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The Role of the gastrointestinal tract and gall bladder in heart disease

Merlin L. Trumbull
University of Nebraska Medical Center

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THE GASTROINTESTINAL TRACT AND GALL BLADDER

IN HEART DISEASE

By

MERLIN L. TRUMBULL

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INTRODUCTION

A study of the gastrointestinal tract and the gall bladder in their relation to heart disease is well worth our attention. The subject raises intricate problems concerning the nature of pain, the innervation of thoracic and abdominal viscera and leads to a better understanding of the intimate relationships existing between the two systems. Moreover, the gastrointestinal symptoms of heart disease are not only as frequent as those which may be termed "thoracic", but are protean in character and of great practical significance. Too frequently mention is made in text books and the literature of some of the abdominal signs and symptoms of heart disease, such as having stated that when a patient complains of his stomach, his heart is at fault, but no explanation is offered. Furthermore, in some of the more recent literature, experimental and clinical evidence is being brought forward, such to the extent that the seat of pathology in some of the cardiac disturbances may actually be found in the gastrointestinal tract and gall bladder. Some contributors, for example, go so far as to say that the entire cause of angina pectoris lies within the gastrointestinal tract.

In view of all this, it is of no small significance to probe more deeply beneath the surface and to inquire into the relationships existing between the circulatory and the gastrointestinal tract and gall bladder. Emphasis throughout this paper is being placed on the more questionable aspects that the gall bladder and gastrointestinal tract play in heart disease.

Hence I have chosen "The Role of the Gastrointestinal Tract and the Gall Bladder in Heart Disease" as the title of this paper. And this chiefly for two reasons: first, because the subject is essentially a practical one, coming, as it does, within the cognizance of all in the course of daily medical and surgical practice, and secondly, for the reason I have already alleged that on this topic surprizingly little is to be found in the text books and literature.

A prophet of old exclaimed, "My bowels, my bowels! I am pained at my very heart". Today many a patient might cry aloud, "My heart, my heart! I am pained at my very bowels". (Cited from Ritchie, 78) Thus, we shall attempt to see why.

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THE ROLE OF THE GASTROINTESTINAL TRACT

The clinical significance of gastrointestinal disturbances in angina pectoris and other cardiac disorders has long been conceded by various writers. The opinions held through the middle ages are summarized by the great physician Fernel who wrote in 1554:

> "Many symptoms vex the ostium at the beginning of the stomach. Some of these result from the fact that this structure is endowed with an extraordinary degree of sensation and is connected with affinity to the principal parts of the heart and to the brain. To these other organs indeed, it is generally agreed, it may communicate its troubles and provoke them in various ways: the heart to cause swooning, syncope, and pain which has been labeled cardialgia; the brain to cause lethargy, catalepsy, brooding, and insociability, melancholy, and delirium, the reasons and causes of all of which are adequately explained thereby."

Fernel also said that palpitation and abnormalities of the pulse may be caused by indigestion, in particular excess of food or drink. (White,75)

About two hundred years later, Senac, according to White (75), wrote that the stomach is one of the commonest causes of palpitation. This he explained by a full stomach pressing against the diaphragm and interferring with respiration as well as compressing the aorta. In addition distention of the stomach might stimulate the nerves which directly induced palpitation according to him.

Clinical Observations

The chief physical signs and symptoms met with as the result of linkage between the circulatory and gastrointestinal tracts may be classified into four groups, which are: (1) dyspepsias of various types, (2) cardiac pain, (3) changes in heart rate and rhythm, and (4) a group of cases in which sudden death occurred as the result of some gastrointestinal disturbance. It is through the agency of the vagus nerve, the afferent depressor nerve, and any other nerve within the cardiac and gastrointestinal areas which conducts afferent impulses to the central nervous system in association with the sympathetic system that the heart and digestive tube become interrelated, and in many respects interdependent. This will be discussed more fully later.

The Dyspepsias

Probably the most frequent complaint common to both circulatory and gastrointestinal systems is that of flatulence with its attendant gaseous eructations. Of the cardiac diseases, it is particularly prominent in angina pectoris and in cases of slow cardiac decompensation. It is also found in chronic rheumatic pan-

carditis, adhesive pericarditis, chronically dilating hearts as from long-standing slowly progressive valvular disease (Brooks, 12), in functional cardiac disorders (56), as well as in acute coronary thrombosis.

Verdon (69) points out that flatulent persons do not necessarily have dilated stomachs, as was formerly thought to be, and on the contrary, he found their stomachs small and contractile. He cites that in four out of five cases of angina pectoris submitted to him for x-ray examination, the stomachs were hyper-irritable and that the barium meal was retained for hardly any length of time. He found the same conditions true in general for cases of hysteria and habitual smokers. Frequently Verdon would terminate anginous attacks by passing a gastric tube only to observe the escape of large amounts of gas. These observations and others to be mentioned later, led this writer to believe that a hyperirritable stomach produced most attacks of angina pectoris.

In 1912, Rhoemheld first described what he called the "gastro-cardiac symptom complex". This is a type of case presenting signs and symptoms of heart disease arising from functional or "pre-organic" disease of the gastrointestinal tract (Niehaus, 47). Such pat-

ients, according to Niehaus, gave symptoms of palpitations, varying degrees of dyspnea, belching, nausea, vomiting, hiccough, and faintness and giddiness. There is a sensation of pressure, crowding and sticking in the region of the heart or more particularly along the left costal margin. Furthermore, he states in some cases it amounts to precordial pain, which may radiate to the arms. Niehaus points out that Rhoemheld and other Germans in the same field attribute this symptom complex to an elevation and impaired mobility of the diaphragm by a distended stomach or colonic flexure. These distended organs rise into the dome of the diaphragm displacing the heart and the latter's relations to the great vessels. In man, both Niehaus and Dally (18) say that this change in the heart's position can be demonstrated clinically by percussion. Finally, Niehaus states:

> "This pressure, exerted over long periods, stretches the diaphragm, and finally results in atrophy. This permits these disturbed relations to exist permanently, together with a decreased diaphragmatic mobility."

Aerophagia or air-swallowing is frequently mentioned as developing in those patients subject to frequent gaseous eructations. Such patients by obtaining relief of distress through belching unconsciously learn to swallow air in a further attempt to eructate more

frequently thereby reducing the chances for the accumulation of distressing flatulence. Verdon (69) brings to our attention that normally people swallow much saliva containing air, which accumulates in the gastrointestinal tract. In tubing anginous patients, he noticed that occasionally the gastric tube would become plugged with a frothy mucous. This led him to consider whether gas in the stomach is free or imprisoned in saliva and mucus. The voluminous eructations of gas following the oral administration of sodium bicarbonate in water was satisfying evidence to him in favor of the latter view, especially in those anginous patients who felt the desire to belch but otherwise could not. Wolffe and Digilio (79) find similar results in cases of coronary thrombosis in which flatulence is a disturbing factor. On other occasions Verdon observed the "spongy and yeasty" character of matter vomited by anginous patients. This further substantiated this belief of his. Dally (18) adds a significant differential diagnostic point by stating that aerophagia is an important factor in pseudocardiac dyspepsia in that forced belching occurs and can be recognized by its loud and noisy character.

That nausea and vomiting, anorexia, and constipation frequently occur in cardiac disorders is commonly accepted. Mention should be made, however, of

the observation of the Jacksons' (31) in cases of coronary thrombosis. According to them, there are reported in the literature over forty cases of rupture of the esophagus following a clinical course resembling closely that of coronary thrombosis. They contend that acute, spasmodic, incoordinated contractions of the esophagus and stomach associated with vomiting are responsible for such autopsy findings. They also believe that angina pectoris represents the clinical picture of partial repture or temporary straining in the esophagus or stomach as the result of the same mechanism. The fact that the vomitus frequently contains blood is in their opinion further evidence of such an event. Anginal attacks have also been known to occur in the presence of constipation and to vanish with regular action of the bowels (18).

In cases of chronic coronary disease, Wolffe and Digilio (79) find that the gastrointestinal manifestations, can with few exceptions, be recognized as expressions of autonomic imbalance. It seems to be expressed either predominantly along the sympathetic or the parasympathetic component of the autonomic system. The former resembles very much the syndrome of chronic biliary disease associated with epigastric fullness,

flatulence, belching, constipation, pyrosis, and epigastric pain. Patients in whom the parasympathetic component predominates present a group of symptoms which contrast with those just mentioned. It closely mimics spastic colitis and peptic ulcer. These patients may complain of abdominal cramps, occasional loose stools alternating with constipation, red beefy tongues, occasional tenesmus, associated with the attacks of precordial pain. Frequently associated with the painful attacks is salivation.

Changes in Heart Rate and Rhythm

The manifestations of the gastrointestinal tract observed clinically in this respect may be, (1) retardation of the rate of the heart, (2) acceleration of the heart rate, (3) sinus arrhythmia, (4) palpitation and ectopic beats, and (5) heart block.

