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Gastric acidity in depressive illness

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GASTRIC ACIDITY IN DEPRESSIVE ILLNESS

by

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What, man! ne'er pull your hat upon your brows;
Give sorrow words. The grief that does not speak,
Whispers the o'er-fraught heart, and bids it break.

Shakespeare, Macbeth

Table of Contents

List of Tables

INTRODUCTION

It is a matter of common observation that a person's psychological state seems to have a marked influence on his somatic function. The purpose of this study is to investigate a possible relationship between depressive illness and the output of gastric acidity. The first part of this paper concerns itself with prior work, early and recent, on the subject of psychic concomitants of gastric function, closest attention being paid to gastrointestinal changes accompanying depressive affect. The second part reports an experiment designed to test the hypothesis that in clinically depressed patients there is a significant decrease in gastric acid output, and that there is a correlation between degree of depression and degree of gastric acid diminution. Although gastric acidity is the only biological correlate of depression under study here, reference will be made to many others in the course of reviewing the literature.

Several approaches have in the past been taken in the investigation of the influence of emotions on somatic function. The literature will be reviewed from an historical viewpoint, from early recognition that emotions may alter physiologic function, to physiological studies on animals and man relating emotion to gastrointestinal activity, and finally to investigations in which depressive affect per se is related to gastric function. Concerning this last, more specific approach, it may be said that there have been few

attempts to relate the type and degree of depression in a statistically significant group of clinically depressed patients under controlled conditions to changes in gastric secretion. Several important studies on isolated subjects with gastric fistulae have dealt with the relationship between depression and gastric function, as well as between various other specific emotional states and gastric function. Changes in gastric secretion associated with experimentally evoked or observed depressions and other affective states have been investigated in groups of well volunteers. Moreover, the relationship of depressive illness to other physiological correlates has been well studied, especially in recent years. The endocrinology and biochemistry of depressive illness have been subjects of intensive investigations in the last decade by several groups. However, study of the relationship of depressive illness to gastric secretion in a group of patients has been largely neglected. To this writer's knowledge, only one group of investigators (Farr et al.) in the mid-1920's, has attempted to correlate depressive illness, in a group of patients, with changes in gastric secretion. The results of these workers will be examined in the next section, with particular interest directed toward the effect of experimental conditions on the validity of their conclusions. The present work, therefore, represents an initial attempt to fill a long-neglected gap in the investigations of the physiological correlates of depressive illness. It is to be most strongly emphasized

that this study is not meant to be interpreted as a completed investigation. It is intended that it be looked upon only as a pilot study, outlining possible directions for further research.

REVIEW OF THE LITERATURE

1. Early Observations.

It is striking how early it was recognized that emotions may affect the gastrointestinal system. An interesting example of how the mental state influences the alimentary canal is given by Burton in his Anatomy of Melancholy, published in 1621:

> A gentlewoman of the same city saw a fat hog cut up, when the entrails were opened, and a noisome savour offended her nose, she much misliked, and would no longer abide; a physician in presence told her, as that hog, so was she, full of filthy excrements, and aggravated the matter by some other loathsome instances, insomuch this nice gentlewoman apprehended it so deeply that she fell forthwith a vomiting, was so mightily distempered in mind and body, that with all his art and persuasion, for some months after, he could not restore her to herself again, she could not forget or remove the object out of her sight.[1]

"Truly," remarks Cannon (1909), alluding to this passage, "here was a moving circle of causation, in which the physician himself probably played the part of a recurrent augmenter of the trouble." (16)

But the first truly scientific correlations between the physiology of the stomach and emotional factors were demonstrated by William Beaumont (1833) in his famous study of Alexis St. Martin (4). A shotgun wound which never closed permitted direct observation of the stomach through a fistula. This investigation served as an early model for

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[1](14) p. 443

future investigations into gastrointestinal physiology and its psychosomatic concomitants. Beaumont showed, in this primarily physiological work, that strong emotions have a marked effect on gastric mucosa and secretions. For example, he discussed how emotions can depress gastric secretion and even cause reflux of bile:

> Derangement of the digestive organs, slight febrile excitement, fright, or any sudden affectation of the passions, cause material alterations in its /the gastric juice's/ appearance....Fear and anger check its secretion, also; -- the latter causes an influx of bile into the stomach, which impairs its solvent properties.[1]

In describing the gastric mucosa and factors that change its appearance, he writes:

> In...predisposition, from whatever cause -- obstructed perspirations, undue excitement by stimulating liquors, overloading the stomach with food -- fear, anger, or whatever depresses or disturbs the nervous system -- the villous coat becomes sometimes red and dry, or at other times, pale and moist, and loses its smooth and healthy appearance; the secretions become vitiated, greatly diminished, or entirely suppressed; the mucous coat scarcely perceptible; the follicles flat and flaccid, with secretions insufficient to protect the vascular and nervous pappillae from irritation.[2]

These findings, though non-specific, were nevertheless important in that they represented the first significant observations implicating emotional factors in changes in alimentary function. Beaumont asserts that strong emotions of whatever type tend to depress gastric function. Whether

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[1](4) p. 84

[2]Ibid., p. 107

or not his observations on the gastrointestinal effects of emotions and physical factors later proved to be accurate is unimportant in the light of the fact that this work pointed the way from speculation to direct scientific observation. His data are, however, in conflict with more recent investigations. (cf. Carlson, 1923 [167]).

In a remarkably prophetic book published in 1850 by the American physician William Sweetser, entitled Mental Hygiene; or, an Examination of the Intellect and Passions. Designed to show how they affect and are affected by the Bodily Functions, and their Influence on Health and Longevity (79), emotions are more explicitly studied, with respect to their influence on somatic function.[1] Numerous statements, largely unsupported by experimental data, but nevertheless insightful and often predictive of later work, relate emotions ("passions") to bodily function and the production of disease.

> The physician should investigate the moral as well as the physical causes of disease... Few, probably, even suspect the amount of bodily infirmity and disease among mankind resulting from moral [i.e., emotional] causes -- how often the frame wastes, and premature decay comes on, under the corroding influences of some painful passion.[2]

He warns that

> while the physician is imputing the infirmities of his patient to all the most familiar causes,

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[1] G.L. Engel, M.D., first brought this book to my attention in a lecture delivered at Yale Medical School, December, 1967.

[2] (79) p. 97

> as bad diet, impure air, want of exercise etc.....it is in reality, some unhappy and unrevealed passion.[1]

Forebodings of the concept of the unconscious appear to be present in the above passage.

Sweetser was also one of the earliest authors to specify the organ systems affected by emotional states, when he asserted that "the effect of the passions is particularly manifested in the vital functions, as in the circulation, digestion, secretions, etc."[2] He becomes even more explicit (and relevant to the subject of the present study) in holding that the effects of "passions" are "declared especially in those organs and functions which have been termed organic or vegetative; as in...the stomach...."[3]

A large part of Sweetser's book is devoted to depressive emotions, variously called "grief," "sadness," "despair," "melancholy," etc., with no strict distinction being drawn among these terms. In discussing the effect of depressive emotions on organic function he specifies the organ system affected and the resulting change in function:

> Each emotion has some special organ or organs on which its power is more particularly expended...as grief, on the digestive organs,[4] /In grief/ the appetite fails, and the powers of digestion become obviously impaired and sometimes altogether suspended.[5]

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[1](79) p. 97, my italics

[2]Ibid. p. 105

[3]Ibid. p. 107

[4]Ibid. p. 108

[5]Ibid. p. 246

In support of his hypothesis that "melancholia...is soon followed by a derangement of some part or parts of the vital organization," Sweetser quotes a famous contemporary, Heberden:

> There is hardly any part of the body which does not sometimes appear to be deeply injured by...dejection of spiritualism; and none more constantly than the stomach and bowels, which hardly ever escape unharmed.[1]

Another statement found in this work, a quote from Laennec, anticipates a twentieth century psychosomatic concept:

> Depressing passions, when operative, seem to contribute to the growth of cancer.[2]

Along with largely speculative works such as Sweetser's, the latter half of the nineteenth century saw sporadic physiological studies relating emotions non-specifically to gastrointestinal function. Bidder and Schmidt, for example, were apparently the first to demonstrate, as early as 1852, the gastric secretory effect of the desire for food in dogs. "It is remarkable that in starving animals the mere sight of food suffices to increase gastric secretion...." (85) Work such as this, however, did not become plentiful until the turn of the century, when a great mass of literature based primarily on physiological approaches began to appear.

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[1](79) p. 206

[2]Ibid. p. 216 cf. Schmale (74)

2. General Emotional States and Gastric Function.

With the end of the nineteenth century there began an era of important landmark discoveries about the gastro-intestinal system, in which a large number of now-famous investigators participated. Common to an important segment of this work was the introduction of psychological correlates. The studies to be considered in this section may be roughly divided into two categories: a) the effects of general classes of emotion on gastric function. Most investigations in this category differentiate between broad categories of emotional state, such as pleasure vs. pain, contentment vs. violence, etc.; b) the effects of specific emotions on gastric function. Concerning this latter, the various studies show strong disagreement as to the direction of change in gastric function in response to a particular emotion.

Pavlov, in his well-known treatise, Die Arbeit der Verdauungsdrüsen, 1899 (69), introduced the concept of conditioned reflex, and in so doing, demonstrated by sham feedings in dogs that craving for food, even in its absence, has a definite secretory effect. When one thinks of the conditioned reflex salivation generally comes to mind. Yet it is not generally as well known that gastric secretion, too, is involved therein. This was shown by the use of an accessory stomach, now known as the "Pavlov pouch." When the bell rang, not only did the mouth water; so did the stomach. Pavlov used the term "psychic secretion" to des-

cribe alimentary secretion in the absence of the actual stimulus of food.

In his investigations with animals in the first decade of the twentieth century, Walter Cannon (16) was the first to postulate a workable mechanism for what he felt to be the most important cause of "visceral inhibition" during emotional stress: the sympathetic nervous system.

> There are, however, other viscera, supplied with smooth muscle and innervated by the sympathetic fibers, which are hidden so deeply in the body and which do not reveal so obviously the disturbances of function accompanying affective states. Special methods must be used to determine whether these organs are also included in the complex of an emotional agitation.[1]

Cannon stressed the importance of inhibitory effects of violent emotions on gastric secretion and the entire alimentary canal, later (15) asserting that this was but one item in the total picture of sympathetic inhibition. Specifically, he stressed worry and anxiety as the emotions most likely to stop gastric secretion and motility in man. In his experiments with cats, rabbits, dogs and guinea pigs, he showed that rage as well as anxiety and distress caused an almost immediate cessation in peristaltic activity of the stomach. He emphasized the apparent universality of these reactions, man included.

