5/47 the drug was given in two gram doses daily.

The dog started to become listless 6/6/47 and gradually went downhill being found dead 7/6/47. The day before death he was very weak and apathetic but almost until the last two days the appetite remained very good.

Thus, in a period of seventy days two grams were given for fifty-one doses and three grams for four doses or a total of one hundred fourteen grams during this time. Cinchophen was given continuously for thirty-four days; it was given thirty-six days using the regime advocated by Stalker's group.

Autopsy findings: Both pleural cavities were filled with purulent fluid. The vagus nerves had been severed. The stomach was the site of an annular ulcer one centimeter above the pyloric sphincter, two centimeters wide at the lesser curvature and three centimeters wide at the greater curvature. The gallbladder was pale and larger than normal as were the bile ducts.

Cause of death: empyema.

"Dickey" Black and white mongrel male.

Weight 30 pounds.
On 4/1/47 the right thorax was entered aseptically in the seventh interspace using morphine and pentobarbital anesthesia and positive intratracheal pressure. The right lower lobe was drawn anterior and superior. The posterior branch of the right vagus was picked up with a hook and followed down to its junction with the posterior branch of the left vagus. About two centimeters were removed beyond this junction and the ends tied. Then, crossing the esophagus, the anterior vagus was hooked and about two centimeters were removed and the cut ends ligated. The chest was closed with white cotton.

The immediate postoperative recovery was good but 4/4/47 a wound infection developed along with rales and dullness in the right chest. The sutures were removed releasing a fair amount of purulent drainage. Sulfathiazole, two grams, was given orally and the wound washed with hydrogen peroxide solution (three per cent) until 4/14/47 when all medication was discontinued except the hydrogen peroxide washes to the wound. On 4/18/47 a long piece of cotton was removed from the wound which had been in the fascia and the wound cleared rapidly after that.

Cinchophen, two grams, was given orally 4/21/47, withheld 4/22/47; administered daily from 4/23/47 to 4/26/47; withheld on 4/27/47; and then from 4/28/47 given four times a week until 6/2/47. On this date three grams of the drug were given and continued until 6/5/47. From then until 7/2/47, two grams of the drug were given daily.
In 6/3/47 the wound broke down, sloughed a long piece of cotton, and healed in a few days. On 6/10/47 the progress was rapidly downhill and 6/29/47 to 7/2/47 his appetite was almost nil.

In seventy-four days the dog received one hundred eighteen grams of cinchophen, two grams for fifty-three doses and three grams for four doses. The last thirty-one days of life he received cinchophen continuously so the dog was on Stalker's regime for forty-three days.

Autopsy findings: Emaciated male dog. The stomach contained an ulcer one and one-half centimeters in diameter, four and one-half centimeters from the pyloric sphincter on the posterior wall, which had perforated centrally. The ulcer had crater edges and was surrounded by heaped up mucosa. Another ulcer was present in the fundus on the lesser curvature one centimeter above the pyloric antrum and one centimeter in diameter. Encircling the antrum there was an area about two and one-half centimeters wide composed of indurated tissue which probably represented a healed lesion. The vagus nerves were destroyed in the chest. The gallbladder was tense, a transparent white and much larger than normal.

Cause of death: sacrificed.

Dog #27 (Snowball) White, brown-eared mongrel German spitz; female.
Weight 20 pounds.

On 4/19/47 the right thorax was opened aseptically in the eighth interspace under morphine-pentobarbital anesthesia uneventfully. Closed the chest and covered it with collodion on gauze.

Postoperative recovery was uneventful and the wound healed primarily.

Two grams cinchophen orally was given four times a week beginning 5/5/47. This was continued until 6/2/47. On this date three grams of the drug were given and continued two more days. From 6/5/47 until death 7/10/47 the animal was given two grams of the drug every day. Up until the last day, the appetite remained excellent. Death was rather sudden.

This dog received thirty-two grams of cinchophen in twenty-eight days, and then seventy-two grams in thirty-six days and nine grams for three days. This was a total of one hundred thirteen grams in eighty-three days. The last thirty-nine days the animal was given cinchophen every day. There was a three pound weight loss.

Autopsy findings: There was an ulcer immediately below the pylorus one and one-half centimeters in diameter which had perforated. A second ulcer one and one-half centimeters in diameter was found directly above the pylorus on the lesser curvature of the stomach. A third ulcer appeared one and one-half centimeters above the pylorus on the posterior surface and was four centimeters in diameter. This ulcer, too, had perforated. The vagus
nerves had been cut successfully in the thorax. The abdominal cavity was filled with gastric contents and purulent material. Weight 17.5 pounds.