Although in the rate of the heart beat, there are wide variations both physiologically and individually, but continued vagus irritation with subsequent slowing of the pulse frequently is the result of some form of dyspepsia (18). Also, in stout people and those indulging heavily in food, wine, and tobacco, Dally (18) often finds a relatively slow pulse, a condition not improbably due to a coexisting coronary sclerosis. He not-

ices that this condition may be intermittent and paroxysmal in reference to gastric digestion or to excessive gastric irritation and be accompanied by weak cardiac action, with small feeble pulse, cold extremities, and in severe cases syncopal attacks, or it may become chronic. Niehaus (47) notices that a bradycardia is often associated with a gastric hyperacidity.

Normally the pulse is increased frequently after a meal. In those cases in which the diaphragm and the heart are displaced by a distended stomach or colonic flexure, there is usually a rapid heart action; also anacidity is associated with a simple or even paroxysmal tachycardia (47). One of the more dramatic evidences of the close relationship between the stomach and heart is the rapid increase in pulse with the development of an acute gastric dilatation postoperatively (9). This rapid increase, according to Best (9), is out of proportion to the accidental or operative trauma. He remarks about the rapid drop in pulse upon the introduction of a constant suction apparatus. Niehaus adds that in this condition the mechanical effect of the distended stomach on the heart is one of the major problems in managing such a case.

During the past year, the writer has observed two

cases in which a relationship between the gastrointestinal tract and an acceleration of the heart rate was very suggestive. One of them, was a male, age 56, who for the past ten years or more has had frequent bouts of "indigestion" and epigastric pain suggesting a peptic ulcer. Six years ago he had a sudden attack of marked and rapid palpitation, which after lasting about an hour suddenly ceased. Since that time he has had frequent similar attacks, which are precipitated by exertion and over-eating. Also with a return of his peptic ulcer symptoms the frequency of these attacks of palpitation increase. The electrocardiogram proved the presence of a paroxysmal ventricular tachycardia during the attacks, whereas otherwise it showed definite evidence of arteriosclerotic heart disease. At the present time this patient is under ulcer management, the outcome of which will be interesting to note.

The other patient, whose main complaint was and had been flatulence, developed an auricular flutter. The final diagnosis after careful study by his doctors was an acute gastritis with functional biliary disease.

Dally (18) incidently mentions that sinus arrhythmia is known to occur due to more or less rhythmic reflexes from the stomach and upper intestine together

with toxic causes due to products of intestinal stasis, caffeine, and tobacco. Palpitation and extrasystoles are of frequent occurrence in different forms of dyspepsia often coming on at night especially after a heavy meal and causing restlessness and broken sleep; they may also occur in healthy hearts by dilatation of the stomach as the results of fermentation (18,47).

Weiss and Ferris (73), and Iglauer and Schwartz (30) have reported instances of heart block in cases of cardiospasm. In the case reported by the former, the patient's condition was so severe that she attempted suicide, since merely swallowing food regularly induced fainting from heart block (Adams-Stokes syndrome). Likewise, heart block in the other case was induced by merely swallowing.

Mackenzie observed an individual with rheumatic heart disease in whom swallowing produced transitory auriculo-ventricular block (cited by 22). Again Fishberg (22) describes a woman, whom he saw, with auricular flutter. Ocular pressure on her resulted in disappearance of the pulse for fifteen seconds with complete unconsciousness of about two minute's duration.

Robinson and Draper (57,58) found that in auricular fibrillation pressure on the right carotid

sinus usually causes marked slowing or stoppage of the ventricles. By the same procedure, they were sometimes able to produce complete auriculo-ventricular dissociation in children.

Cardiac Pain

The gastrointestinal tract plays a dual role in heart disease in the production of pain, by being frequently the source of pain or that to which pain is referred. Under both conditions it is closely related to what is usually accepted as being heart disease. It is common knowledge that the taking of food and flatulence frequently cause epigastric as well as precordial distress often passing over into definite pain.

However, there are certain other aspects of cardiac pain, which are to be considered here. The presence of severe abdominal pain in the acute coronary thrombosis patients presents a striking clinical picture and its presence is well appreciated by most writers on the subject. But coronary disease offers other types of gastrointestinal pain, which Wright (81) has classified roughly into four groups.

The first group is the flatulent dyspeptic, which is the most frequent. He states that such individuals

least of all believe that the symptoms are cardiac in origin. The second group complain of epigastric fulness coming on when they exert themselves immediately after a meal. In the third group are those cases which simulate that of acute indigestion following an unusual or heavy meal. Usually they show some accompanying signs of cardiac failure. The last group contains those in whom the abdominal pain is so acute as to simulate an acute abdominal catastrophe.

The commonly accepted theory of coronary spasm as causing angina pectoris has been attacked by some writers largely as the result of certain clinical observations. That relief from epigastric fulness and some types of cardiac pain is afforded by the discharge of gas either by eructations or per rectum is a common clinical observation. Furthermore, several authors (26,46,66,69, and 71) have been noting that by directing therapy partly toward the gastrointestinal tract in such cases, and thereby diminishing the amount of abdominal distention, cardiac pain and nocturnal dyspnea has been mitigated.

Verdon's (69) practice of gastric intubation to relieve gastric distention in anginal patients has already been mentioned. Morrison and Swalm (46) had

noticed that several of their patients with angina pectoris and gastrointestinal disorders failed to respond to the usual management of this disease, i.e., by the administration of the xanthine derivatives as well as the nitrites and by curtailment of their activities, etc. But on intensive therapy directed toward the gastrointestinal tract, the frequency and severity of anginal paroxysms was reduced.

There is yet to be considered one other interesting clinical observation in this regard. Von Bergmann has described a whole series of patients with x-rays showing that "hiatus hernia" or dilatation of the esophagus at or just above the cardia is frequently found in patients having angina pectoris. He described seeing such a hernia which would balloon up suddenly just above the diaphragm when the patient breathed deeply. Furthermore, he states that many of these hernias are developed suddenly during fits of vomiting or straining. (Cited from 31)

Ritchie (56) adds that commonly associated with such hernias is a congenitally short esophagus; and that not only may they be a frequent cause of dysphagia, regurgitation and paroxysmal epigastric pain, which may simulate that of angina pectoris or coronary thrombosis,

but by vagal influence induce either bradycardia or tachycardia.

Closely related to this is the observation of Verdon (69) some years earlier. He found that when the stomach is distended with food or gas, the lower portion of the esophagus is drawn down and expanding funnel-wise is incorporated into the gastric wall. As a result of this mergence, the intraesophageal pressure would be increased with a subsequent development of referred pain in the intercostal and brachial nerves.

Edeiken (20) reported a case of angina pectoris in which there was evidence of coronary and aortic disease and spasm of the cardia and in which attacks of pain similar in final distribution, but occasionally somewhat different in initial location, was produced by swallowing. In reviewing the literature, he found that in Verbrycke's series of twenty-three cases of cardiospasm associated with aneurysm, aortitis, angina pectoris, pain was not associated with cardiospasm; however, he quotes Starling and Camps as having reported the occurrence of dyspnea, cough, palpitation and anginal pain in cardiospasm. In the latter series, the esophagus was markedly dilated, and dilatation of the cardia was followed by relief of cardiac and respira-

tory symptoms. Furthermore, Morrison and Swalm (46) noted that during pneumatic dilatation of the esophagus for cardiospasm, substernal pain with radiation simulating anginal pain would occasionally occur.

Sudden Death

When mentioning sudden death, cardiac failure independent of other conditions is practically always implied at least. And it is interesting to note the presence in the literature of a few scattered reports of such an accident wherein attention is drawn to the gastrointestinal tract. In thirteen cases of cardiospasm being treated, Lendrum (37) reported four died suddenly, and these could not be explained satisfactorily by postmortem examination; Crittenden and Ivy (17) wrote of two cases reported to them. One was a postoperative case of carcinoma of the stomach, which was to be treated by lavage. The passage of the stomach tube resulted in sudden death, which could not be explained. The other case had carcinoma of the cardia with an angina pectoris. During the passage of a stomach tube in an attempt to secure some gastric contents, the patient stated he felt very ill, and as the tube was being withdrawn, he died.

Experimental Observations

Some of the clinical evidence concerning the role of the gastrointestinal tract in heart disease has been pointed out, and now our attention will be focused on the experimental approach of the same subject.

Goltz (cited from 8) experiment of tapping the viscera in the frog in 1863 producing a slowing of the heart rate, is probably the beginning of experimental work on this subject. That modification in cardiac rhythm occurs after visceral irritation is accepted and it is generally believed that such variations are instigated by the vagus nerve.