Cannon was also among the first important investigators to alert the physician to emotional stress as a contributing

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[1](16) p. 480

factor in a large percentage of cases of "gastric indigestion." He was well ahead of his time when he warned that many who come for treatment of digestive disorders are suffering from ills which are "functional" in character and "nervous" in origin:

> A refined and sensitive woman who had digestive difficulties, came with her husband to be examined. They went to a hotel for the night. The next morning the woman appeared at the consultant's office an hour after having eaten a test meal. An examination of the gastric contents revealed no free acid, no digestion of the test breakfast, and the presence of a considerable amount of the supper of the previous evening. The explanation of this stasis of the food in the stomach came from the family doctor, who reported that the husband had made the visit to the city an occasion for becoming uncontrollably drunk, and that he had by his escapades given his wife a night of turbulent anxiety. The second morning, after the woman had a good rest, the gastric contents were again examined; the proper acidity was found, and the test breakfast had been normally digested and discharged.[1]

Of prophetic importance was Cannon's early recognition of what was not commonly understood at that time:

> ...the subtle changes wrought by these emotional disturbances are not brought to consciousness, and are clearly defined solely through physiological studies. (16)

In 1909 Cannon felt it would be an error to assume a predominant role of the psychic state in the etiology of digestive disease. (16) But his plea was strong, when he asked that

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[1](16) p. 481

> the mental state of the patient...be considered before passing judgment on the nature of his trouble, for just as feelings of comfort and peace of mind are fundamental to normal digestion, so discomfort and mental discord may be fundamental to disturbed digestion.[1]

In a later work (15) he made an even stronger case for the necessity of looking into the psychological factors in anyone with a gastrointestinal complaint. Fully eighty percent of digestive disorders, he asserted, are based upon emotional disturbances![2,3]

Meanwhile, as medicine was beginning to learn the importance of emotional factors in gastrointestinal disease, many investigators, especially in the 1920's, carried out further physiological studies dealing in a general way with the effects of emotions on gastric motility and secretion in well animals and humans. Several standard techniques had evolved since Beaumont's early observations. More subjects with gastric or small bowel fistulae were studied. Barium studies and balloon-pressure techniques were used to investigate gastric tone and motility.

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[1](16) p. 487.

[2]It is of interest that this statement was made in 1933, one year prior to publication of Alexander's first major exposition of his "specificity hypothesis," which relates to specific unconscious determinants in the etiology of actual organic gastrointestinal diseases. (1)

[3]The 1930's brought further pleas for recognition of emotional factors in gastrointestinal diseases. One such is that of Molsen, in 1930, (64) who advocated more careful study of the gastrointestinal system in neurotics, feeling that they were more susceptible to misdiagnosis than others. "Many are deprived of appendices and gall bladders without... relief."

Carlson's work in the field of gastrointestinal physiology includes his well-known study of Mr. V., a patient with a gastric fistula. (18) In Mr. V., he found that "depressant" emotions, i.e., fear, anger, and anxiety, as well as painful stimuli caused a marked decrease in gastric secretion. Strong emotions of pleasure were also seen to depress secretion.

Schrottenbach's findings in 1921 seem to be in basic agreement with those of Carlson's. Speaking sharply to a boy with a gastric fistula effected a complete cessation of gastric secretion. (76)

Several studies on gastric motility further elucidated the relationship of emotions to gastrointestinal function. Lehman and Gibson (1924) studied a man with jejunal fistula. (55) During periods when their patient was "mentally depressed," they noted reverse peristalsis. Alvarez (3) did experimental studies on the influence of emotions on peristalsis. He found, predictably -- establishing in humans what Pavlov and others had shown in animals -- that thoughts of food stimulated increased gastric peristalsis. He was one of the first to illustrate, by means of barium studies, that strong emotional states inhibit gastric emptying. He further stressed the importance of fright and pain in inhibiting gastric secretion by reporting the case of a little girl who had fallen out of a tree and broken her arm, shortly after having eaten. While under anesthesia several hours later, she vomited the contents of her stomach,

and it was found that the food she had eaten so many hours before remained almost completely undigested. Even the teeth marks remained on a piece of fruit.

Somewhat earlier, using the balloon-pressure technique, Brunswick had studied the relationship of emotional stimuli to gastrointestinal tone. (10) Measuring tonus change in the stomach and rectum, he found that the specificity of changes was limited solely to the difference between pleasant and unpleasant emotions. He postulated that, accompanying unpleasant emotions, there was a sympathetically induced decrease in gastric tone. Henry's findings of 1931 showed that gastrointestinal motility is specifically retarded in depression and accelerated in elation. (45)[1]

Thus far the studies considered merely indicate that strong emotions in general had an inhibiting effect on the entire alimentary canal, causing a decrease in secretions, tone, or motility, or reversal of persitalsis. The discrepancies found in the direction of change in gastric function may be a result of the differences in specific affects that make up the composite of "strong emotion" in the various studies. Studies dealing specifically with the effect of a particular emotion or group of them on gastrointestinal function have yet to be discussed.

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[1]Thus they disagree with both Carlson (where pleasure caused decrease in gastric function) and Brunswick (whose distinctions were limited to pleasure vs. unpleasure).

3. Specific Emotional States and Gastric Function

Experimental, largely hypnotic, production of specific emotions, and correlations of spontaneous emotional states with gastric function in "normal" volunteers without apparent psychiatric or gastrointestinal disorder are the sources of several important findings. There is considerable disagreement among these studies as to 1) the nature of the emotions themselves producing gastrointestinal changes, and 2) the direction of the changes in secretion or motility in specific emotional states.

As early as 1900 the French physiologist Leconte (54) determined in dogs, and believed to be true in man, a definite effect of "depressing emotions" on the digestive system:

> D'après ces expériences on voit combien une émotion déprimante peut être fatale à la digestion: non seulement, elle peut couper l'appétit, comme les personnes nerveuses l'affirment si souvent, mais elle peut supprimer toute la sécrétion gastrique.[1]

Direct experimentation with human subjects, however, is not discussed. The author seems merely to surmise the same to be true of humans.

Human secretory studies took their first major advance of the twentieth century in the work of Bennett and Venables, 1920. (7) They claimed to be the first to show that in normal (i.e., non-fistulous) humans, specific emotions

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[1] /From these experiments it is seen how a depressing emotion can be fatal to digestion; not only can it curtail the appetite, as nervous persons so often attest, but it can totally suppress gastric secretion./ Author's translation.

can moderate digestion in a specific way. Their subjects, all healthy medical students, were studied by means of gastric intubation. After obtaining a baseline curve of acid secretion of each subject, they suggested various emotional states by means of light hypnosis, and took a second set of samples. In comparing the normal, pre-hypnotic curve with the post-suggestion curve for each subject, they made the following conclusions: When the feeling of nausea or anxiety was hypnotically evoked, the secretion of free acid was diminished. They attributed this to sympathetic inhibition. On the other hand, when hunger was suggested they found no change from the baseline, but when the satisfaction of hunger was suggested, there was a sharlp rise in HCl secretion. Depressive emotion was not among those investigated by Bennett and Venables. It was not until Kehoe and Ironside's work, forty years later, that hypnotically evoked depression was studied in a systematic way.

The studies of Wittkower (1935) contribute to the fund of both knowledge and discord on the subject of the effects of specific emotional states on gastric function. (85) His study, which also made use of the gastric tube, advanced a step farther than Bennett and Venables in its use of both hypnotically evoked and waking spontaneous emotions. Normal subjects were studied (doctors and other professionals). Both hypnotically and spontaneously, the emotions of disgust, fear, sadness, anger and joy were correlated with gastric acidity, emptying time, and quantity of fluid secreted.

Their results are at variance with all earlier published data in that every emotion studied was associated with a lower HCl secretion than in the "normal" baseline state. In contrast with all previous and most future work is his finding that equal stimuli (emotions) did not cause similar results in all subjects. The same emotion in different subjects caused different changes in gastric function -- hypoacidity in one, hyperacidity in another, and "varying quantities" of secretion in others. Complete irregularity of physiological reaction to the same emotional stimulus with different subjects was thus postulated. Wittkower thought that the manner of the gastric reaction was personally determined, without any hint of a general trend for each emotion. Thus the general reaction of the stomach for the entire group of subjects was not considered a function of either the intensity or the type of emotion. However, the author found that the various emotions in each individual subject always produced the same physiological changes. This study also showed, as did others, (18) that salivary flow parallels gastric secretion.

The primary purpose of Wittkower's paper was to show the influence of various specific emotions on gastric function. Depression itself was not included. The closest he came to depressive affect was "sadness."

In the study of the relationship of emotions to gastroduodenal function in patients with peptic ulcer and other gastrointestinal disturbances, Mittelmann and Wolff (1942)

grouped the effects of emotions in entirely new ways. (63) Contrary to all other studies, they found that every one of the following unpleasant affects--tension, anxiety, anger, resentment, guilt, desperation, and frustration--caused a rise in free HCl secretion (plus mucus and pepsin) and increased peristaltic contractions of the stomach. Increased acid output was also seen during dreams of resentment and vengeance. On the other hand, security and relaxation tended to lower acid secretions toward normal levels. Their formulation was that in states of "emotional hostility," HCl secretion will rise. These workers were among the first to suggest a psychodynamic mechanism for this rise in acid output. Excess secretion under stress, they contend, is an attempt to resolve hostility and gain security through eating. Presumably, therefore, when security already exists, there is no "need" for an increased acid output.

Contrary to the results of Mittelmann and Wolff, Margolin (58) found [with his co-experimenters, Crider and Walker (19)] a definite fall in gastric secretion in anger, resentment and fright. The first experimenter to stress the importance of unconscious forces as a potent determinant of gastric function, Margolin based his findings on a psychoanalytic study of a young woman with a gastric fistula (1951). On a theoretical basis, Alexander had been suggesting the same thing for many years; (1, 2) but Margolin was the first to experimentally corroborate Alexander's ideas. Margolin used psychoanalytic techniques for

the first time in this type of experimental situation to account for certain variables such as the patient's reaction to instrumentation and manipulation during the experiment. Repressed instinctual needs mobilized by stimuli in the experimental situation which were about to come into consciousness were shown to be associated with increased gastric secretion and motility. Reaction formation as the dominant defense tended to be associated with a lowering of gastric function.

The experimenters themselves, Crider and Walker (Margolin did not participate in the actual physiological experiments), found that a state of happiness was associated with active gastric secretion and motility. Pain, contrary to several earlier studies mentioned, caused an increase in motility, but had little effect on secretion or color. Unlike several other studies discussed, sustained "emotional tension" seemed to produce no increase in gastric secretion or motility. Finally, this study is important because it was the first investigation of a female with a gastric fistula.

Of all the physiologically oriented investigations which broadly attempted to correlate various emotions with gastrointestinal function, in no case was depression, clinical or induced, investigated in any detail whatever. Moreover, there was great disagreement: 1) do certain emotions have a specific physiological effect on gastric function in a large population of subjects? 2) if specific emotions do

have a specific effect, what is it? There is such disagreement as to the direction the secretions and motility take in response to a particular emotion that one can find almost any effect one wishes for any particular emotional state.