Cause of death: perforated gastric and duodenal ulcers.

6. Vagotomy And Cinchophen (Creighton Regime)

(Five Dogs)

"Eight-ball" Black and white long hair; male.

Weight 25 pounds.

About three centimeters of the anterior and posterior vagus nerves were removed intrathoracically under positive pressure and morphine-pentobarbital anesthesia 7/1/47. The closure was done with interrupted cotton.

Recovery was uneventful on a sulfathiazole-vitamin regime for four days. Cinchophen, two grams daily orally, was begun 7/6/47. The dog was found dead 7/13/47.

This animal received twelve grams of cinchophen in six days.

Autopsy findings: There was a large ulcer one centimeter in diameter at the lesser curvature on the pylorus. On the posterior stomach wall, from the pylorus to three centimeters above it, were ten smaller ulcers. The gallbladder was enlarged as were the ducts and were pale. The vagus nerves had been cut in the thorax.

Cause of death: distemper.

Dog # 95 Black and white mongrel pup; female.

Weight 19 pounds.
Under morphine-pentobarbital anesthesia the right thorax was opened aseptically 6/24/47 under positive intratracheal pressure in the seventh interspace and a three centimeter portion removed from the anterior and posterior vagus nerves. The chest was closed with interrupted cotton. The animal was placed on routine sulfathiazole and vitamin therapy, recovering uneventfully. Cinchophen administration, two grams per day was begun 7/1/47. This was given for six days and then one day rest, then three more days, the animal being found dead on the tenth day of July.

This animal received sixteen grams of cinchophen in nine days.

Autopsy findings: An ulcer one-quarter of a centimeter in diameter was found immediately above the pylorus on the posterior wall of the stomach. Two ulcers three millimeters in diameter were found immediately below the pylorus on the posterior stomach wall. One ulcer was found seven and one-half centimeters above the pylorus on the posterior wall of the stomach three millimeters by two centimeters in size. The gallbladder was very large. The vagi had been severed in the chest.

Cause of death: cinchophen toxicity.

"Albino" Pure white long-tailed mongrel; male.

Weight 16 pounds

The right chest was aseptically opened under
-90-
morphine-pentobarbital anesthesia and positive intratracheal pressure in the seventh interspace. A three centimeter section was closed with interrupted white cotton.

The recovery was uneventful on sulfathiazole and vitamin therapy, the wound healing by primary intention.

Cinchophen was begun 6/20/47 and 6/21/47. After a day of rest 6/22/47, two grams of the drug was given orally six days a week. The dog was found dead on 7/10/47 after having been listless and experiencing a three pound loss in weight.

This dog received forty-six grams of cinchophen in twenty-six days.

Autopsy findings: An ulcer one centimeter in diameter was found immediately above the pylorus and two ulcers, two and one-half centimeters in diameter, two centimeters above the pylorus. The ulcers were found on the posterior surface of the stomach. The nerves, vagus, were found to have been cut correctly in the thorax.

Cause of death: distemper.

"One Eye" Black and white mongrel; female.

Weight 15 pounds.

The right thorax was opened aseptically under morphine and pentobarbital anesthesia keeping the lungs inflated with positive intratracheal pressure. The vagus nerves were successfully cut but with a little difficulty. By mistake the thorax was entered in the sixth interspace.
The wound was closed with interrupted white cotton.

The dog recovered very well postoperatively on a sulfathiazole-vitamin regime and the wound healed without infection. Cinchophen was begun 6/21/47, two grams orally per day, with the exception of 6/22/47 when none was given. The drug was given until 6/25/47 but the dog was found dead in the cage 6/26/47. She was normal in all respects just the day before death.

The dog received six grams of cinchophen in four days.

Autopsy findings: The stomach and duodenum were tremendously dilated but were empty except for worms. No signs of obstruction were in the alimentary tract. There were what appeared to be small pin-point ulcers, two in number, one-inch from the pylorus on the anterior wall. Dissection of the vagus nerves in the thorax confirmed that they were completely severed at operation.

Cause of death: Acute gastric dilatation.

Dog #170 White short-hair, long-tail, brown eared mongrel; female.

Weight 24 pounds.