In view of the close clinical association of flatulence and heart disease, it is natural that much work (from a relative standpoint, however) in artificially distending the various portions of the gastrointestinal viscera has been done. In Verdon's book, entitled Angina Pectoris, written in 1920 (69), he makes reference to the work of Dr. Hertz, who found that when intra-gastric pressure is raised to twelve mm. of mercury, sensations of pressure are felt as well as a desire to eructate gas. On increasing the pressure to higher levels, these sensations merged into pain. It

was also noticed that increased intra-gastric pressure initiated peristaltic contractions, and simultaneous to these the gastric sensations would be felt. This work was done on apparently healthy adults.

Wayne and Graybiel (71) repeated these experiments on patients whose exercise tolerance was known to be reduced by a heavy meal. Gastric inflation with air up to three liters in amount produced an unpleasant feeling of fulness in the epigastrium, passing off quickly when the flow of air was temporarily stopped. X-ray examination always showed an increase in the amount in the stomach, and in some cases even showed displacement of the stomach. Exertion at this stage showed that exercise tolerance, blood pressure, and pulse rates were identical with those recorded in control tests before the inflation of the stomach. They repeated these experiments on five normal young adults. In three, x-ray examination showed that the heart had been displaced. Discomfort, pain, and the desire to eructate gradually passed off after large amounts of air had been passed into the stomach and retained.

More recently, Morrison and Swalm (46) investigated the behavior of the esophagus and stomach during typical attacks of angina pectoris. Their subjects were two

typical cases of angina pectoris, one of hypertensive heart disease, and one case of arteriosclerotic heart disease. On distention of the esophagus and stomach at various levels, typical anginal seizures occurred in the two anginal patients requiring a pressure between 40 and 60 mm. of mercury. The other two patients experienced a feeling of severe epigastric distress and substernal fulness. At no time did they find disturbances in the esophageal or gastric behavior; and in all of the four cases with the exception of one anginal patient, electrocardiographic changes (particularly in the ST-segment) were noted.

While the gastric dilatation was being done in one of their anginal patients, total cardiac standstill occurred during the anginal paroxysm. Morrison and Swalm thought that this was a sinus block, although this was not noted at the time. The patient was in acute pain and fainted, but normal cardiac rhythm was re-established as indicated by the kymographic record, at the moment of release of intragastric pressure.

In one of Crittenden and Ivy's (17) students a prolonged ventricular standstill occurred while swallowing the gastric tube. The student reported that he felt very ill and dizzy at the time. Verdon quotes Gary and

Parsons as having demonstrated that traction on the stomach and esophagus caused vagal inhibition on the heart, and when the stimulus was strong to bring cardiac standstill permanently.

Weiss and Davis (72) investigated the effect on the heart of distention of various portions of the esophagus in a group of normal subjects. No cardiac abnormality or irregularity was found in any case.

The effect of esophageal or gastric distention in the lower animals is best illustrated and studied by the subsequent changes in heart rate and rhythm, for pain and distress are much less easily detected. These same effects are also noted by other forms of stimulation.

In 1921, Carlson and Luckhardt (16) stated as a result of their experiments that stimulation of the gastrointestinal tract and genitourinary tract in the frog caused reflex cardiac inhibition. They also found that this effect was lost in cruarized preparations. More recently, Scott and Ivy (61) found that the mechanical and chemical stimulation of most of the abdominal viscera in the frog might excite the cardiac inhibitory mechanism. Prolonged distention of the stomach causes acceleration of the heart in the dog; and in one out of

twelve dogs studied by Burgess, Scott, and Ivy (15), it caused the occurrence of rhythmically recurring ectopic beats. In experiments on 82 anesthetized dogs, Owen (50) found that distention and deflation of the hollow organs failed to produce extrasystoles or other cardiac irregularities other than changes in the rate. He also found in one dog that injection of 50 c.c. of 5 per cent hydrochloric acid into the duodenum was followed by a series of extrasystoles. Owen also found that distention of the esophagus produced extrasystoles in two out of five rabbits and of the stomach in one out of four. It may be significant that of the four dogs in which "spontaneous" extrasystoles were present, marked distention of the stomach increased the frequency of the extrasystoles in one,

The results of experiments designed to increase the irritability of the cardiac mechanism to visceral excitation indicate that such is the case. Crittenden and Ivy (17) demonstrated this on icteric animals. This is described later. In one dog in which previous coronary damage had been produced, Owen noticed an extrasystole on distention of both the colon and the urinary bladder.

The study of Crittenden and Ivy seem to indicate

that nausea, retching, and vomiting, induced by injections of apomorphine, may cause in normal unanesthetized dogs cardiac irregularities such as heart-blocks, cardiac arrests, ventricular and auricular extrasystoles. These occurred most often during retching. Regarding the heart rate, nausea usually caused a tachycardia and retching a bradycardia. They also found that 10 per cent of the students observed showed electrocardiographic changes such as extrasystoles, arrests, and A-V blocks while nauseated or retching during the swallowing of a stomach tube. In one student there was no change in rate, while in the others there was an increase which was dependent upon the ease with which the tube was swallowed.

Gastric distention in patients whose exercise tolerance was known to be reduced following a heavy meal raised the pulse rate only temporarily with a subsequent drop back to normal (71). In this same study, dilatation of the stomachs of five healthy young adults caused a drop in the pulse in three of them of from eight to twenty beats a minute. No change occurred in the other two cases until epigastric pain appeared, and then there was an increased rate.

Maher and his associates (43) made an electrocar-

diographic study of viscerocardiac reflexes during major operations, and found some interesting but inconstant changes. In one case a decrease in the Pr-interval was noted when dilatation of the rectum was done. A decrease in voltage occurred once when there was straining, in one case when the pylorus was crushed, and once each when a rectum and an appendix was being ligated. In a slightly jaundiced patient, the amplitude of the R-wave was decreased 2 mm. during the operation, but was increased 2 to 4 mm. postoperatively. Dilatation of the rectum caused a diphasic complex in another patient. Once the T-wave disappeared on manipulation of the duodenum, and again on placing an appendiceal ligature.

In this same study, traction on the appendix and its mesentery caused a drop of 75 beats perminute. Extrasystoles appeared once when clamping of a hemorrhoid was done. Sex and age seemed to have no effect on the findings; even their two patients with definite cardiac pathology showed no particular changes from the others. Crittenden and Ivy (17) found in all their experimental procedures referred to previously changes in the P-wave, QRS-complex, and the T-wave, but, also, none of the changes were characteristic.

The work of the Jacksons (31) of stimulating the esophagus and stomach of dogs with electrodes gave a variety of interesting results. Changes such as variations in the respiratory rate, slowing of the heart, and the sudden development of auricular fibrillation could be readily produced. In the anesthetized animal stimulation within the lumen of the esophagus at most points above the level of the apex of the heart produced vigorous muscular movements in some area of the chest, fore limbs, neck, abdomen, and other parts of the body. Weaker stimulation in non-anesthetized dogs gave "unmistakable symptoms of pain" in addition to movement of the same muscles. They found that the innervation of the esophagus appeared to be unilateral for when the stimulating points were turned to the right, the movements and evidence of pain were on that side, and vice versa for stimulation on the left half of the esophagus. If stimulation was toward the front or the back of the esophageal lumen, then the movements would be found on both sides. The similarity of their findings to angina pectoris is rather striking.

There yet remains one branch of experimental work which is particularly significant in our subject, and that consists of the effect of viscerocardiac reflexes

on the coronary flow. Although there exists some discussion as to whether the vagi or the sympathetics carry vasodilator impulses to the coronary arteries and vice versa, the main conclusions of the following experimental observations is not seriously altered, for both systems are innervated by the same nerves and the effect is what we are particularly interested in. Greene (27) finds that stimulation of the celiac ganglion produces reflex dilatation of the coronary vessels, the maximal dilatation amounted to an increase of 180 per cent over the initial normal. If the stimulation was mild it was less apt to be followed by a secondary vasoconstriction than if there were increased stimulation.

He stimulated a number of abdominal branches of the vagus nerve terminating in different regions of the gastric wall and hepatic structure, and concluded that the coronary reflex control through afferent vagal pathways has been slight, considered in terms of volume change. Nevertheless, the reaction to afferent vagal stimulation is more often a positive coronary dilatation.

Hinrichsen and Ivy (29) observed essentially the same thing in their experiments, with the exception

that the amount of increased flow was less marked, and that they did not obtain any diphasic reaction characterized by coronary dilatation followed by constriction. Both contributors found results far in the minority, however, which yielded coronary vasoconstriction on visceral stimulation.

The results of Gilbert, LeRoy, and Fenn (26) on thirteen dogs gave a decreased flow in the left circumflex coronary artery in eleven cases and an increase twice, even though the blood pressure raised more often than not. After atropinization or vagotomy, their findings were practically reversed.

Physiologic Considerations

It is evident from the foregoing clinical and experimental observations that one or more reflex nerve arcs exist between the gastrointestinal tract and the heart. Although evidences of suchreflexes are not consistently found at all times under varying conditions, the fact remains that in a certain percentage of cases definite changes are produced directly related, in time at least, with a definite stimulus. It is in order, then, to investigate the nervous connections existing between the two systems.