4. Depression and Gastric Function.

The following investigations, covering a period of forty years, are concerned with the specific relationship of depressive affect to gastric secretion. Strikingly few studies of gastric function in depression exist. Apparently only one group of investigators, Farr et al., in a series of two articles in the mid-1920's, has attempted to correlate clinical depression -- in more than one patient -- with gastric secretion. (29,30) All others have either limited their investigations to studies of isolated patients with gastric fistulae, as Engel et al. (27,28) and Wolff and Wolf (87,88) or have artificially induced depressive affect in a group of normals, as Kehoe and Ironside. (50,51)

Farr et al., the only group of investigators in the literature who studied the gastric secretory effects of clinical depression in a patient population, published two articles in the middle 1920's. In the first, (29) gastric intubation with a test breakfast was employed, and free and total acid and pepsin were determined by a fractional collectional method. Various groups of psychiatric illnesses were compared, such as manic-depressive, "dementia praecox,"

and "miscellaneous psychoses." The authors were struck by the correlation, in their first paper, between the degree of depression and the lack of cooperation (about which more will be said later). They also found a correlation between degree of depression and the degree of suppression or delay of gastric HCl secretion. Their results showed that out of a group of twenty-four depressed patients half had hypochlorhydria. It was noted that several depressed patients (number unknown) needed mechanical restraint (wet pack) owing to "lack of cooperation," "resentment," and "violent resistance." They hypothesized that in the depressed population sympathetic inhibition of gastric secretion was largely responsible for the results. They also found that in the neurotically depressed patients their results were inconclusive, that in those with dementia HCl secretion was normal or high, and that in "miscellaneous" psychoses HCl was high. Their second study in 1925-6 (30) employed a larger population of depressed patients. Here it was found that other etiological factors may have been present, such as pernicious anemia, nephritis, gall bladder disease, and gastritis, which might have influenced their results. The results of this later study diametrically contradict the former. It was found that the depressed group did not differ significantly from the general patient population in gastric HCl secretion. They were therefore "forced to conclude" that "long-continued" depression did not inhibit gastric secretion, but that acute emotion, such as anxiety and anger,

did. This is the opposite effect of that reported in their first publication, in which the depression seemed well-correlated with decreased HCl, and that other patients with the so-called "acute" affect states had normal or high values. The authors made no attempt in their second paper to discuss acutely depressed patients, and thus did not admit depression into the category of "acute emotion."

For numerous reasons the validity of the above results must be questioned. The greatest problem is lack of controlled conditions. The authors themselves made it clear that "several" of the depressed population resisted the experimental procedures violently, requiring wet packs. One can but question whether, under such conditions, the effects of whatever depression these patients had might not have been effaced by the artifact of restraint and the overlay of violent resistance and resentment. Further, it is not clear what physiological units the authors are using when they refer to "acidity." They are never defined. As the authors themselves raise the question of several organic diseases obscuring the validity of their results, the reader must ask the same question. Moreover, the authors failed in either paper to define the limits of high, normal, or low acidity. Statistical methods were not employed, raising further questions about their generalizations.

Because of the technical faults of these two studies by Farr et al., and because their final conclusion was that the depressed group did not show any significant effect on

gastric function, there remains confusion with regard to the relationship of gastric acidity to clinical depression. Other studies must be considered. None of these investigates patient populations, or populations with endogenous, non-experimental depression. Rather, the remaining major studies have as their subjects isolated individuals with depressive affect, or groups of healthy volunteers with experimentally induced depression.

Wolff and Wolf's classical study of Tom, (87,88) their patient with a gastric fistula, represents the first psychologically sophisticated attempt to study the interrelationships of depression and gastrointestinal function. In this study emotions were generally spontaneous, not experimentally induced, although several occasions were reported where artificially contrived situations were used to evoke certain emotions. Fear, sadness, dejection, self-reproach, and depression, comprising an emotional constellation of withdrawal or desire for escape from "charged conflict situations," were accompanied by pallor of the gastric mucosa, increased emptying time, and decreased HCl output.

Anxiety, hostility, resentment, and pleasurable thoughts of eating, all considered to be a part of the emotional constellation of aggression and the will to fight back, were associated with increased HCl secretion and decreased emptying time. When Tom was observed in a specifically hostile or resentful state, the stomach acted as if "ready to devour a large meal," with engorgement, blushing of the

mucosa, and a tripling of HCl output. Degree and duration of secretion were found to be proportional to the intensity and duration of emotion. The results seemed to demonstrate experimentally what Alexander had postulated in his works on the psychogenic etiology of peptic ulcer, where gastric acidity is often high.

Wolff and Wolf advanced considerably the concept of depression in describing it as a total physiological reaction to an adverse situation which cannot be changed. Thus depression in their patient meant anorexia, dejection and hopelessness, lack of vocal inflection, apathetic appearance, expressionless facies, and few bodily movements. Decreased HCl secretion was but one part of a generalized shut-down. It was one manifestation of the reaction to being "defeated by the threat." It remained for such workers as Engel and Schmale to further define depression as a total biological process serving as a protective, energy-conserving mechanism.

The studies of Engel et al. (27,28) on Monica, an infant with gastric fistula, represent an important contribution to the understanding of the biology of depression, with the major emphasis on gastric function. They defined "depression" in their patient as the infantile anlage of adult depression, terming it the depression-withdrawal reaction. This reaction typically occurred when the infant was confronted by a stranger from whom she could not, of course, escape. She reacted with sad facies, muscular hypotinia and immobility, decreased oral activity, unchanged

cardiac rate, an eventual state of sleep, and markedly diminished gastric acidity (in milliequivalents per minute) -- significantly lower, in fact, than in any other emotional constellation. This "total biological response" could be provoked and terminated at will, depending upon the presence or absence of a stranger. The reaction was never observed when the baby was alone. When the depression-withdrawal reaction supervened, even histamine stimulation failed to provoke a rise in gastric acidity. However, with the departure of the stranger there was an abrupt increase in secretion. Moreover, it was found that when such a stranger attempted to communicate with the infant, her HCl secretion rose. This rise was attributed to a response termed "depression-unpleasure," which was considered a mixture of the depressive response and elements of the flight-fight anxiety pattern. HCl secretion was found to be highest in rage [consistent with Wolff and Wolf's psychodynamic formulation of increased HCl secretion (88)]. Bibring's concept of "the ego's shocking awareness of helplessness in regard to its aspirations," (Engel [28] and) Schmale's concept of helplessness-hopelessness (74) seem to be similar descriptions of the adult version of the "depression-withdrawal reaction" described in Monica.

Engel's basic biologic pattern of depression, as described above in Monica, was explained as a response to outside stimuli when energy sources are depleted. The generalized reduction in muscular and visceral activity re-

flects an attempt to conserve energy in the face of repeated failures of the fight-flight response. Psychodynamically, it represents a withdrawal of cathexes from the external world.

Engel et al. admonish against applying their principles to the general case, as did Wolff and Wolf in their study, primarily because the source of their data was but one infant girl.

A different approach to the investigation of gastric correlations of depression is the work of Kehoe and Ironside. These workers used hypnosis in the experimental evocation of depressive responses in normal, healthy volunteers.[1] The combination of gastric intubation and hypnosis allowed the investigators to analyze the periodic gastric acid output as they induced various affective states. Five categories of affective states were considered: anger, anxiety, contentment, depression, and helplessness-hopelessness, which latter term comprised futility, defeat, giving up, or entrapment in an inescapable and unpleasant predicement. An affect rating and total HCl determination were carried out for each periodic specimen. A positive correlation was found between the rate of total acid secretion and coincident dominant affective responses under hypnosis. In non-hypnotized "control phases," the trends were similar

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[1]Volunteers cannot be considered an unselected population, free from endogenous affective states. It is possible that volunteers as such are neither entirely "normal" nor "healthy."

to those found in the hypnotized group, except that the results were not statistically significant. Gastric acid was found to be highest in anger (cf. Engel et al. [27,28]) and lowest in "helplessness-hopelessness" (cf. Schmale [74]).

After initial pre-hypnotic and early hypnotic phases, depressive affect was induced by the single word stimulus "depression." It was during this depressive stage that gastric HCl values were lowest for any of the five affective states. Interestingly, it was found that there was no statistically significant difference between gastric acidity in the depressive state and the early hypnotic state. No significant correlation was found between gastric secretory rate and any one of the various affects. Therefore, the authors considered it impossible to draw any conclusions as to cause and effect. The total rate of HCl secretion was highest overall in anger, decreased in contentment and anxiety (contradicting Wolff and Wolf), and lowest in depression and helplessness-hopelessness. This was found to be true only when the affects mentioned were the dominant ones.

The authors found it difficult to identify the dominant affect when their subjects were not hypnotized. Ikemi et al. (46) have shown that hypnosis alone does not significantly alter gastric secretion. Therefore, the authors postulated that during hypnosis the various affects are experienced more intensely than in the waking state.

Other pertinent findings of these investigators included a positive correlation between mean HCl secretory

rate for each of the various affective phenomena and "mastery of experimental conflict." Applied to clinical depression, this might imply that gastric secretion would be higher when defense mechanisms are operative than when they are ineffective.

In general, experiences that gave or promised satisfaction were associated with a rise in gastric HCl, and vice versa. This finding lends support to the work of Bennett and Venables over forty years earlier, who found a sharp rise in acid secretion only when the satisfaction of hunger was suggested, not merely hunger alone. From the viewpoint of ego-functions -- "ability vs. inability"; "possibility vs. impossibility"; "adaptation vs. stress" -- in the first term of each pair HCl was found to rise, in the second, to fall. Therefore, the authors suggest that when the prospect for satiety is a hopeless cause, acidity falls. This would appear to parallel Engel's "depression-withdrawal," and Schmale's and Engel's "helplessness-hopelessness."

Table I. Summary Chart of Agreement or Disagreement

Name	Anger	Anxiety	Fear	Sadness	Depression	Disgust	Pleasure/Happy	Hunger	Nausea	Guilt
Beaumont	↓		↓							
Sweetser			↓	↓	↓					
Bidder/Sch.								↑		
Pavlov								↑		
Leconte				↓	↓					
Cannon	↓	↓	↓			↓				
Carlson	↓	↓	↓				↓			
Schrotten.			↓							
Alvarez			↓							
Bennett/Ven.	↑→↓							-,↑	↓	
Wittkower	↑/↓		↑/↓	↑/↓		↑/↓	↑/↓			
Mittelm./W.	↑	↑					—			↑
Margolin	↓		↓							
Crider/Walk.						↓	↑			
Farr et al.	↑			↓,-						
Wolff/Wolf	↑	↑	↓	↓	↓		↑		↓	↓
Engel	↑				↓	↓	—			
Kehoe/Irons.	↑	↓		↓	↓		↓	-,↑	↓	

↑ = increased gastric acidity

↓ = decreased gastric acidity

— = no change

The above chart summarizes the principal studies mentioned. There is strong disagreement as to the direction of change in gastric acidity in virtually every emotional state considered. The most uniform agreement is found in depression, where acidity is decreased. It is important to emphasize again, however, that none of the above studies, with the exception of Farr et al., is concerned with clinical depressive illness in a significant number of patients. And, as seen, that group of investigators not only retracted their original assumption that acidity is decreased in depression, but employed experimental methods which by today's standards are open to question. What is clearly lacking, therefore, in the fund of data relating depressive affect to gastric secretion is a clinical study of a number of patients with depressive illness. This is the purpose of the present study.