A transthoracic supradiaphragmatic vagotomy was performed 6/26/47 aseptically employing morphine-pentobarbital anesthesia and positive intratracheal pressure. Approximately four centimeters of each nerve was removed.

To control a small amount of oozing caused by cutting the
right posterior vagus, a "Gelfoam" sponge was pressed against the esophagus for two minutes and left in place. This sponge controlled the bleeding very nicely. The chest was closed with interrupted cotton.

On the sulfathiazole-vitamin regime recovery was uneventful.

Two grams of cinchophen orally was begun 7/1/47 and given six days a week. Progress was downhill and the dog was found dead 7/11/47.

This animal received eighteen grams of cinchophen in ten days.

Autopsy findings: There was a large ulcer three centimeters in diameter immediately above the pylorus on the greater curvature of the stomach. A number of small ulcers appeared one centimeter above the pylorus on the posterior wall of the stomach. There was also a small ulcer three millimeters in diameter one centimeter above the pylorus on the lesser curvature. Though there was a generalized peritonitis present, a perforation could not be found. The gallbladder and bile ducts were pale and distended.

Cause of death: generalized peritonitis, etiology unknown.

H. Summary of Results

Two unoperated dogs used to determine the potency of a new batch of cinchophen developed ulcer (Table 2).
### Table 2

**CONTROL GROUP**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Total Grams of Cinchophen</th>
<th>Days</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Little Wire&quot;</td>
<td>18</td>
<td>10</td>
<td>Three ulcers near pylorus</td>
</tr>
<tr>
<td>&quot;Colonel Brown&quot;</td>
<td>12</td>
<td>6</td>
<td>One small ulcer on pyloric sphincter</td>
</tr>
</tbody>
</table>

*Vagus nerves intact*

Vagotomy was performed in seventeen dogs. Four dogs or twenty-four per cent died following surgery before receiving cinchophen (Table 3).

### Table 3

**VAGOTOMY BUT DOGS DIED BEFORE RECEIVING CINCHOPHEN**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Postoperative Span</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>#87</td>
<td>4 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>#90</td>
<td>33 days</td>
<td>Violence</td>
</tr>
<tr>
<td>#4</td>
<td>12 days</td>
<td>Empyema of thorax</td>
</tr>
<tr>
<td>#29</td>
<td>4 days</td>
<td>Empyema of thorax</td>
</tr>
</tbody>
</table>
Two dogs were only partially vagotomized by mistake and developed an ulcer when given cinchophen (Table 4). Two dogs received cinchophen for a very short period of time before death but failed to develop an ulcer (Table 5). The remaining nine dogs developed peptic ulcer when given cinchophen (Table 6).

**TABLE 4**

CINCHOPHEN ADMINISTRATION TO PARTIALLY VAGOTOMIZED DOGS

<table>
<thead>
<tr>
<th>Dog</th>
<th>Vagus Branch</th>
<th>Total Grams</th>
<th>Cinchophen Days</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Collie&quot;</td>
<td>Left vagus</td>
<td>60</td>
<td>39</td>
<td>Four pyloric antral ulcers</td>
</tr>
<tr>
<td>&quot;Old Shep&quot;</td>
<td>Left posterior vagus</td>
<td>64</td>
<td>32</td>
<td>Three pyloric antral ulcers</td>
</tr>
</tbody>
</table>