It is well known that the heart and the gastro-intestinal system are innervated by the autonomic system, the former through the vagus, of the parasympathetic division and the cardiac nerves coming from the sympathetic division. The upper portion of the gastro-intestinal tract is innervated by the vagus of the parasympathetic division, and by direct branches of the sympathetics from the spinal ganglia to the esophagus and by the splanchnics to the stomach. In addition to the well known cervical cardiac nerves, there are the thoracic and cardiac nerves, belonging to the sympathetic system, discovered recently by Brauecker and by Ionesco and Enachesco (taken from 74).

All the cervical and thoracic cardiac nerves have been shown to carry fibers of the somatic afferent type except the superior cardiac nerve, which Ranson and Billingsley calim is a purely motor pathway (74). Thus it is seen that the sensory nerves from the heart converge on the upper four or five thoracic sympathetic ganglia. White (74) states further that:

> "Peripheral to these ganglia the cardiac rami are exceedingly complex and anatomical variations most frequent, but here the cardiac pathways are condensed and relatively constant in position. This arrangement is of prime importance for the surgeon."

Morrison and Swalm (46) state:

> "Although the vagus nerve has no known sensory afferent fibers from the esophagus and stomach and the sensation of pain from these organs cannot be propagated directly by the vagus, still it is well known that unconscious stimuli resulting in vasomotor (constrictor) and reflex inhibitory changes in the heart are transmitted by the vagus. Ranson, and Ranson and Billingsley, and Stohr have shown by histologic studies and Heinbecker has shown by studies in electrical conduction that both the vagal and the sympathetic cardiac rami are mixed sensory-motor nerves and have termed these afferent constituents the 'viscero-sensory' fibers. This is extremely significant in view of the anatomic fact that the ganglion nodosum of the vagus and the upper sympathetic thoracic ganglions originate axons which pass directly and uninterruptedly to sensory endings in the heart and coronary arteries."

As was briefly mentioned above, the stomach is innervated not only by the terminal branches of the vagi, but also by branches from the celiac plexus of the sympathetic trunk and that the greater splanchnic nerve terminates in the celiac ganglion. This has branches which can be traced upward in the sympathetic trunk as high as the first or second sympathetic thoracic ganglions (46), which are among the direct transmitters of sensory pathways for pain in the heart--as was pointed out above. Likewise, besides the esophageal branches of the vagus, the sympathetic nerves form plexuses of nerves and ganglia between the muscle layers of the esophagus.

It is through these intimate nerve relationships that the ease by which nerve impulses, vasomotor stimuli and reflexes are effected between the esophagus, the stomach and the heart. But thus far, only the possible courses of the gastrointestinal effects on the heart have been accounted for. At the present time it appears that only theories have been advanced to explain the origin of gastrointestinal pain arising from only the heart with the one exception to be mentioned next.

It has long been known that distention alone of the gastrointestinal tract is the only mechanism capable of producing definite localized sensations in the stomach and intestines. This adequately explains the abdominal distress produced in flatulence arising from cardiac disturbances as well as from other sources.

Wright (81) mentions several of the existing theories concerning abdominal pain. The first one is that of reflex origin,

> "the pain taking an unusual course due to the sympathetic supply being unusually low or because an unusual part of the heart is involved".

He investigated the latter by noting the sites of lesions in all coronary cases which went to postmortem and found that the abdominal pain is not associated with any special site of lesion. Again the pain may be due

to reflex spasm of abdominal arteries. Wright mentions that those who favor this explanation point out that during an attack of angina pectoris, when the pain is felt in the left arm, this arm is sometimes pale and cold due to vascular spasm.

Another theory that has been mentioned is distention of the stomach as a result of air-swallowing or by reflex atony of the stomach and bowel. Some writers, especially Jackson and Jackson (31) and Verdon (69), believe that abdominal pain is due to acute, spasmodic and incoordinated contractions of the esophagus and stomach.

Congestion and dilatation of the liver with a drag on its supporting ligaments is frequently mentioned as causing abdominal pain in heart failure. Levine (40) and Boyd (11) as well as others consider the pain as arising from tension on the liver capsule due to the hepatic enlargement.. Realizing that an engorged liver may contain as much as 1500 c.c. of blood, or about one-fourth of even the increased circulating blood volume of such patients (22), it is easily understood just how the liver may become so enlarged, and thus greatly stretching its capsule.

Wright adds:

> "So much for the possible causes of pain--which is the correct one I do not know. It is unlikely that all abdominal symptoms are due to a single cause. It is sometimes difficult to understand why some patients do not have abdominal symptoms. A few days ago I attended an autopsy on a man who died of coronary thrombosis--there was considerable hepatic congestion; ten gall stones were found in the gall bladder; his kidneys had numerous infarcts. Yet this man had no abdominal symptoms."

Brooks (13) tells of a case of just the opposite character. His patient had had for years a tender and rigid area in the region of the appendix and caecum, but had never suffered apparently as a result of this lesion, and she had been refused surgery because of her known severe grade of aortic and coronary disease. When angered or excited her frequent attacks of angina pectoris were almost always introduced by agonizing pain in the region of the appendix, usually promptly relieved by nitroglycerine. In spite of numerous offers from ambitious surgeons she lived to finally die from an acute coronary thrombosis, characterized as in the attacks of angina by preponderating cramp-like pain in the region of the appendix.

Discussion

Thus far clinical and experimental observations concerning the part the gastrointestinal tract plays

in heart disease have been presented. Now an evaluation by the various writers on the subject will be undertaken.

A significant feature indicated by the studies and observations on gastric distention and stimulation by other means demonstrates that gas formation in the stomach or esophagus can produce cardiac derangement, being severe in some cases. Thus Morrison and Swalm (46) were able to induce typical attacks of angina pectoris in anginal patients and epigastric distress in patients with arteriosclerotic and hypertensive heart disease by bastric distention. Verdon (69) interrupted attacks of angina by gastric intubation with the escape of large amounts of gas; Iglauer and Schwartz (30) reported their case of cardiospasm who had anginal attacks on swallowing; and the work of the Jacksons (31) produced experimentally attacks similar to angina pectoris in dogs. These findings raise the question as to the possibility of the gastrointestinal tract as being an etiological factor if not the sole one in angina pectoris and other cardiac conditions involving pain and even changes in cardiac rhythm and rate.

Verdon believed that epigastric distress, nausea, the desire to eructate gas, and globus were initiatory symptoms of a "rising tonus in the gastro-esophageal

muscle" due to the accumulation of gas. Then when the tonus had reached a certain intensity, these symptoms merged into pain, which had always been ascribed to the heart. He contends that those earlier symptoms, which denote gastrointestinal disturbance, are banished from consciousness and cease to be recognized as partakers in the syndrome. Then, "after disappearance of differential signs, the viscus at fault remains masked".

The Jacksons expressed a similar opinion in:

> "And yet if one can get a true history of the exact location of the very first sensation which a patient feels in an attack of angina or coronary thrombosis, and if the physician can imagine that such an instrument as an ice pick were passed backward through the initial point of pain to the posterior wall of the body, it will very generally be found that the instrument would pass through the esophagus or the upper part of the stomach. But secondary radiating pain in the other regions may often be so severe that its point of origin is lost sight of entirely."

It is also Verdon's opinion that anginous patients have hyperirritable stomachs which are intolerant of gas, and eructations are frequent particularly when the tonus of the gastric musculature is raised by exertion, emotion, or eating. He observed such an irritability in anginous patients fluoroscopically. According to his hypothesis, the gastric irritability is due to irritable centers in the spinal cord or medulla, which

become exicted by increased intragastric pressure. The gas becomes entrapped in the stomach for he refers to Starling who had shown that both esophageal and pyloric orifices are closed when the vagi are subjected to irritation. It is on this basis that Verdon explained the origin of anginal attacks.

One point worthy of mention here is the article by Bastedo (6) who reviewed the action of atropine and summarized the more recent concensus of opinions regarding the action of the vagi. He states that the stimulation of either the splanchnics or the vagi may result in increased tone when the stomach, pylorus, or cardia is hypertonic and in decreased tone when the stomach is hypertonic.

Nevertheless, Verdon's clinical results are consistent with his hypothesis. Furthermore, perhaps practically every article on angina pectoris from Heberden on down has not failed to note that the relief of pain in this type of case is often associated with the eructation of gas.

Jackson and Jackson (31) concluded from their work on esophageal and gastric stimulation in dogs that angina pectoris was due to acute, spasmodic, incoordinated contractions of the esophagus and stomach. By this re-

action air or other stomach contents are entrapped either in the esophagus or in one portion of the stomach and the traumatic effect on the wall of the viscus is responsible for the pain produced. The trauma may vary from complete rupture (and they found over forty cases of esophageal rupture with clinical signs similar to angina pectoris or coronary thrombosis in the literature) to mere strain on the muscular wall of either the esophagus or the stomach. They believe the presence of blood, which is frequently found, in the vomitus is further evidence of such trauma; also that the act of vomiting, itself, may be responsible for even greater damage. Furthermore, they feel that an insufficient amount of emphasis has been placed on such findings in the field of cardiology. It was their opinion that the coronary arteries had nothing whatever to do with angina, but stated that angina may often secondarily involve the heart.