5. Biochemical and Endocrinological Correlates of Depression.

A brief review of normal gastric physiology seems advisable as a frame of reference for the discussion to follow, which will consider recent literature dealing with the biochemistry and endocrinology of depression, primarily as they relate to altered gastric function. A final section will be devoted to the relationship of depression to disease.

A. Gastric Physiology

The major sources for this review are Ganong (35) and James (47). Influences on gastric function are two-fold, local and systemic. Food acts locally on the stomach and small intestine both mechanically and chemically. Systemically, there are neural and hormonal effects. Locally, acetylcholine (Ach) is liberated at the endings of the postganglionic cholinergic neurons in the stomach. There is evidence that Ach liberation is mediated by the vagi and by local reflex activity in the stomach wall itself. Ach increases acid secretion in two ways: 1) it acts directly on the parietal cells of the fundus, stimulating the secretion of HCl; 2) it causes liberation of gastrin, a proteinaceous hormone, from the antral mucosa. In HCl production, gastrin and Ach potentiate one another in their stimulatory effect. It is also known that stimulation of the vagi increases gastric secretion, but vagotomy does not abolish secretion. It is known that pepsin production quite definitely parallels elaboration of HCl.

Another hormone, enterogastrone, is liberated from the duodenal mucosa into the general circulation and thence travels to the stomach wall, where it causes inhibition of gastric secretion and motility. The presence of fat, carbohydrate, or HCl in the duodenum causes release of enterogastrone. Adrenocortical hormones are known to stimulate increased production of HCl, whereas adrenal medullary

hormones seem to have an inhibitory effect (as Cannon had postulated in 1909).

Thus, there are probably two centrally mediated mechanisms for stimulation of HCl secretion. One is via the anterior hypothalamus, by way of the vagi and thence to the stomach wall, where acetylcholine is liberated. The other has as its probable origin the posterior hypothalamus, which by way of the anterior pituitary, adrenal cortex and glucocorticoids causes a release of HCl by a direct effect on the stomach.

It is known that insulin has a stimulating effect on gastric secretion. This effect is probably secondary to hypoglycemia, which in turn causes ACTH stimulation of the adrenal cortex. The adrenal steroids themselves are thus the vehicle for insulin-mediated gastric secretion. Insulin probably also has a direct stimulatory effect of its own on gastric secretion.

Another way of viewing gastric secretion is to consider its four known phases; these phases, however, may all be in progress at the same time.

Cephalic phase. This phase is initiated by the smell, taste, or mere anticipation of food, and causes an increased gastric secretion. The probable mechanism is vagal and possibly augmented by the pituitary-adrenal cortical axis. Hypoglycemia may also play a role, which implies that stress may stimulate increased gastric acidity.

Mastication phase.[1] The presence and chewing of food in the mouth has a vagus-mediated stimulatory effect on HCl and pepsin production.

Gastric phase. Local and systemic effects (both neural and humoral) are operative here. Food in the stomach, via chemical and/or mechanical stimulation of the antral mucosa, cause release of gastrin into the bloodstream, which in turn acts directly on the mucosa of the fundus to increase acid production. This process is inhibited by HCl.

Intestinal phase. Food in the duodenum stimulates the release of gastrin, which in turn stimulates gastric secretion. In addition, the gastric inhibitory hormone, enterogastrone, is released by the presence of lipid in the duodenum.

Histamine is found in gastric secretion. By chemical and neural stimulation, histamine causes an increase in HCl secretion. It is known that such antagonists as diphenhydramine (Benadryl) block all systemic effects of histamine except the secretory effect, which remains intact no matter how high the dose of Benadryl. The relative importance of histamine in the normal regulation of gastric acidity is not known.

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[1] The existence of this phase is controversial. Both Ganong and Fenton [in Ruch and Fulton (70)], for example, fail to mention it. James (47) accepts it as a distinct phase.

B. Physiology of Depression

Catecholamines

Bunney et al, have reviewed recent work on the relationship of catecholamines to depressive illness. (12) The role of norepinephrine (NOR) in depression was deduced from observations of the antidepressive effects of two classes of drugs, the imipramine type and monoamine oxidase (MAO) inhibitors. Both types affect functional NOR in the brain. Imipramine, according to Bunney et al., probably decreases NOR uptake in the central nervous system (CNS), thus increasing NOR availability at nerve endings. Monoamine oxidase (MAO) inhibitors block NOR breakdown. On the other hand, reserpine and α-methyl DOPA cause decreased brain NOR and are associated in a significant number of cases with episodes of clinical depression in patients treated with these drugs for hypertension. This evidence, of course, is indirect in a consideration of the relationship of clinical depression to catecholamines.

In their review, Bunney et al, report on the work of Schildkraut et al., who found that the urinary excretion of VMA (a metabolite of epinephrine) is reduced after successful therapy for depression with imipramine and an MAO inhibitor.

Bunney et al. (12) found in their series that urinary NOR and other catecholamine excretion is significantly higher in psychotic depressives than in neurotic depressives.

This was found only in acutely psychotic depressive episodes, not chronic. In the latter, urinary NOR levels were found to be between those of the acutely psychotic depressives and the neurotic depressives. The authors explain that three factors affect catecholamine levels in the blood: psychic stress associated with psychiatric illness, external stress, and physical activity. Their work is compared with that of Curtis, who found no deviation of urinary catecholamine excretion from normal values in a mixed population of various psychotic patients exclusive of severe depressives. Bunney et al. contend that the greatest increase in NOR excretion occurs in acute psychotic depressives, as stated, and here their statistics indicate that the elevated NOR levels are not merely the result of non-specific stress. The authors stress the fact that, in view of the impermeability of the blood-brain barrier to NOR and other catecholamines, their hypothesis is not necessarily incompatible with the work of other investigators, who found decreased levels of brain NOR in depressed patients. (23) Increased synthesis and breakdown of NOR may make less functional NOR available to the brain. Catecholamine metabolism in depressive illness has not as yet been definitely elucidated, but increased NOR levels would have an inhibitory effect on gastric secretion. (35)

Adrenal Steriods

Since Selye first introduced the concept of the "general adaptation syndrome," it has been known that emotional stress is accompanied by changes in adrenal steriod levels. Several workers have been engaged in the past decade determining whether there is a relationship between steriod metabolism and depressive illness. A number of studies have shown that plasma glucocorticoid levels are elevated in depression, and fall again with clinical improvement. (23) In 1962 Gibbons et al. (36) demonstrated a positive correlation between plasma 17-hydroxycorticosteroid (17-OHCS) levels and severity of clinical depression. It was found that patients with psychotic depression had the highest plasma cortisol levels, and that these levels returned to normal with clinical improvement. The same author, in 1964 (38), showed that urinary cortisol secretion rates rose to two to three times their normal values in the most severely depressed patients studied, and found a high correlation between plasma cortisol levels and urinary 17-OHCS secretion rates. He made the conclusion that, as a group, depressed patients show increased adrenocortical activity. McClure (60) studied the diurnal variation of plasma cortisol in a group of depressed patients and a comparable group of healthy controls. He found that cortisol levels in the depressed group remained high throughout the 24 hour cycle, and discovered a good correlation between the severity of depression and the level of plasma cortisol.

One interesting finding was that cortisol levels tended to be higher in the retarded depressives than in the agitated depressives (cf. Bunney, 13). He hypothesized that 1) cortisol level is a good indication of the severity of depression, and 2) high plasma cortisol level may be responsible for the early morning awakening experienced by so many depressed patients.

Bunney et al. (13) made longitudinal studies of urinary 17-OHCS levels and independently evaluated behavior ratings in a group of seventeen depressed inpatients. As a group, the depressed patients were found to have significantly higher than normal 17-OHCS excretion. However, one-third of the patients were found to have levels which were normal or even below normal. This was explained by the finding that the latter group had very active defenses, tending to use denial most frequently, though still as depressed as the patients in the group where elevated 17-OHCS levels were found. The high 17-OHCS group was found to be composed of patients "involved in the struggle," with defective defense mechanisms, ego-alien symptoms, and much anxiety and agitation. Thus, compensation seemed to be associated with low steroid excretion levels, and decompensation with high levels. At the same time it was shown (11) that the onsets of psychotic depressive crises were associated with high urinary 17-OHCS excretion levels.

In support of the above findings, Sachar et al. (73) have studied a group of six women hospitalized for reactive

depression. During the course of psychotherapy, confrontation of the precipitating object loss proved to be more painful (for the great majority of patients) than the previous depressive equilibrium state. At the time of the critical theraputic confrontation, there was a transient rise in corticosteroid excretion, which fell again after resolution of the object loss.

Some findings, however, seem to be at variance with much of the above. Fawcett and Bunney (31) cite the work of Kurland, who found that urinary 17-OHCS was elevated only in the initial phase of depressive illness. This was interpreted as indicating a relative adrenal insufficiency (of active compounds) in severe depressive illness. Kurland found prednisone effective in producing clinical improvement of the depression in patients who had been unresponsive to other antidepressive medications. This result seemed to support the conclusion that in this sample at least, relative hypoadrenalism was indeed present. Fawcett and Bunney suggest an explanation for this apparent paradox. Why, they ask, is there obvious hyperadrenalism in certain groups of depressed patients studied, and relative hypoadrenalism in other patients? There are, they conclude, several subgroups of depressed patients, requiring further investigation. For example, difference in method of assay may be responsible for the discrepancy; equally responsible might be different breakdown rates, antagonism by other hormones, or plasma binding. The most plausible hypothesis is that with the commonly used assay techniques, no dis-

tinction is made between active steroid and inactive metabolites. Hence, the strong possibility of an erroneous impression from an apparent elevation of 17-OHCS, if the bulk of these compounds is inactive. They also enunciate a number of other postulates to resolve the conflict which are too numerous to consider here. Suffice it to say that the majority of studies (23) show an elevation of plasma cortisol and urinary 17-OHCS in the depressed population, as differentiated from other mentally ill populations. Many authors have found a high positive correlation between degree of steroid elevation and severity of depression. The triad of steroid elevation, depression, and gastric secretion will be further elucidated in the Discussion of the Experiment.