**TABLE 5**

CINCHOPHEN ADMINISTRATION TO VAGOTOMIZED DOGS OVER A SHORT PERIOD

<table>
<thead>
<tr>
<th>Dog</th>
<th>Total Grams of Cinchophen</th>
<th>Days</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Bulldog&quot;</td>
<td>4</td>
<td>2</td>
<td>Stomach and duodenum normal</td>
</tr>
<tr>
<td>#21</td>
<td>18</td>
<td>9</td>
<td>Stomach and duodenum normal</td>
</tr>
<tr>
<td>Dog</td>
<td>Total Grams of Cinchophen</td>
<td>Days</td>
<td>Results</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------</td>
<td>------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>&quot;Eight-ball&quot;*</td>
<td>12</td>
<td>6</td>
<td>Numerous antral ulcers</td>
</tr>
<tr>
<td>#95</td>
<td>16</td>
<td>9</td>
<td>Three antral ulcers One fundic ulcer</td>
</tr>
<tr>
<td>&quot;Albino&quot;*</td>
<td>46</td>
<td>26</td>
<td>Three pyloric antral ulcers</td>
</tr>
<tr>
<td>&quot;One-eye&quot;*</td>
<td>6</td>
<td>4</td>
<td>Two pin-point antral ulcers</td>
</tr>
<tr>
<td>#170*</td>
<td>18</td>
<td>10</td>
<td>Antral ulcers</td>
</tr>
<tr>
<td>&quot;Shep&quot;**</td>
<td>92</td>
<td>60</td>
<td>Large antral ulcer Large annular pyloric ulcer</td>
</tr>
<tr>
<td>&quot;Boxer&quot;**</td>
<td>114</td>
<td>72</td>
<td>Large annular pyloric ulcer</td>
</tr>
<tr>
<td>&quot;Dickey&quot;**</td>
<td>118</td>
<td>74</td>
<td>Perforated antral ulcer Healed annular ulcer</td>
</tr>
<tr>
<td>&quot;Snowball&quot;**</td>
<td>113</td>
<td>83</td>
<td>Perforated pyloric ulcer Antral ulcers</td>
</tr>
</tbody>
</table>

*Creighton Regime

**Modified Stalker Regime
Using proven cinchophen regimes, ulcer occurred in nine of eleven vagatomized dogs. Considering that cinchophen ulcer appears in an average of thirty-six days under the Creighton regime (56), and the dogs failing to develop an ulcer received the drug in this manner, it is readily seen that these animals did not receive the drug long enough to be considered significant in their failure to develop ulcer.

It is not incorrect to say, therefore, that in dogs who received cinchophen over a significant period of time, peptic ulcer, chronic, developed in one hundred per cent of the cases.
CHAPTER VI

DISCUSSION, SUMMARY AND CONCLUSIONS

A. Discussion

Evidently the beneficial effect of lowered acidity produced by surgical interruption of the vagi was offset by the concomitant increase in emptying time. The prolonged retention, of course, permitted longer exposure of the gastric mucosa to the stomach contents. This point was well illustrated in several animals who were tubed after a fast of twenty-four hours and putrefied particles of food removed by gavage. Pavlov (130) had pointed out that in several animals surviving section of the vagi, putrefaction of the retained food occurred rather than digestion because of the decrease in acid and pepsin. The dogs lost weight because of this but he was able to overcome the weight loss by stimulating gastric secretion for a time with beef broth before placing meat in the stomach. Thus, he made up for the absent cephalic or psychic phase which, in the dog, seems to be very important from the standpoint of digestion. The delay was also reported by Meek and Herrin (131) who observed an increase in gastric retention following vagotomy above the diaphragm.
Obviously this decrease in motility is an undesirable effect of vagotomy in the dog and from the standpoint of therapy, renders this procedure valueless in the prevention of cinchophen-ulcer. To overcome this retention would necessitate the performance of some type of surgery designed to facilitate swift evacuation of the stomach contents, e.g. gastroenterostomy.

We have seen that where enterogastric regurgitation and gastric emptying were optimum (50,55,59), cinchophen-ulcer was absent. Clearly it would be unnecessary and useless to perform vagotomy along with such procedures to reduce the incidence of peptic ulcer caused by cinchophen. Since vagotomy decreases the total volume of acidity, these findings suggest that one of the normal protective mechanisms of the stomach is missing or impaired during cinchophen administration.

Vagotomy alone has produced a peptic ulcer in dogs but only in rare instances. Meek reported two in a series of thirteen dogs but Beazell and Ivy (133) found none in sixty vagotomized dogs. In the present investigation, peptic ulcer was present in one hundred percent of vagotomized dogs who received cinchophen over a significant period of time. Definitely, therefore, cinchophen does not act by stimulating the vagus nerve centrally. It is also apparent that the main action of the drug in the formation of ulcer is not by an absolute increase in gastric acidity.

Reviewing the various known mechanisms of reduc-
tion of gastric acidity demonstrates that only one alternative remains to explain the action of cinchophen in the genesis of peptic ulcer—the protective role of mucus:

I. Extragastric factors:

A. Dilution with saliva; this, of course, is of little importance normally and the same is true in cinchophen-ulcer.

B. Neutralization and dilution with food; this has little bearing for it is constant before and during cinchophen ingestion. The dogs who received cinchophen four days with a three day rest had healthy appetites and ate normally until almost the last three or four days.

C. Duodenal regurgitation: apparently this has something to do with the formation of cinchophen-ulcer. The reason probably is that this is decreased along with evacuation due to increased pyloric sphincter activity (55).