As evidenced by the negative kymograms of patients during and after anginal attacks, Morrison and Swalm (46) found that the esophagus and stomach were inactive during the paroxysms of angina pectoris. Thus their findings refute the assertions of Verdon and the Jacksons in so far as gastrointestinal contractions are concerned.

This study was the only one found in the literature reporting on actual experimental evidence concerning the relationship and interdependence of the digestive tract and cardiovascular disease in the human subject.

Other clinical and experimental work on gastric and esophageal distention by Weiss and Davis (72), Wayne and Graybiel (71), Best (9), the work of Rhoemheld cited by Niehaus (47), Crittenden and Ivy (17), Dally (18), Maher and his associates (43), and others seem to indicate at least that gastrointestinal disturbances can initiate changes in heart rate and rhythm sufficiently often to admit the presence of such an exciting force. The negative results of Wayne and Graybiel on distention of the stomachs of patients whose exercise tolerance was known to be limited after a heavy meal can not necessarily be applied clinically, for in the latter certain other factors are present. They produced distention by inflating the stomach with air, while, as Niehaus points out, the anginous patient of this type has a stomach distended with food.

Perhaps the greater amount of blood in the mesenteric vessels needed for digestive purposes in the latter as compared to the former experimental case accounts for the difference in subjective response. It follows

that with an increased amount of blood in the visceral vessels following meals that there should be some drop in blood pressure, and Best and Taylor (8) state that there may be a small drop in the diastolic pressure (although there usually is a small rise in systolic pressure also). Furthermore, since Anrep and Segall (2) have shown that coronary flow practically parallels and is dependent largely on the arterial pressure, it may be that in anginous patients, whose coronary vessels usually are already sclerotic, there is sufficient change in coronary flow to precipitate an anginal attack.

The writer is well aware that this deduction may be somewhat overestimated since it is being based on relatively narrow physiological variations. Yet physiological variables such as these used are based on results found in presumably healthy individuals, but the cases under question are pathological.

Moreover, if we will accept temporarily at least the commonly accepted theory of coronary spasm or myocardial ischemia as being the origin of cardiac pain, the difference in response to the two conditions under analysis may be explained in the manner in which Sutton and Leuth (65), Greene (27), and Hinrichsen and Ivy (29) express the relation of visceral distention and excita-

tion to angina pectoris in man. They believe that the failure of reflex coronary dilatation under conditions which augment cardiac activity accounts for the association of angina with visceral excitation. They all independently found that as a rule visceral excitation produced coronary vasodilatation, but in a few instances either no change occurred in the minute volume of the coronary vessels or there was a vasoconstriction. Greene observed a diphasic effect, as mentioned earlier, of first a coronary vasodilatation followed by a vasoconstriction if the stimulus was great enough. Applied clinically, this same mechanism may account for anginal attacks on exertion after meals.

In lieu of the work and theories advanced particularly by Verdon and the Jacksons, a consideration of cardiac pain is quite in order. Is that which we commonly call cardiac pain possibly of extracardiac origin, or is it that certain clinical syndromes so closely simulate heart disease that a differentiation between the two has not heretofore been adequately made? Perhaps if this could be answered, such divergent opinions could be vindicated.

Since Parry (51) pointed out the baneful effects of cardiac ischemia in 1799 in the production of cardiac

pain, this theory has remained the most popular. At that time he wrote:

> "The rigidity of the coronary arteries may act proportionately to the extent of the ossification, as a mechanical impediment to the free motion of the heart; and though a quantity of blood may circulate through these arteries, sufficient to nourish the heart, as appears, in some instances, from the size and firmness of that organ, yet there may probably be less than what is requisite for ready and vigorous action. Hence a heart so diseased may be fit for the purposes of common circulation, during a state of bodily and mental tranquility, and of health otherwise good, but when any unusual exertion is required, its powers may fail, that paroxysms of the Syncope Anginosa are readily excited by those passions, the tendency of which is to stimulate the heart to excessive contraction."

That explanation is largely held by many up to the present time. Sir Thomas Lewis (42) has developed a theory regarding muscular ischemia and its relation to anginal pain, which has been found fairly adequate. He believes that when muscles deprived of their blood supply are exercised, the pain that develops is due to some chemical or physico-chemical substance arising directly or indirectly out of the contraction process; that this substance, which he calls the 'P' factor, has its seat in the tissue spaces, but is dependent upon a process occurring within the muscle fibers as a result of its contraction; and that during muscular exercise with the circulation free the change within the

muscle fibers that ultimately underlies pain occurs, but pain does not develop, since the 'P' factor can not accumulate in the tissue spaces while these are under the influence of a free stream of blood.

Although this hypothesis of Lewis will explain the mechanism of pain in cardiac disease, it does not necessarily conflict with those theories advanced by Verdon and the Jacksons. And this is avoided, since, although the pain-precipitating forces are widely separated in these two main theories of pain, both have a common innervation, which can refer pain to the same areas. In other words, the vagus nerve having afferent sensory fibers from both systems is capable, therefore, to refer sensations of pain to the same areas in either case. And by the same token, gastrointestinal disturbances are able to effect reflexly changes in the heart sufficient to register pain. Similarly it may operate in the reverse manner.

Certain other findings tend to indirectly at least make one feel that all the factors involved in cardiac pain and disease are not known. Davis(19) found in one series of coronary thrombosis cases that pain was absent in sixteen out of thirty-six cases, and in twenty-one out of fifty-three in another series. It is ob-

vious that varying degrees of myocardial ischemia develop in all cases of coronary thrombosis, yet not always does pain occur. Furthermore, as Katz (33) points out, it is known that epinephrine increases the coronary flow and dilates the coronary vessels, and yet despite such an action, angina pectoris may result. In addition most reports in the literature of electrocardiograms taken during anginal attacks present evidence of significant changes in the tracings, particularly in the ventricular deflections. These changes are taken as support of the theory of the coronary spasm or the functional myocardial ischemia mechanism as the cause of angina pectoris. However, articles by Wood and Wolferth (80), and one by Faleiro, mentioned by Morrison and Swalm (46), report no changes in the electrocardiograms during anginal attacks in some of their cases. Concluding from this, Wood and Wolferth contended that coronary spasm or functional myocardial ischemia may not be the only factor in the pathogenesis of anginal seizures.

All of these observations tend to throw doubt on the theory of coronary spasm as the cause of anginal pain.

Some attempts have been made to account for some of these less frequent observations, which are not completely explained by the hypothesis of Lewis. Herrick

(28) explains the absence of pain or precordial distress in some cases by:

> "It has been suggested that normally certain areas of the heart are not only less vital than others, indifferent or silent they have been called, but also less sensitive. At autopsy fresh infarcts are sometimes found associated with multiple areas of fibrosis that speak for previous obstruction of small branches, yet no pain has been noted, no pain even announcing the recent infarctions. There has evidently been a very gradual and progressive narrowing of the artery by sclerotic processes. The area irrigated by the artery has become relatively inactive, relatively anesthetized by destruction of the vessels, nerves, and functioning muscles, so that a painful response to the new obstruction is lacking. The final complete obstruction comes without a sudden shock, the element of surprize is lacking as the heart is in a sense prepared for the supreme insult. Abrupt heart failure with its dyspnea and other phenomena may be present, but pain may be lacking."

Sutton (64) believes that it may be due to the formation of an area of absolute ischemia, an anemic infarct, whereas the syndrome characterized by "severe, enduring, substernal or epigastric pain, unprovoked by effort" is due to the formation of an area of relative ischemia.

Regarding the negative electrocardiograms during anginal attacks, Wood and Wolferth (80) found that occasionally in experimental occlusion of a large coronary artery, with the consequent production of definite changes in the appearance and action of the heart, caused

no change in the electrocardiogram. This, they contend, shows that the absence of electrocardiographic changes during an attack of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur.

The therapeutic response of angina pectoris to the nitrites from the standpoint of its pharmacological action might even favor the extracardiogenic causes of heart pain over that arising from within the heart. Sollmann (62) states that the nitrites relax the gall bladder wall, relax spasmodic contractures in the gastrointestinal tract, and dilate the splanchnic vessels as well as the coronary vessels. From the splanchnic dilatation there occurs the sudden drop in blood pressure, which is well known clinically to occur.

Therefore, since coronary circulation is most dependent upon the maintenance of adequate arterial blood pressure, how can the circulation to a presumably relatively ischemic area of the myocardium be expected to improve sufficiently to supply an adequate amount of blood thereby aleviating the pain? Yet the immediate relief from anginal pain with the nitrites is striking.