C. Depression and Mechanisms of Certain Diseases

The relationship of depression to disease may be epitomized in a study directly related to gastric secretion. In 1959 Lewin (56) investigated a group of ten patients admitted to a medical service with pernicious anemia. Though not admitted as psychiatric patients, they all shared one factor in common: depression. This was unrelated to either the stage of the combined system disease or to its treatment with vitamin B_{12}. In most cases the depression was of the reactive type, reflecting an object-loss situation, and in every case the depressive symptoms preceded the onset of the symptoms of anemia. Because of this, the

anemia could not be implicated as a cause of the depressive symptoms. It is known, argued Lewin, that the cause of pernicious anemia is a depletion, not a total lack of, intrinsic factor. Could depression, he asked, somehow cause pernicious anemia? There is no evidence, in patients without pernicious anemia, of a correlation between intrinsic factor and other products of gastric secretion, such as HCl. However, it is known (86) that in adults with pernicious anemia there is achlorhydria and very little secretion of gastric juice, although children with pernicious anemia may be normochlorhydric. Further, Mirsky (62) has shown a high incidence of pernicious anemia in hyposecretors of pepsinogen. It is also known, Lewin postulates, that since there is some activity of intrinsic factor even in pernicious anemia, there must exist a critical level of intrinsic factor secretion below which pernicious anemia develops. Some persons, the author asserts, may have a genetically determined low level of intrinsic factor, but not low enough to cause pernicious anemia. If, as in Engel's study of Monica (27,28), depression reduces gastric secretion, may it not also reduce intrinsic factor to a level below the critical mark? Here, Lewin assumes that what is true for Monica is true for the general case, although the authors themselves had warned, in their study of Monica, against applying the results obtained from the study of a single infant to the general population.

Schmale (74) has related depression to the onset of disease in a large number of patients. Disease, he feels, is a possible manifestation of depression. 42 unselected medical patients were studied for pre-disease object-relation changes and affects as a reflection of such changes. 5 patients reported a feeling of "helplessness-hopelessness" immediately before the onset of the disease without known object loss. 41 of the 42 gave verbal and non-verbal evidence of actual, threatened, or symbolic object-loss, and had feelings of "helplessness-hopelessness" at the onset of their medical disease. 31 of the 42 had onset of their disease within only one week of feelings of "helplessness-hopelessness." Separation and depression, as defined by the author, represent an unsuccessful resolution of an object-loss, leading to feelings of "helplessness and hopelessness." The author lists and documents a striking number of medical diseases which have frequently occurred soon after object-loss and may thus be associated with depression. Among these are cancer, thyrotoxicosis, asthma, obesity, tuberculosis, ulcerative colitis, leukemia, lymphoma, rheumatoid arthritis, congestive heart failure, systemic lupus erythematosis, Raynaud's disease, diabetes mellitus, infectious hepatitis, dysfunctional uterine bleeding, and death itself. No attempt is made to define the mechanisms of production of these conditions.

Peptic ulcer is another disease process which some investigators have related to depression. Kraines, for example (53), finds in his series that there is a relationship in some cases between ulcer and manic-depressive illness. The pathogenesis of peptic ulcer, he asserts, is the result of a hypothalamic disorder which brings on vagal and endocrine changes. Psychic trauma plays a major role in causing hypothalamic disturbances. Manic-depressive illness is also, according to the author, partly a result of hypothalamic dysfunction. In his series of manic-depressives, he found that 70% had psychosomatic symptoms largely referred to the gastrointestinal system--sour eructations, for example. These symptoms occurred on the depressive downswing and upswing, but not at the depressive nadir or during other intense melancholic periods. His study gives no exact figures on the incidence of ulcer in manic-depressive illness. 3% of his patients had ulcers, and others had "ulcer symptoms." In general, symptoms seemed to be present most often in periods of mood change, not during stable periods of depression or mania. The author postulates that many patients with a primary diagnosis of peptic ulcer or ulcer syndrome are actually experiencing depressive equivalents. "Perhaps manic-depressive illness [not necessarily depression in a more general sense] should be put on the suspect list" as an etiological agent in peptic ulcer. Three of his patients with previously intractable duodenal ulcer, treated with

electroshock therapy, enjoyed a remission of both their depressions and their ulcer symptoms.

Whether the relationship found was causal or coincidental, Kraines could not conclude. In addition, the study is biased in many ways. It lacks controls; it considers only manic-depression in the broad spectrum of depressive illness; and it uses no statistical methods. However, the trend is postulated, at least for manic-depression.

Gosling (42) carried out more thorough studies and came to a similar conclusion. In comparing 268 male psychiatric in-patients to a sample of "normal" working males, he found the incidence of peptic ulcer lower in the psychotic group, and higher in the neurotic, than in the "normal" group, i.e., neurotic > normal > psychotic. The low values for the psychotic group were attributed to a very low incidence of ulcer found in the schizophrenics studied. Within the neurotic group, the highest incidence of ulcer was found in the depressives; alcoholics and asthmatics also had a high rate of ulcer disease. Gosling questions the reliability of his own findings several times, but, as in the above paper, indicates a trend. He postulates that peptic ulcer is an index of vulnerability to stress. At one end of the scale are the withdrawn schizophrenics, at the other, the hyper-reactive neurotics. The former are immune, the latter prone, to ulcer disease. Gosling suggests the possibility that susceptibility to peptic ulcer may be associated with susceptibility to depression.

The controls used are not comparable to the psychiatric population: they are neither hospitalized nor are they screened for freedom from neurosis or psychosis, by Gosling's admission.

Neither study experimentally investigates the possible mechanisms by which depression may be associated with or play a role in the production of peptic ulcer. With several other studies, they merely postulate an association between the two entities.

EXPERIMENTAL

PURPOSE

The purpose of this experiment is to investigate the relationship between gastric acidity and depressive illness, using as subjects a group of hospitalized psychiatric patients. The hypotheses to be tested are: 1) clinical depression is associated with a statistically significant decrease in gastric HCl secretion; 2) there is a significant correlation between the degree of depression and the degree of diminution of gastric HCl secretion.

MATERIALS AND METHODS

A. Clinical Material.

16 inpatients at Fairfield Hills Hospital, Newtown, Conn., 4 males and 12 females, were the subjects of this study. Patients were selected for study without regard for age or sex, the only criteria for selection being 1) a primary admitting diagnosis of depression, regardless of type; 2) no recent therapy with psychopharmacological agents or other drugs; 3) the patient's informed consent, after the purpose and procedures of the project were explained to him. Of 19 patients interviewed, 16 agreed and were able to participate, 1 agreed to participate but was unable to tolerate the gastric intubation procedure, and 2 refused to participate.

B. Experimental Design and Procedures.

Psychological Measures: as soon as possible after hospitalization, usually 12-48 hours, each patient was interviewed for approximately one and one-half hours, during which the psychiatric, medical, and family histories were taken, with emphasis on the present illness. At the beginning of the interview the entire procedure was fully explained to the patient. At the end of the interview, the Beck Depression Inventory was filled out by the patient, with clarification from the experimenter when needed, and the Wechsler Depression Rating Scale was filled out by the experimenter.

Measures of depression included the following:

1. Clinical assessment by the hospital staff.
2. Beck Depression Inventory.
3. Wechsler Depression Rating Scale.
4. Clinical assessment by the experimenter (E) of the type and degree of depressive illness in each patient, based on the psychiatric, medical and family history as elicited from the pre-test interview, and on the behavior of the patient during the interview and on the day of the experiment. This assessment was made without knowledge of the physiological data. E rated the degree of depression quantitatively on a seven-point scale, using 0.5 point intervals from 0 to 3:

0 Not depressed
0.5
1 Mildly depressed

1.5
2 Moderately depressed
2.5
3 Severely depressed

5. Independent evaluation of the degree of depressive illness in each patient was done by two psychiatrists (M/S),[1] based solely on the pre-experimental psychiatric, medical and family histories as recorded by E. They had no knowledge of the assessment by the hospital staff or experimenter, the Beck and Wechsler scores, the physiological measures, or one another's ratings. A four-point scale for quantifying the degree of depression was used by the two psychiatrists:

0 Not depressed
1 Mildly depressed
2 Moderately depressed
3 Severely depressed

The ratings by (M) and (S) were combined by averaging the independent ratings of the two psychiatrists. This was felt justified, since in 10 of the 16 patients rated (62.5%), there was absolute agreement (same rating) and in the other 6, there was no more than 1 point disagreement.

Physiological measures: on the morning following the interview, after a 12-hour fast, a Levin gastric tube (Pharmaseal K-10 Kaslow, size 16 French, disposable plastic) was passed into the stomach and an augmented histamine test was performed, with the patient lying on his left side.[2]

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[1]I wish to thank Drs. F. Patrick McKegney (M) and Edward Senay (S) for their participation as the evaluating psychiatrists.

[2]A.W. Kay. Effect of large doses of histamine on Gastric Secretion of HCl. An Augmented Histamine Test. Br. Med. J. 2:77, 1953.

The gastric contents were aspirated by continuous manual suction using a 50 c.c. glass syringe with a metal adapter, and collected over a period of two hours in 8 separate 15-minute samples, following the collection of the initial overnight fasting sample. After 1/2 hour 50 mg. of diphenhydramine hydrochloride (Benadryl--Parke, Davis) was injected intramuscularly; after 1 hour histamine phosphate (Lilly), 0.04 mg. per kg. of body weight, was injected subcutaneously. This dose of histamine phosphate was large enough to maximally stimulate all the parietal cells to secrete at the same time so as to obtain the maximum output of acid.[1] Benadryl prevented all the systemic effects of histamine except for its effect on the parietal cells.[2] During the aspiration of the gastric contents, a detailed record was kept of everything the patient said, including the number of patient-initiated conversations, reaction to the test procedure, and the type and degree of affect present during each 15-minute period.[3] No conversation was initiated by the experimenter. Special attention was given to the effectiveness or ineffectiveness of the patient's defenses (compensation vs. decompensation).

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[1]A.W. Kay. Effect of large doses of histamine on Gastric Secretion of HCl. An Augmented Histamine Test. Br. Med. J. 2:77, 1953.

[2]Ibid.

[3]See protocol, Appendix (B).

Gastric contents were analyzed for volume, pH, free and total acid. Free acid concentration (mEq/L) was obtained by titrating the undiluted gastric juice with 0.1 N NaOH to pH 3.5, using a Beckmann pH meter. Total acid concentration was similarly obtained by titrating to pH 7.0. Finally, determinations of basal acid output (BAO), total acid output (TAO), and maximal output (MAO) were made. These values were calculated as follows:[1]

$$BAO = \frac{V_1T_1 + V_2T_2 + V_3T_3 + V_4T_4}{1000}$$

BAO in mEq HCl/hour
V_{1-4}= volume of each of 4 pre-histamine samples in c.c.
T_{1-4}= total acid concentration of each of 4 pre-histamine samples in mEq/L

$$TAO = \frac{V_5T_5 + V_6T_6 + V_7T_7 + V_8T_8}{1000}$$

TAO in mEq HCl/hour
V_{5-8}= volume of each of 4 post-histamine samples in c.c.
T_{5-8}= total acid concentration of each of 4 post-histamine samples in mEq/L

$$MAO = \frac{2(V_6T_6 + V_7T_7)}{1000}$$

MAO in mEq HCl/hour
a measure of maximal parietal cell capacity to secrete HCl

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[1]The methods, drugs and equipment used in the physiological determinations were made available by Howard M. Spiro, M.D., and the Laboratory of Gastroenterology, Yale-New Haven Hospital.