D. Enterogastrone: the primary function of this hormone is cessation of gastric secretion of acid (134). Increased acidity has been shown not to be the important factor in cinchophen-ulcer so the drug must not act this way.

II. Intragastric factors:

A. Inhibition of parietal cell secretion by high concentrations of hydrochloric acid (136,136):
cinchophen produces very little increase in total volume of acid and in vagotomized dogs this volume is significantly reduced. Consequently, whether or not the factor of inhibition was functioning is unimportant.

B. Evacuation of the stomach: this is the most valuable factor of all, as far as the stomach itself is concerned, in the neutralization of gastric acidity. Needless to say, if the stomach is empty there is little acid present except that which is lying on the surface of the mucosa. This factor, as mentioned previously, is probably concerned in part with the formation of cinchophen-ulcer since the findings of Davis, et al (55), would indicate that increased pyloric activity is present during cinchophen administration. Undoubtedly, the marked delay in emptying time in vagotomized animals is responsible for the relative increase in gastric acidity for where emptying of the stomach is rapid, cinchophen-ulcer does not form even though there is not a marked decrease per se in the production of gastric acid as there is with vagotomy.

C. Mucus secretion: this protective mechanism has been the most underestimated of all fac-
tors in the control of gastric acidity, its significance being dismissed by pioneer investigators as negligible. Just recently the importance of this role has been brought out by Wolf and Wolff (64) after slumbering for several years in Whitlow's (68) unpublished Master's thesis at Loyola University. No one knows very much about the secretion of mucus other than the fact that it suddenly occurs in the face of trauma to the gastric mucosa. Where the source of mucus lies, other than the chief cells and goblet cells, or what factors are responsible for its integrity and formation, are unanswered questions. Personally, the fact that a true peptic ulcer was produced in the presence of normal acid and pepsin merely by brushing aside the protective coating of mucus was the most significant observation in the study of peptic ulcer since Pavlov's promulgation of "sham feeding". Whether mucus or perhaps the primary synthesis of this mucoprotein occurs in the liver or in the chief or mucus secreting cells of the stomach, or whether both are involved in the production of potent mucus remains to be seen. However, inactivation of mucus by cinchophen in some manner would seem the most logical way for
cinchophen to produce its deleterious effect on the stomach since all other avenues appear to be ruled out.

B. Summary and Conclusions

(1) The vagus nerves run a standard course in the thorax of the dog.

(2) Refutation of Pavlov's conception of the distribution of the left (anterior) vagus to the stomach by Jemerin and Hollander was confirmed.

(3) Undoubtedly Heidenhain- and Pavlov-pouches vary in the percentage of uninterrupted vagal fibers but it is incorrect to consider them vagally free.

(4) A morphine-pentobarbital anesthesia, in the dog, has more advantages in thoracic surgery than a morphine-intratracheal ether anesthesia.

(5) Gentleness is the rule when inserting the metal tracheal cannula so as not to push it through the trachea.

(6) Great care must be taken at all times by the anesthetist so as not to rupture an alveolus when aerating or inflating the lung preparatory to closure, for a relatively small amount of pressure is necessary to inflate the lung.

(7) The insulin test for vagal intactness post-operatively, is not practical, as it is, for use in the dog.

(8) Surgical interruption of the vagus nerves
above the diaphragm had no effect whatsoever on the incidence of peptic ulcer produced by cinchophen.

(9) Cinchophen, therefore, does not produce peptic ulcer by central stimulation of the vagus nerve.

(10) The increase in total volume of gastric secretion during cinchophen administration per se is not the mode of action employed by cinchophen to produce peptic ulcer.

(11) Experimentally, the beneficial effect of reduced gastric acidity concomitant with vagotomy, is offset by the associated increase in emptying time—thus, gastric contents maintain contact with the gastric mucosa for much longer periods of time than normal.

(12) Contrary to expectations, conclusions regarding the vagal integrity of the pouches used by Stalker, Bollman and Mann, cannot be drawn since it was found that the vagus had no effect on cinchophen-ulcer formation.

(13) From these findings it would appear that the etiology of peptic ulcer caused by cinchophen lies in a defect of one of the protective mechanisms of the stomach, permitting a normal or slightly increased amount of hydrochloric acid and pepsin to attack the mucosal wall over a fairly long period of time and produce the pathologic changes designated chronic peptic ulcer.
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