The action of the nitrites on the gastrointestinal tract and the gall bladder lends support to the theories advanced by Verdon and the Jacksons. As the

Jacksons (31) bring out, the relaxing action of the nitrites on the smooth muscle of the gastrointestinal tract inhibits the spasmodic contractions present there and allows the escape of the otherwise imprisoned gas or other contents of the esophagus or stomach and thereby interrupting the pain. Willius (78) and Walters and his associates (70) are obtaining rather gratifying results by the use of the nitrites on relieving pain of cholecystic disease.

Finally as to which one of these two widely diverging theories concerning the origin of cardiac pain is true, it can not be said as yet. Probably both play a part, one predominating in some cases and the other in other cases. Even more probable is the presence of two separate pathological processes which can not be easily distinguished clinically. It is difficult to discount arguments in favor of the gastrointestinal tract as the exciting force in the production of what is commonly thought to be heart pain. White's (76) arguments against the alimentary origin of cardiac pain are disappointingly inadequate and fail to refute the contentions of Verdon and the Jacksons.

There is one other aspect in which some evidence tends to point toward the digestive tract as a preci-

pitating factor in what is more commonly accepted as heart disease. Reference is being made to the cause of sudden death. In 1916, Allbutt (1) advanced his theory of vagal inhibition, by which he believed that with sufficient vagal stimulation cardiac standstill and death could be produced. However, as Levy and Bruenn (41) expressed it, this theory has not found much support. Nevertheless, there are sufficiently frequent cases reported in the literature of sudden death from apparently the direct result of gastro-intestinal manipulations, other cases of sudden death unaccounted for, as well as reports of temporary cardiac standstill, to justify consideration of Allbutt's theory in this connection. Such cases as sudden death in treatment for cardiospasm, passage of gall stones, heart block in cardiospasm and swallowing and in passage of gastric tubes have already been cited. Therefore, the possibility of the gastrointestinal tract in the production of some cases of sudden death is strongly suggested.

Fishberg (22) points out that it has long been known that in organic cardiac disease the heart is especially susceptible to vagal inhibition. He states that the susceptibility of the bundle of His to vagal

inhibition is especially great when its condictivity is already depressed by disease, by digitalis, or by experimental injury; and under such circumstances, vagal stimulation may convert partial into complete auriculoventricular block, which can again be removed by the administration of atropine. Bearing this in mind, it is very probable that some of Levy and Bruenn's (41) cases of sudden death which he labeled "acute fatal coronary insufficiency" died via vagal inhibition. It is apparent that in cases of cardiospasm, vomiting, flatulence, and spasmodic contractions of the esophagus that strong vagal stimulation does occur. Certainly the clinical and experimental observations mentioned offer some support to Allbutt 's hypothesis.

Conclusions

The intimate nervous relationships between the heart and the gastrointestinal tract account for the occurrence of some of the changes in cardiac rates and rhythms found in disturbances of the digestive tract. Due to this very close autonomic nervous connection, the actions and disturbances of one system so closely affect the other and vice versa, that disease of one will upset the autonomic balance between the two, thereby reflexly implicating the other secondarily.

From the evidence presented, it appears that angina pectoris may not be so much a disease, but rather a symptom-complex of varied etiology.

Clinical and experimental findings are seen often enough to conclude that disturbances in the digestive system may reflexly affect the heart producing sudden death through vagal inhibition.

THE ROLE OF THE GALL BLADDER

There has long been a general impression among surgeons and internists that there is more than a casual association betwen diseases of the gall bladder and diseases of the heart or disturbances of its mechanisms. It has been thought that gall bladder operations are complicated more often by postoperative deaths and cardiac accidents than are other operative procedures of similar gravity.

Clinical Reports

As early as 1875, Gangolphe (25) reported nine cases of gall bladder disease with cardiac lesions believing that there was a definite relationship between the two conditions. He thought the principle effect upon the heart was on the papillary muscles. However, Revillout (54) states that Guneau de Mussy was the first to mention the development of cardiac murmurs in cases of jaundice; and this was effected by the paralyzing influence of bile salts upon the vasomotor and general circulatory system.

Fabre (21), in 1877, described eight cases of jaundice, the heart being affected in five. He attri-

buted it to a myocarditis due to the accumulation of bile salts in the blood.

A year later, Tessier (67) went so far as to classify the cardiac disturbances due to gastrohepatic diseases, as: (1) intensification of the second sound, (2) doubling of the second sound, (3) a tricuspid murmur, and (4) complete tricuspid incompetence with venous pulse.

Rendu (53), in 1883, reported a case of hepatic colic and icterus in which there was marked arrhythmia; and another of catarrhal jaundice with gallop rhythm but no arrhythmia. A little later, Leva (39) described two cases of ulcerative endocarditis resulting from disease of the gall bladder.

In 1893, Oddo (48) reported a case of a man having gall stone colic for years, who suddenly developed a typical attack of biliary colic and jaundice. Two days later there was a feeble arrhythmic pulse with signs of pericarditis from which he died a few days later.

Any relationship between gall bladder disease and heart disease was not much championed by American men until Riseman (55) and Babcock (3,4) began to contribute to the literature in 1907 and 1909 respectively.

Riseman wrote about the development of mitral systolic murmurs during attacks of biliary colic, and which disappeared after the subsidence of the pain. This he considered due to pain causing dilatation and temporary insufficiency of the mitral valve. He interpreted this as meaning that a weakened heart muscle was present, and he stated that gall bladder patients who had heart murmurs must be anesthetized and operated with especial care.

Babcock (4) pointed out that chronic cholecystitis often produced from an arrhythmia and precordial oppression and dyspnea to demonstrable dilatation and incompetence dating from some attack of biliary colic or acute cholecystitis and thenceforth maintained by recurrences of the acute disturbance. Such patients often sought aid referable to their heart.

He divided thirteen cases with definite gall bladder pathology into four classes depending upon the type of cardiac involvement present, as: (1) cases of pronounced cardiac incompetence showing considerable dilatation with arrhythmia and feeble heart action with murmurs, (2) cases in which there have been attacks of pain that have been called angina pectoris, and which

attacks were followed by evidences of myocardial inadequacy, (3) cases of intermittence of pulse of long and intractable standing, but without dyspnea or other marked subjective symptoms of myocardial inadequacy, and (4) cases of valvular disease in which cardiac competence was destroyed either by outspoken attacks of hepatic colic or distressing symptoms thought referable to the stomach at first.

His operative results on these cases were rather encouraging from the standpoint of cardiac improvement, although most of them died before any very conclusive evidence could be obtained. He suggests that a previous state of the myocardium may have some effect in determining what cases of chronic cholecystitis will develop cardiac symptoms. He was well aware of the fact that disease of the heart and of the gall bladder may coexist, and also that frequently the symptoms of one are so closely interchangeable with the other that accurate diagnosis is often very difficult. This is particularly true in cases of cholecystitis with or without the formation of calculi sufficient to excite distinct colic.

Osler (49) was aware that palpitation and distress about the heart may be present and that occasionally a

mitral murmur developed during the paroxysm in gall bladder disease, but he added that the cardiac conditions described by some writers as coming on acutely in biliary colic are possibly pre-existent in these patients.

In a study based on 109 consecutive cases of cholecystitis by Schwartz and Herman (60), it was found that heart disease was the most common associated condition and was present in 63 per cent of all the patients. This exceeded the more commonly accepted associated condition of obesity in gall bladder disease by slightly over 11 per cent. Furthermore, as may be expected, the percentage of associated cardiac involvement began in the third decade of life (46.6 per cent) and rose rather sharply in the fifth decade (58.6 per cent) to find definite evidence in all patients above sixty years of age. The most common type of heart pathology was what they called "chronic myocardial disease". This they defined as:

> "a typeof myocardial insufficiency for which no definite etiologic factors are evident, and is probably caused by the combined action of the infected gall bladder plus obesity".

Less striking were the results reported by Willius and Fitzpatrick on 596 patients with chronic disease of the gall bladder. 229 or 38.4 per cent showed

heart involvement, and the hypertensive heart was the most common type of diseased heart with 113 cases or 49.3 per cent. Five cases of angina were noted, or 0.84 per cent of the entire series.

Schwartz and Herman also found that there was no apparent difference in the effect upon the heart in either the mild or the severe types of cholecystitis. Also, their studies showed that when the male is subject to cholecystitis, it is more apt to occur at a later period in life and to be more severe and associated with a marked degree of myocardial involvement.