Because of the maximal stimulatory effect of histamine on the parietal cells, it was decided to use BAO as the primary index of gastric acid output, although TAO and MAO were also correlated with depression.

BAO values depend to a large extent on age, sex and weight.[1] There exists a normal range of BAO for any combination of these parameters. In order to meet the statistical problem of comparing gastric acid outputs which vary normally from individual to individual, a list of mean BAO's, MAO's and TAO's was made available, corrected for age, sex and weight in a large number of subjects.[2] These values provided a "normal control" population with which to compare the patient population. However, it was by no means a true control population for three reasons: 1) the population used in compiling the "normal" values consisted partially of subjects with various gastrointestinal disorders; 2) there is no information available regarding their psychiatric status; 3) a non-hospitalized group of subjects is not comparable to an inpatient psychiatric population. Nevertheless, these are the best available figures for "normal" gastric acid outputs, corrected for age, sex and weight, in a large population.

A data analysis was undertaken in such a way as to keep each variable discrete and independent from others. The purpose of this analysis was to determine whether a

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[1] Walter Thayer, M.D., Rhode Island Hospital, Providence, R.I.

[2] Ibid.

definite relationship existed between the degree of depression and gastric acid output in terms of BAO. Two types of statistical calculations were employed. Split-rank correlation was used to determine whether there was a significant difference, in whatever measure under consideration, between mean values of the two variables. The population was split-ranked in terms of both degree of depression and gastric acid output. The major statistical test employed in split-ranking was the t-test of differences between two independent means.[1] Split-ranking permitted the use of 1/2 of the experimental population as a "control" group; for example, the least depressed 1/2 of the population, in terms of E or M/S rating, vs. the most depressed 1/2.

The second type of statistical calculation used was the product-moment correlation coefficient, an expression of the degree of relationship between two sets of paired variables, for example, Beck scores and BAO values.[2]

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[1] Formula for t-test: $$t = \frac{M_1 - M_2}{\sqrt{\left[\frac{N_1 \Sigma X_1^2 - (\Sigma X_1)^2}{N_1} + \frac{N_2 \Sigma X_2^2 - (\Sigma X_2)^2}{N_2}\right]\left[\frac{1}{N_1} + \frac{1}{N_2}\right]}{N_1 + N_2 - 2}}}$$

[2] Product-moment correlation coefficient $$r = \frac{N \Sigma XY - (\Sigma X)(\Sigma Y)}{\sqrt{N \Sigma X^2 - (\Sigma X)^2}\sqrt{N \Sigma Y^2 - (\Sigma Y)^2}}$$

Since it had been hypothesized in advance that the degree of depression and BAO were inversely correlated, one-tailed tests of significance were used. Thus, in the t-test, P-values were actually 1/2 their calculated value. It was further hypothesized that MAO and TAO would not be significantly altered, whatever the degree of depression. It was decided in advance to accept a correlation of $P \leqslant 0.05$ (5%) as significant.[1]

RESULTS

The results of the experiment will be presented in the following order: measures of depression and agreement among them; correlation between the various measures of depression and gastric acid output; correlation between other factors and gastric acid output.

Measures of Depression.

As previously mentioned, five measures were used to assess the degree of depression in each patient: clinical evaluation of the hospital staff; Beck Depression Inventory score; Wechsler Depression Rating Scale score; experimenter's rating (E); psychiatrists' ratings combined as an M/S rating (see Appendix A). Concerning the first measure, there were no means of quantifying the opinions of the hospital staff; therefore, they were not used in the statistical calculations, but only in the original selections of the patients for study.

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[1]Martin Harrow, Ph.D., gave generous advice on statistical methodology.

Their admitting diagnoses of depression served as the most important criteria for selection.

A product-moment correlation between the Beck and Wechsler scales revealed that there was no significant agreement between the two scales ($r = .402$, $P > .1$). The trend, however, was in the positive direction.

The numerical ratings of the degree of depression by E and M/S were studied for degree of agreement between the two. A product-moment correlation showed an agreement closely approaching a 5% level of significance ($r = .484$, P sl. $> .05$ [for $P = .05$, $r = .497$]).

Product-moment correlation between the clinical ratings (E and M/S) and the Beck and Wechsler scores yielded the following results: the only correlation showing statistical significance was that between E and Wechsler ($r = .596$, $P < .02$). This finding must be considered in the light of the fact that E had filled out the Wechsler scales. No significant agreement was found between M/S ratings and Wechsler scores (positive correlation, $r = .134$, $P = N.S.$), M/S and the Beck scores (negative correlation, $r = -.04$, $P = N.S.$), or E and the Beck scale (positive correlation, $r = .096$, $P = N.S.$).

In summary (see Table II) there were significant or very nearly significant correlations between E and M/S ratings, and E and Wechsler scores. Among the rest of all possible correlations between the four quantitative depression ratings, no significant or nearly significant correlations

were found. The Beck scale correlated least with all other measures, often negatively. There was a wide variation in ratings of depression among the subject group by all measures used, from not- or minimally depressed to severely depressed.

Table II. Product-Moment Correlations between Psychological Measures

	Wechsler	E	M/S
Beck	r = .402 P > .1	r = .096 P = N.S.	r = -.04 P = N.S.
Wechsler		r = .596 P < .02	r = .134 P = N.S.
E			r = .484 P sl. > .05

Depression and Gastric Acidity.

The primary question under investigation is whether there is a significant correlation between BAO and any of the above-discussed measures of depression.

Two expressions of BAO are employed in the statistical correlations: absolute values of BAO (BAOabs), and deviation from the expected mean BAO, corrected for age, sex and weight of each subject (BAOn-BAO), the latter making use of the "control" figures.[1]

[1]For the sake of brevity, "BAOn-BAO" is used as an expression of deviation from the mean. Actually, in the statistical calculations themselves, the expression "(BAO-BAOn) + 4" was used to avoid negative numbers. This in no way altered the P-values obtained.

Patient BAO vs. "Normal" BAO:

The first test examined is whether there is a significant difference between the BAOabs values of the depressed patient population studied and the comparable "normal" expected values. Using the t-test of differences between two independent means, there proved to be no statistically significant difference ($t = .593$, $P > .25$). However, the mean patient value (1.752 mEq/hour) was 14.9% lower than the mean "control" value (2.06 mEq/hour). Furthermore, 10/16 (62.5%) of the patient population had BAO values below the expected range, 3 of the remaining 6 were in the normal range, and 3 were above the normal range. Thus, as a group, the depressed population had lower than "normal," but not significantly lower, BAOabs values.

A) Beck Depression Inventory. Product - moment correlation of Beck scores with BAO values did not reveal significant relationships. No significant agreement was found between either BAOabs values and Beck scores ($r = .262$, P = N.S.) or BAOn-BAO values and Beck scores ($r = .320$, $P > .1$). In fact, it may be seen that correlations are positive, and thus opposite to the original hypothesis, high Beck score being associated with high BAO, and the inverse.

When split-ranking was done with the t-test of differences between mean BAOabs values for those patients with high (n=7) vs. low (n=8) Beck scores, a difference of greater than 10% significance was found, again in the direction

opposite to that postulated ($t = 1.632$, $P > .1$). Likewise, in the t-test of differences between mean BAOn-BAO values in high ($n=7$) vs. low ($n=8$) Beck scores, high gastric acidity was associated with high Beck scores, and vice versa, at a greater than 5% level of significance ($t = 2.093$, $.1 > P > .05$). Therefore, using the least depressed half of the patient population--as determined by the Beck scores--as a "control" group compared against the most depressed half, there was no significant difference in either mean BAOabs or mean BAOn-BAO values.

A t-test was also used to determine whether there was a significant difference in Beck scores between that half of the patient population with the highest BAOabs values ($n=8$) and that half with the lowest ($n=8$). Once again, non-significance was found ($t = .47$, $P = N.S.$). In no case, therefore, was there a significant inverse correlation between BAO and degree of depression, as measured by the Beck Depression Inventory.

B) Wechsler Depression Rating Scale. The same statistical tests were carried out as in (A). No significant correlations, positive or negative, were found between BAOabs or BAOn-BAO values and the Wechsler scores. However, unlike that found with the Beck scale, the direction of correlation was uniformly that which had been originally postulated, i.e., high Wechsler scores associated with low BAO values, and the inverse.

Product-moment correlation between BAOabs values and Wechsler scores yielded r = .027, P = N.S.; between BAOn-BAO values and Wechsler scores, r = .135, P = N.S.

Split-ranking the Wechsler scores by a t-test to measure the difference in mean BAOabs values yielded t = -.903, P > .15; in mean BAOn-BAO values, t = -.745, P > .2. A t-test split-ranking BAOabs values into high/normal (n=7) vs. low (n=9), measuring the difference in mean Wechsler scores, yielded t = -.368, P > .35.

C) Clinical Ratings of the Experimenter (E). Product-moment correlations between BAOabs values and E ratings revealed r = -.325, P > .1; between BAOn-BAO values and E ratings, r = -.335, P > .1. Though not statistically significant, these correlations were strongly in the postulated inverse direction: a high E rating of depression was associated with a low BAO.

When the depressed population was split-ranked by a t-test in terms of low (0-1, n=7) vs. high (1.5-3, n=9) E ratings, statistically significant differences were found in mean BAOabs values (t = -2.056, .05 > P > .025) and mean BAOn-BAO values (t = -1.783, .05 > P > .025). Conversely, when the BAOabs values were split-ranked into high (n=8) vs. low (n=8), a difference in mean E ratings of depression approaching significance was found (t = -1.524, .1 > P > .05). Thus, there appears to be a significant inverse relationship between E's ratings of degree of depression and basal acid output.

D) Independent Ratings of Two Psychiatrists (M/S). Product-moment correlation between BAOabs values and M/S ratings demonstrated an inverse relationship as postulated, which, however, was not statistically significant ($r = -.1918$, $P = N.S.$). By the same operation BAOn-BAO values were shown to have an inverse relationship of near-significance with the M/S ratings ($r = -.462$, $.1 > P > .05$, in contrast to $P > .1$ in E vs. BAOn-BAO).

When the M/S ratings were split-ranked with a t-test between low (0-1.5, n=7) and high (2-3, n=9), the difference in BAOabs values was strongly in the direction postulated, but not significant ($t = -1.256$, $.15 > P > .1$). Similar split-ranking of M/S ratings with respect to BAOn-BAO showed a slightly greater significance ($t = -1.291$, $P > .1$). Conversely, when the BAOabs values were split-ranked between low (n=8) and high/normal (n=8), M/S ratings of depression were found to be significantly higher in low BAOabs values than in high/normal, as originally postulated. ($t = -1.82$, $.05 > P > .025$).

Split-ranking with the t-test, therefore, showed a significantly greater degree of depressive illness, as rated independently by M/S, in that half of the experimental population with the lowest BAOabs values than in that half with high/normal BAOabs values. This finding is in agreement with the original hypothesis. However, split-ranking in terms of low vs. high M/S ratings showed BAO differences of only near-significance. These findings are the converse of

those in (C), where split-ranking in terms of low vs. high/normal BAOabs values showed a difference in E ratings of only near-significance, whereas the same operation with respect to low vs. high E ratings showed significance. The reasons for this discrepancy are not clear; however, it should be noted that in none of the t-tests in (C) or (D) did P exceed .15, and that in all cases the direction of the difference was as postulated: the lowest BAO was found in that half of the experimental population with the greatest degree of depression, as rated by E and M/S, and the inverse. On the other hand, the greatest degree of depression occurred in that half of the population with the lowest BAO, and the inverse.

To summarize the findings of (A) through (D) [see Table III, next page], no significant correlations were found between BAOabs or BAOn-BAO values and the scores of either the Beck Depression Inventory or the Wechsler Depression Rating Scale. However, the Wechsler scores showed a consistently higher inverse correlation with BAO than did the Beck scores, which often demonstrated weakly positive correlations, opposite to that postulated.

On the other hand, significant inverse correlations were demonstrated between the clinical ratings of the independent evaluators (E and M/S) and BAOabs or BAOn-BAO values when the technique of split-ranking was employed. Product-moment correlation consistently yielded trends which were strongly in the direction of the postulated inverse

relationship, but only one correlation approached significance, that between M/S and BAOn-BAO (.1> P >.05).

Table III. Correlation of Psychological Measures of Depression and Basal Acid Output

	BAOabs	BAOn-BAO
Beck	PMC:* r = .262, P = N.S. t-test: H v. L Beck, t = 1.632, P = N.S.	PMC: r = .320, P = N.S. t-test: H v. L Beck, t = 2.093, .1 > P > .05 opp. to postulated dir.
Wechsler	PMC: r = .027, P = N.S. t-test: H v L Wechsler, t = -.903, P > .15**	PMC: r = .135, P = N.S. t-test: H v L Weshsler, t = -.745, P > .2**
E	PMC: r = -.325, P > .1 t-tests: E(0-1 v. 1.5-3), t = -2.056, .05 > P > .025** BAO H/N v. L, t = -1.524, .1 > P > .05**	PMC: r = -.335, P > .1 t-test: E(0-1 v. 1.5-3), t = -1.783, .05 > P > .025**
M/S	PMC: r = -.1918, P > .1 t-tests: M/S (0-1.5 v. 2-3), t = -1.256, .15 > P > .1** BAO H/N v. L, t = -1.82, .05 > P > .025**	PMC: r = -.462, .1 > P > .05 t-test: M/S (0-1.5 v. 2-3), t = -1.291, P > .1**

* Product-moment correlation.

** Result of dividing calculated P by 1/2 because of advance postulation of direction of difference.

Regarding the two expressions of BAO (BAOabs and BAOn-BAO), the number and type of significant correlations for each was approximately the same (see Table III). However, BAOn-BAO values almost uniformly showed a slightly greater degree of significance in the hypothesized direction in every category (A-D). Assuming that BAOn-BAO values provide a more accurate means of comparing the patient BAO's with one another, this slightly greater degree of significance may lend support to the original experimental hypthesis of an inverse correlation between degree of depression and gastric acidity.

MAO and TAO.

These measures of gastric acid output were not emphasized as measures of actual secretory function because of the fact that they are both expressions of the maximal capacity of the parietal cells to produce acid after a histamine challenge. The importance of this point lies in the fact that the MAO and TAO values provided a means of establishing whether or not the diminished BAO found in depression was secondary to an endogenous inability of the parietal cells to produce acid, such as might be found in pernicious anemia. If a significant number of patients were found to be achlorhydric or hypochlorhydric even after a histamine challenge, the validity of the hypothesized association between gastric acid diminution and depression might seriously be questioned. Comparison of the patient

MAO's and TAO's with the "normal" values reveals that there was no significant decrease in either of these measures in the experimental population as a group. In fact, both patient mean MAO values and mean TAO values were slightly, though not significantly, above the "normal" means:

Mean control MAO = 11.565	Mean control TAO = 8.40
Mean patient MAO = 15.0	Mean patient TAO = 10.04

Of the 16 patient MAO values, 6 were above the normal range, 8 were in the normal range, and 2 were below normal. Of the 16 patient TAO values, 7 were above the normal range, 6 were in the normal range, and 3 were below normal. Only 2 patients had both low MAO and TAO values; these patients also had low BAO values. The other 8/10 patients in the low BAO range had normal or high MAO and/or TAO values. No patients had achlorhydria. It may be concluded from these findings that the great majority of the diminished BAO values found in the experimental population were not likely to be secondary to an organic condition (such as pernicious anemia) associated with a diminished capacity for parietal cell production of HCl.

Compensation vs. Decompensation.

It was noticed that patient agitation, decompensation and general ineffectiveness of defense mechanisms on the test day were often accompanied by a pressure of speech, recorded as the number of patient-initiated conversations or remarks made during the course of the 2-hour procedure (see Appendix A). In all, 5 patients were found by the com-

bined evaluations of E and M/S to be acutely agitated or decompensated on the test day, as revealed by their statements, appearance, and behavior. One patient, for example (#16), held the experimenter's or nurse's hand during portions of the test, and made statements revealing increased depression and agitation over the previous day's interview ("I'm so insecure...very low today...seems I'll never sleep normally again. I'm sorry...I'm going to fail..."). Another patient (#1) seemed very apprehensive, unkempt and tearful on the test day, markedly deteriorated from the previous day. His many episodes of crying were punctuated by such statements as, "I want to go home...this place is like a jail...why can't I see my kids...I can't stand being locked up in a jail and left alone...they want to break me down by locking me up..." 4 of the 5 decompensated patients (80%) made a very large number of initiations: whereas the mean number of initiations for the entire experimental population was 18.1, the mean number for the 5 decompensated patients was 30. The question was investigated as to whether decompensation per se, as a manifestation of the severity of the patient's depressive illness, was associated with a depressed gastric HCl secretion. It was found that 4 of the 5 decompensated patients had BAOabs values below the normal range; the remaining 1 was in the normal range. In order to more accurately investigate this question, a split-rank correlation (t-test) was done for the

entire patient population, comparing BAOabs values in large (17-50, n=8) vs. small (1-8, n=8) number of patient initiations. It was found that patients who made a large number of initiations had nearly significantly lower BAOabs values than patients who made a small number of initiations ($t = 1.642$, P sl.$> .05$). Association was thus shown between decompensation (inoperative or ineffective defense mechanisms), pressure of speech, and diminution of gastric HCl. In order to determine whether pressure of speech was itself a manifestation of the severity of depression, a product-moment correlation was carried out between the number of patient initiations and the E ratings of depression. There was a weakly positive correlation, although it did not approach significance ($r < .05$, P = N.S.). Thus, pressure of speech during the experimental procedure was not necessarily a manifestation of the severity of depression, but did appear to be a measure of the degree of decompensation, and was associated with low BAOabs values.

Somatic Complaints.

The frequent occurrence of somatic symptoms in depressed patients is well known (44). An attempt was made in the present experiment to investigate 1) whether the patients studied had a high degree of somatic complaints; 2) what relationship, if any, such complaints might have to degree of depression and gastric acid output. From the medical histories taken during the pre-test interview, it was discovered that as a group, the patients reported an extraordin-

arily large number of somatic complaints and symptoms, referred largely to the gastrointestinal tract. 13 of the 16 patients studied had a history of one or several significant gastrointestinal complaints; most of these patients had additional somatic complaints. In the histories of 10 of these 13 patients there was no apparent organic basis for their symptoms. For example, patients (1, 3, 4, 6, 8, 9, and 15) had a strong history of recent non-specific gastrointestinal symptoms such as nausea and vomiting, weight-loss, anorexia, dysphagia, diarrhea, and constipation, without known associated organic disease. There was no statistical association between the degree of somatic symptomatology and degree of depression or BAO. It may be concluded, however, that the unusually high degree of such symptomatology in these patients, without very much apparent organic pathology, is consistent with the oft-noted occurrence of somatic symptoms in depressed patients.

DISCUSSION

Not since the studies of Farr et al. (29, 30) has gastric acidity been investigated in a population of clinically depressed patients. The results of the present study disagree with that group of investigators, who found in their second paper (30) that depressed patients did not differ significantly from the general patient population in terms of gastric acid secretion.

However, the present experiment seems to be in agreement with the more recent work. It shows in a group of patients what Engel et al. found to be true for Monica (27,28) and Wolff and Wolf for Tom (87,88); that depressive affect is frequently associated with diminished gastric HCl.

The results of this study imply that what is true for Engel's "depression-withdrawal" reaction in Monica may also be true for a clinically depressed population; that diminished gastric acid output may be an "energy-conserving" part of the "basic biological pattern of depression"; and that diminished gastric HCl may be a part of the biological expression of Schmale and Engle's "helplessness-hopelessness." (75)

Diminished gastric acidity in depressive illness may, in addition, be a biological concomitant of Freud's concept of the ego's wish to incorporate the lost object into itself, in accordance with the oral phase of development, which, according to Freud, corresponds to "the refusal of nourishment met with in severe forms of melancholia." (34)

Further, the present paper tends to corroborate the findings in the "healthy volunteer" population of Kehoe and Ironside (50,51): decreased gastric acidity is associated with depressive affect. The present study's findings on compensation vs. decompensation also suggest a clinical analogy to the studies of Kehoe and Ironside. Those workers found that mastery of the experimental conflict--analagous to clinically operative defense mechanisms--was associated

with high HCl secretion, while inability to master the experimental conflict--analagous to clinical breakdown of defense mechanisms--was accompanied by decreased HCl. The relationship between decompensation, decreased BAO, and increased pressure of speech in the present study may reflect a clinical parallel to these findings of Kehoe and Ironside.

Possible Mechanisms in Depression and Disease.