Leech (36) studied one hundred and sixteen operative patients with gall bladder disease with particular reference to the presence or absence of associated lesions of the heart. The mortality in this series was no higher than the general operative mortality in the same hospital. Fifty per cent of the deaths occurred in patients who had lesions of the heart, as shown by the presence of both murmurs and enlargement, yet only about 25 per cent of the total cases presented heart lesions. The patients with heart lesions who died showed abnormal electrocardiograms but nothing to indicate a particular association with gall bladder dis-

ease. That 50 per cent of the fatal cases showed marked jaundice is considered an indication of the severity and length of the existence of the infection. Approximately 36 per cent of the patients gave a history of definite cardiac disease previously, differing slightly or not at all from any other series of patients of the same age incidence. In five of the patients a cardiac murmur disappeared after operation. Electrocardiographic studies revealed nothing significant, nor was ther anything characteristic in the bacteriology of the gall bladder contents. In fact, many of the gall bladders seemed to be sterile.

This same question was approached from a different angle of study by Fitz-Hugh and Wolferth (23), by observing electrocardiographic changes pre- and postoperatively in patients with gall bladder disease, and definite heart damage. All six of their patients exhibited cardiac symptoms chiefly anginoid in character but for the most part not of the effort type. All had abnormal electrocardiographic changes, showing chiefly flat or inverted T-waves in the first two leads. In four of their cases the T-waves became upright within nine months (two of them within three months), one

showing changes towards normal in seventeen days; the fifth one, who was severly decompensated and had a chronic auricular fibrillation, became well compensated and the arrhythmia disappeared for two months following surgery. The sixth case became complicated with acute pancreatitis.

Rehfuss (52) studied 200 consecutive cases of gall bladder disease and found that in 71 cases or 35.5.per cent there was evidence of cardiac consciousness in some form. In six, or three per cent it suggested angina pectoris.

Straus and Hamburger (63) in 1924 reported four cases of diseased gall bladders associated with definite cardiac irregularities, shown either by the electrocardiogram or by the pulse. In three of the cases the irregularities disappeared postoperatively.

Experimental Evidence

That cardiac irregularities may be induced reflexly from visceral excitation is supported by certain exerpimental evidence. Schrager and Ivy (59) in discussing the symptoms produced by distention of the gall bladder and biliary ducts in dogs reported that changes in blood pressure and heart rate are caused, which, however, are not uniform. These results were confirmed

by Scott and Ivy (61). However, they found that the effect of distention of the biliary passages in the frog was less effective than in the dog. Mechanical stimulation and even distention of the frog's gall baldder and biliary passages had no effect on the cardiac rhythm analogous to that sometimes observed when a similar stimulus was applied to the stomach or the intestines. In the cat a rise in blood pressure occurs on distention of the common bile duct without a decided change in the heart rate.

Scott and Ivy concluded that the experimental evidence does not indicate definitely the existence of a direct reflex connection between the biliary passages and the cardiac activity, since a definite disturbance of the heart on stimulation of the biliary tract is the exception rather than the rule. They point out that in the experiments performed on dogs and frogs thus far, only normal mechanisms have been excited presumably. However, Bellet (7) observed later in dogs no change in the heart function upon distention of the gall bladder in the presence of a normal heart but where the heart was diseased, serious cardiac disturbances were observed.

Judging from some of the variable results obtained

from distention of the gall bladder, Schrager and Ivy (59) expressed the belief that the reaction of the cardiovascular system to distention of the biliary passages is dependent on the functional state of the cardiovascular system at the time the distention occurs.

In a different approach to establish the presence or absence of gall bladder-heart reflexes, Buchbinder (14) reported some interesting experiments on the frog in regard to the effects of incision of the gall bladder on cardiac activity. He observed that simple incision of the gall bladder caused a transient arrest of the heart, lasting from one to ten seconds, followed by a sinus bradycardia lasting from one to ten minutes. Occasionally, he observed dilatation and permanent arrest. These effects were attributed to a reflex vagus inhibition due to the acute change in pressure in the biliary tract incident to the incision of the gall bladder.

However, Scott and Ivy (61) later demonstrated that this phenomenon was due to local chemical irritation by the bile on nerve endings in the peritoneum or surrounding organs which reflexly excite the cardio-inhibitory mechanism. In addition, both Carlson and Luckhardt (16) and Scott and Ivy failed to obtain

cardiac inhibition in the dog when bile was injected into the peritoneal cavity showing that the viscero-cardiac reflex mechanisms are different from those of the frog.

Being suggested by the clinical and experimental evidence already cited, Owens (50) concluded that jaundice, biliary tract disease, or liver injury might lead to a sensitization of the mechanism concerned in the production of cardiac arrhythmias on visceral excitation. He found that in one of ten dogs the production of jaundice caused a shifting of the pace-maker within the sinus node. In one of four anesthetized dogs in which jaundice had been present for one week, a ventricular extrasystole resulted on distention of the gall bladder. In five unanesthetized dogs marked and more uniform cardiac arrhythmias resulted on distention of the biliary passages. However, the arrhythmias were closely associated with or related in time of occurrence to the production of nausea and vomiting.

Having already demonstrated that nausea, retching, and vomiting caused cardiac irregularities, Critten and Ivy (17) carried these experiments of Owens a step farther. They assumed that bile salts increased the tone

of the vagus. Therefore, icterus would increase the cardiac irregularities after apomorphine and after distention of the biliary passages. Icterus per se gave variable results, for ectopic beats occurred after icterus, but in some animals such beats disappeared after the animals were icteric. No accentuation of the sinus arrhythmia, as reported by Buchbinder, was observed, but the rate changes showed a tendency toward an increase in the majority of animals. The depth of the icteric coloration of the sclera did not parallel the extent of the cardiac irregularities. The results in the icteric animals receiving apomorphine showed more cardiac irregularities than were observed before the animals became icteric. This is in accordance with their original hypothesis.

With a submaximal stimulus by apomorphine, it was noted that the cardiac irregularities paralleled the degree of icterus. The distention of the biliary system caused nausea, retching, vomiting and pain, all of which were associated with cardiac irregularities which closely paralleled the degree of icterus present.

Far less observations have been made on man from the standpoint of viscerocardiac reflexes. Lennox,

Graves, and Levine (38) in a study of 48 patients during surgical operation, as well as Marvin and his associates (44,45) in a similar study of 60 patients do no report any changes in the electrocardiogram which could be attributed to manipulation of the viscera.

Bettman and Rubinfeld studied the electrocardiographic manifestations during cholecystectomy under spinal anesthesia. They found that the rate changes were variable, but the usual effects of anesthesia, pressure, clamping and pullong on the gall bladder were to increase the heart rate over control periods; while both the release of the gall bladded tension and the occlusion of the cystic duct usually caused inhibition of the heart. Arrhythmias occurred in only three patients. The frequency of ectopic beats increased in one patient who already had them present. The second showed ectopic beats, while the third developed a sinus arrhythmia.

In a more extensive electrocardiographic study of patients undergoing abdominal surgery, Maher, Crittenden, and Shapiro (43) found frequent changes directly associated with some operative visceral stimulation. Once the PR-interval was shortened 0.03 seconds when

the gall bladder was being pulled up, while on another occasion the QRS-complex became widened and notched with the same visceral manipulation. In one patient with slight jaundice the height of the R-wave was decreased 2 mm. during anesthesia and operation, but was increased to 2 to 4 mm. postoperatively. Pulling on the gall bladder decreased the rate 45 beats per minute in two cases, and 25 beats per minute in another. Auricular extrasystoles began in one cholecystectomy case while the skin incision was being made and disappeared when the gall stone was removed. They appeared again when the peritoneum was being closed. In a cholecystectomy under ether, interpolated beats of nodal origin appeared when the cystic duct was being cut. In their three jaundiced patients, changes in them produced were no different in character and frequency from those not jaundiced.

Etiological Theories

No evidence yet has made it possible to prove definitely just why diseases of the biliary tract should result in cardiovascular damage, nor has it been answered why some cases seem to be drawn into the gall bladder picture and others have not. Perhaps a sound

heart can stand the effect of infection and reflex vagal stimulation and quickly recover, while another may be more seriously affected, especially since gall bladder disease occurs chiefly in the middle age when hyperthyroidism, valvular disease, arteriosclerosis, and obesity are not frequent and have already impaired the heart.

However, there are a number of theories which have been advanced concerning this subject. Among the earlier contributors, it has been mentioned already that Revillout (54) believed that cardiac murmurs developing in gall bladder disease was due to the paralyzing effect of bile salts upon the vasomotor and general circulatory system, while Fabre (21) simply attributed such changes to the accumulation of bile salts in the blood. Riseman (55) attributed the development of a mitral systolic murmur in gall bladder colic to a temporary cardiac dilatation through strain and increased tension.

In 1909, Babcock (4) advanced four possible mechanisms to explain the baneful effects on the heart in some cases of gall bladder disease. The first one was through the circulation in the blood of bacteria or their toxins to produce probably a chronic myocarditis.

Undoubtedly valvular cardiac disease might result from a mild bacteremia of such origin, but even more probable is the opinion that circulatory toxins resulting from biliary tract infection may cause cardiac damage (35). Thornton (68) feels that the gall bladder may be the source of a chronic focus of infection, acting on the myocardium and coronary vessels, and like any other focal infections, it may favor the progress of disease even if it is not the immediate cause of it.

The depressing influence of bile constituents on the myocardium was Babcock's second theory. This he supported by the bradycardia and other effects to prove a toxic action of the pigment biliverdin on the myocardium. He adds further that:

> "not only may there be chronic, though slight, toxic effects on the heart, but the increase in blood pressure caused by the bile salts may be a factor in gradually overcoming the functional integrity of an already degenerated heart muscle. Given on top of this an acute exacerbation of the chronic cholecystitis and we have all the factors necessary to acute myocardial incompetence."

Flint (24), in his paper entitled, "The Cholecystic Heart", expounded on the irritable character of the heart muscle in the presence of cholecystitis. He explained this as beind due to an increase in the

permeability of the living cell menbrane, thereby increasing the irritability of the cardiac muscle and increasing the rate of the heart beat. He held that the reverse is true; that is, that a diminution of the bile salts circulating in the blood causes a decrease in the permeability of the lining cell membrane and a diminished irritability. In jaundice, according to him, the bile salts circulating in the blood are diminished, which accounts for the slow pulse associated with this disease.

Babcock's third theory is that of irritation of the splanchnics. Since the splanchnic nerves are the regulators of the circulation, he reasoned that it may be that disturbance of the intra-abdominal circulation may prove an added factor by unfavorably affecting an already weakened heart and to lead to its dilatation and incompetence. No further mention of the possible role of this mechanism was noted in the literature.

The last theory advanced by Babcock, and the one which has received the most experimental evidence is the reflex effect of the gall bladder on the breast. The work of Crittenden and Ivy, Scott and Ivy, Owens and Buchbinder have quite conclusively demonstrated the presence of gall bladder-heart reflexes in frogs and dogs.

Bellet (7) demonstrated serious cardiac disturbances in dogs whose hearts were already damaged. Crittenden and Ivy (17), Bettman and Rubenfeld (10), and Maher and his associates (43) have likewise demonstrated the same in man.

Recently in discussing a paper (not yet published) by Stroud, Barnes (5) pointed out that there is some evidence that disturbances in lipid metabolism are associated both with coronary disease and with disease of the biliary tract. He further stated that,

> "If Dr. Stroud had found that removal of an infected gall bladder resulted in reduction in the lipids, one would feel a bit more encouraged to think that possibly such a procedure might expected to improve disease of the coronary vessels."

Discussion

A natural question to raise at this point, is that concerning the incidence of cardiac involvement in gall bladder disease. Is there more than just an incidental association between heart disease and gall bladder disease than there is to be expected with any series of patients of the same ages? In the series reported by Schwartz and Herman (60), 63 percent of their patients showed cardiac involvement; while Willius and Fitzpatrick (77) reported an incidence of about 39 per centage. Leech (36) found only 25 per cent, while Reh-

fuss reported a frequency of 35.5 per cent. It is interesting to note in a recent report by Johnson (32) on 2,400 routine electrocardiograms of apparently healthy men the incidence of abnormal findings. The average age of this group was 47.8 years. 10.4 per cent showed definite impairment, while 55.8 per cent were considered borderline cases. (Of the former 87.2 per cent were symptom-free.) This report of Johnson's may at least approximately serve as a measure to the incidence of heart disease in an apparently healthy group of about the same average age as those we are interested in. By comparing the two, i.e., those of the gall bladder series and Johnson's series, a definitely increased incidence of cardiac involvement is seen in the former. However, Leech considers his percentage approximately that which is to be expected in such an age group irrespective of co-existing diseases. The other men, whose reports are given, feel that the incidence of heart disease is higher than that to be coincidently expected, and that there is a definite relationship between gall bladder disease and heart disease.

Bellet expresses the opinion of many clinicians when he says:

"Neither the evidence available in the litera-

> ture nor our own clinical experience justifies the conclusion that gall bladder pathology can act as an etiologic agent in producing actual myocardial changes in an otherwise normal heart. It can, however, act as an aggravating factor in the presence of already existing myocardial disease; in such cases it may precipitate serious cardiac disturbances."

Judging from their experimental results, Schrager and Ivy concluded that the functional status of the cardiovascular system is the determining factor in the reaction from distention of the biliary passages. Bettman, and Scott and Ivy concurred with this. Babcock (4) expressed the clinical corollary of this by suggesting that a previous state of the myocardium may have some effect in determining what cases of chronic cholecystitis will develop cardiac symptoms.

In some cases biliary tract disease may cause cardiac disease but in other cases there may be primarily a more independent relationships. Klemmer and Klemmer (35) express this opinion and explain it as follows:

> "Both cardiac and biliary tract disease may exist during the early part of the patient's life. If no troublesome symptoms occur from the biliary disease, it receives no treatment, either surgical or medical. However, later in life the heart begins to lose its reserve power, and to show signs of decompensation. Now a vicious circle may occur. The weaker the circulation due to cardiac insufficiency, the more the passive congestion of the liver, and the less readily the liver can perform its functions of formation of digestive ferments, glycogen storage, detoxication, etc. A

> previously diseased biliary tract renders the condition even less favorable. On the other hand, the poorer the function of the liver, the more toxic products in the blood and the more the embarrassment of circulation through congestion in the organ itself, and also from actual pressure on the heart by gaseous distention of the stomach and intestines. In other words, while the heart has a large reserve of energy and is not forced in its work, chronic biliary disease will not be so vital a consideration. But as soon as the heart begins to labor we have the recognized symptoms of coexisting cardiac and biliary disease."

The evidence given to demonstrate the presence of gall bladder-cardiac reflexes is rather convincing in favor of them, even though they were not consistently found in all cases. The fact remains that in a certain percentage of cases, changes were produced which were directly related, in time at least with a definite stimulus. As Maher and his associates (43) expressed it, the positive results which were obtained were probably due to the fact that in exceptional instances at least there was sufficient gap in the inhibitions to admit a viscerocardiac reflex.

The work of Owens and particularly that of Crittenden and Ivy in showing that jaundice sensitizes the vagus mechanism is especially interesting. They were able to demonstrate that with a given stimulus the cardiac response would be proportional to the degree of

icterus. Although these findings were not tried in man, perhaps the bradycardia so frequently observed in the jaundiced patient may be accounted for through this mechanism. The same may be said for some of the arrhythmias, particularly the paroxysmal forms, such as auricular fibrillation, auricular flutter, and the several ectopic beats as well as for some of the transient forms of heart blocks.

The results of Fitz-Hugh and Wolferth (23) in their electrocardiographic study of operative gall bladder cases merit further consideration, for certainly their patients gave comparatively serious electrocardiographic changes before surgery was instituted. With the return of the T-wave to the upright position, as it did in their cases, it appears that not only may gall bladder disease injure the myocardium, but that the process, at least to a certain extent, is reversible. These men feel that the majority of patients with coronary and myocardial types of heart disease, who have associated gall stones, are usually greatly benefited by proper surgery. However, they make the following reservations:

> "(1) that many patients with gall stones fail to present electrocardiographic or other evidence

> of cardiac disease, (2) that not all patients with associated gall stone disease and heart disease are benefited by gall bladder surgery, and (3) that occasionally a catastrophic coronary occlusion may occur during a bout of smouldering calculous cholecystitis or choledochitis as well as during or soon after operation for relief of the latter conditions."

Katz (34) is somewhat undetermined as to whether gall bladder disease perpetuates or aggravates coronary disease, but he feels that there is no doubt that reflexes can come from the gall bladder which affect the heart. In addition, in the presence of gall bladder disease, such reflexes may when coronary disease is already present, aggravate the symptoms of both the gall bladder and the heart. He believes they may actually lead to coronary spasm. He has seen some selected cases in which gall bladder operations seemed helpful, and he explains the mechanism accordingly:

> "Pain is a sensation, and painful stimuli that may be below the threshold in the heart may summate with painful stimuli from the gall bladder, and the two together reach the field of consciousness of the patient."

In such cases, Katz believes that removal of the gall bladder may eliminate one factor contributing to the pain and make the patient more comfortable. Barnes (5) adds that he has never been impressed with the fact that the removal of an infected gall bladder or a gall bladder with stones has influenced the degree or progress

of coronary sclerosis.

Conclusions

The balance of clinical evidence shows a tendency for a greater incidence of heart disease in patients suffering from gall bladder pathology than would otherwise be expected in persons of the same age group. The cause of this apparent relationship is undetermined as yet. Some selected cases in whom there is cardiac pain or disturbances of rhythm are benefited by gall bladder surgery.

The presence of gall bladder-heart reflexes has been adequately demonstrated, although they are not constant. It appears that the greater the existing cardiac damage, the more frequent do these reflexes manifest themselves.

Experimental evidence demonstrates that icterus sensitizes the vagus mechanism in the dog.

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