Schmale (74) demonstrated a relationship between depression and the onset of a variety of organic diseases. Peptic ulcer, discussed earlier, may be another manifestation of the increased vulnerability to disease provoked by depression. If a statistical association were eventually shown to exist between depression and peptic ulcer, it would be important to consider possible mechanisms and their relationship to the findings of the present study; this relationship will be discussed presently. Gray (43) helps to provide a possible mechanism for ulcerogenesis in depression in his summary of recent work on neurogenic and hormonal mechanisms for stress pathways from the brain to the stomach. Adrenal steroids, via the hypothalamic-pituitary-adrenal axis, have been shown to increase gastric HCl and pepsin, increase tissue, plasma, and urine pepsinogen, decrease the mucus protective barrier of the stomach, and interfere with connective tissue repair. Adrenal steroids, in other words, provide a possible physiological factor in peptic ulcer formation. Patients with Addison's

disease, according to Gray, have been shown to be gastric hyposecretors, while those with Cushing's disease show an increase in uropepsin. These findings imply 1) the existence of extravagal influences on gastric secretion, as outlined in the review of gastric physiology, above; 2) that excess adrenal steroids play a role in the production of peptic ulcer, as has actually been shown to occur. (90)

When the above findings are examined alongside those of McClure (60), Bunney et al. (13), and others (23), most of whom discovered an increased adrenal steroid level in depression, a possible mechanism for the production of peptic ulcer in depressive illness comes to light. The excess adrenal steroid level, found in depressed patients, could act on the stomach in the manner outlined by Gray and create a physiological setting for the genesis of an ulcerative lesion. However, if this mechanism were the primary one, it would seem to contradict the results of the present experiment, where a general diminution in gastric HCl is found. How can the simultaneous existence of increased adrenal steroid levels and decreased HCl output be explained? First, it may be questioned whether the elevated steroid levels of depression are sustained and high enough to produce the gastric secretory changes suggested by Gray.[1] Second, it is possible that other mechanisms,

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[1] Cf. Fawcett and Bunney. (31)

antagonistic to the formation of excess gastric acidity, are present in the depressive state, but still allowing for the development of peptic ulcer. It is well known that excess gastric acidity is not a prerequisite for the development of peptic ulcer.[1] It will be remembered that norepinephrine and other catecholamine excretion is elevated in depression, according to several authorities. (23) The inhibitory effects of catecholamines on gastric secretion may suppress HCl levels to normal or below normal. There may also be diminished vagal stimulation in depression. Another theory for the formation of peptic ulcer in depression, which does not require increased acid production, must therefore be invoked in order to remain consistent with the finding of diminished HCl secretion. If, as Schmale postulates, depression increases vulnerability to disease, albeit by an unknown mechanism, then a normal or even low level of gastric secretion may still be sufficient to cause mucosal ulceration. It is possible that increased adrenal steroids might further provoke ulcerogenesis by decreasing the gastric mucus protective barrier and interfering with connective tissue repair, rather than increasing gastric acidity. Increased catecholamines could inhibit HCl increase without inhibiting other steroid effects.

From the above, two possible mechanisms by which gastric HCl secretion is diminished in depression come to light:

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[1](90), p. 976.

1) increased NOR and other catecholamines, which have an inhibitory effect on HCl secretion (see earlier review of gastric physiology); 2) diminished vagotonia, by an unknown central mechanism.

The relationship of depression to pernicious anemia (PA) has already been considered. Schmale's concept (74) of disease as a sequela of depression seems well illustrated by Lewin's study (56), where depression was regularly found to precede the onset of PA. It will be remembered that Lewin postulated the existence of a genetically determined borderline level of intrinsic factor (IF) in some individuals which, if those individuals become clinically depressed, may be diminished below a critical level and thus provoke the onset of PA. It is known that PA is associated, in adults, with achlorhydria. (62) Further, it is known that IF secretion parallels the secretion of other gastric juices, such as pepsin and HCl. (62) To demonstrate that depression might provoke the onset of PA, it must therefore be shown that depression is associated with a decrease in gastric secretion. Lewin suggests this is the case, citing Engel's study of Monica (27, 28) as a prototype for the behavior of the adult stomach during depression, though the authors of the Monica study had warned against over-generalization. A more appropriate model might be the adult stomach itself. The present paper represents an initial attempt at providing such a model. If borne out by further work, the results of the present experiment would lend

support to Lewin's hypothesis regarding the onset of certain cases of PA.

Criteria of Depression.

Two categories of criteria were used: the standardized Beck and Wechsler Scales, and the clinical ratings of E and M/S. It is seen in the Results that the Beck and Wechsler scores, especially the former, correlated less well with each other and with the BAO values than did the clinical ratings. One possible reason is that the Beck was entirely self-rated by the patient. Asking the patient to rate his own degree of depression on the basis of his own subjective opinions raises many questions about the possible influence of the patient's fantasies, guilts and defenses, such as denial or turning against the self, upon the semi-objective choices demanded. Obviously, a patient might not be aware of recent appetite- or weight-loss, or change in his behavior towards others. This might account for the wide discrepancies between the Beck scores and all other measures of depression. The Wechsler scale had three parts, two of which required the observer to estimate the patient's opinions of himself, thus creating a situation similar to that found in the Beck scale. But, possibly because the remaining third comprised the experimenter's (E's) opinions, a greater correlation was found with the clinical ratings of E and M/S, and with BAO values, than was found in the Beck scale.

In general, the E ratings showed a slightly greater number of significant correlations than did the M/S ratings. This is possibly a reflection of the fact that the experimenter took into account the patient's behavior and affect on the day of the test, while M/S did not. The importance of the degree of depression on the test day, as differentiated from depression previous to the test day, is thus emphasized.

Suggestions for Further Research

Future work in this area could incorporate several changes and improvements in method, as well as broaden the scope of study.

One of the shortcomings of the present experiment is the lack of a true control population. Such a population should comprise a large number of non-depressed inpatients in the same hospital setting (schizophrenics, for example), put through the identical experimental procedure. A larger sample of experimental patients, moreover, could improve statistical accuracy. Finally, longitudinal studies over a long period of time are needed, so that gastric acidity may be followed throughout the course of the illness, as treatment progresses, as the patient improves or does not improve. An attempt should be made to discover whether clinical improvement in depressive illness is associated with a rise in gastric acid output. Patients could even be followed, with gastric function tests, long after discharge from the hospital.

Gastric intubation as a method of accurately determining gastric acidity is at present impossible to circumvent. Nevertheless, the stress of the anticipation of the procedure and the procedure itself may have altered gastric secretion. Possible mechanical effects of the tube itself as a mucosal irritant must also be considered. This problem could eventually be avoided if an orally administered drug like Diagnex Blue, which is split by gastric HCl and subsequently found in the urine, were made available. Unlike Diagnex Blue, such an agent would have to be far more than just a screening test for determining the presence or absence of HCl, but would have to assess gastric acidity quantitatively.

The scope of future investigations could be broadened to include a Schilling test, with and without intrinsic factor administration, to determine the relationship of intrinsic factor secretion to depression, in order to substantiate Lewin's findings (56) and further elucidate the relationship of depression to PA. Serum cortisol or urinary 17-OHCS (cf. Bunney et al. [137]) could also be determined to ascertain the relationship of adrenal steroid secretion to gastric secretion and depression. Such determinations might further elucidate the possible role of steroids in the production of organic disease in depression, such as peptic ulcer.

Finally, there might be a reconsideration of the methods used for determining degree of depression. Less attention

might be paid to overt behavior, and more to psychodynamics in at least one of the measures. In a psychophysiological study of gastric secretion in a case of peptic ulcer, Shay and Sun (77,78) reported no correlation between overt behavior and the type of gastric secretory response. Unconscious mental conflicts seemed to be more important in gastric secretory stimulation.

SUMMARY

16 inpatients in a psychiatric hospital were studied, all diagnosed by the following criteria as having some degree of depressive illness: Beck Depression Inventory, Wechsler Depression Rating Scale, and three independent clinical ratings based on the psychiatric, medical, and family histories taken during the course of an interview (E and M/S). The interview, history-taking, and depression ratings were carried out on the afternoon before the administration of a gastric function test. The following morning, an augmented histamine test was performed. During this test a detailed record was kept of the patient's behavior and affect. The gastric contents were analyzed for BAO, TAO and MAO.

A data analysis was undertaken in such a way as to keep each variable discrete and independent from others. By means of product-moment correlation and split-ranking with the t-test of differences between two independent means, several significant inverse correlations were discovered between the clinical depression ratings (E, M/S) and BAO.

The results of this study appear to demonstrate in a depressed population what Engel et al. and Wolff and Wolf found in individuals, and what Kehoe and Ironside discovered in a volunteer group: that depressive affect is associated with diminished gastric acidity.

It is thought that diminished gastric HCl may be a part of the "basic biological pattern of depression," as postulated by Engel et al., and a biological expression of Schmale and Engel's "helplessness-hopelessness."

Further work is necessary to confirm the findings of this study.

APPENDIX

Appendix A. Table of Data.

Pt.	Age	Sex	BAO	MAO	TAO	BAOn	Beck	Wechsler	E	M/S	# of inits.
1	31	M	0.176	1.710	0.855	3.274	22	68	3	3	50+
2	52	F	0.917	20.164	15.808	1.711	22	60	1.5	2	45
3	60	F	0.185	12.758	9.135	1.412	31	85	2.5	2	36
4	48	F	0.015	12.636	8.939	1.711	18	66	2.5	2	5
5	32	F	0.160	2.210	1.060	1.702	40	65	1	2	45
6	39	F	0.129	18.388	11.362	3.274	22	65	2	2	2
7	16	F	4.300	13.848	9.984	1.167	35	70	2	2	8
8	51	M	5.114	19.344	17.216	3.290	--	60	1	2	2
9	43	F	0	20.576	16.310	1.784	4	52	0	2	17
10	48	M	2.922	26.086	20.891	3.290	7	57	1	1.5	1
11	54	M	0.496	14.072	8.836	3.051	18	51	1.5	1.5	18
12	45	F	0.110	9.486	0.566	1.784	26	62	2	1.5	2
13	20	F	5.269	23.296	21.382	1.396	24	63	1	1.5	5
14	21	F	2.248	19.308	16.262	1.346	37	50	0	1.5	2
15	31	F	3.786	7.910	6.145	1.702	29	77	1	1	19
16	70	F	2.216	18.28	13.606	1.167	22	63	2	1.5	35

Appendix B. Sample Experimental Protocol.

Protocol #

Name
Address
Age Sex Birthday
Hospital # Date of history Date of test
Date of retest

A. Psychiatric history

(Appendix B, contd.)

B. Medical history

(Appendix B, contd.)

C. Family history

D. Drug history and sensitivities

(Appendix B, contd.)

E. Depression rating

1. Wechsler score _____

2. Beck score _____

(Appendix B, contd.)

Initial Test

Date:
Time:
Observer:
Experimenter:

A. Patient's response to our appearance

B. Events the night preceding

C. Drugs the night before

(Appendix B, contd.)

D. Intubation rating: note exact time

1. mechanical difficulty

none mild moderate great

2. responses of S and E

E. Time of benodryl injection:
Time of histolog injection:
Time samples collected

a. Basal:

(Appendix B, contd.)

F. Five minute interview

G. Can we identify this S's predominant defenses

(Appendix B, contd. There are 8 of these pages in the actual protocol, one for each 15-minute sample.)

Interaction scoring

# of quarter

a. Anxiety Ax (circle one)

none mild moderate severe

b. Compliance Co

none mild moderate severe

c. Ambivalence toward the procedure Am

none mild moderate severe

d. Anger An

none mild moderate severe

e. Depression D

none mild moderate severe

f. Contentment - placidity Cp

none mild moderate very

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