# A STUDY OF GASTRO-INTESTINAL MOTILITY

A Thesis

By

Dso Li-Liang

Submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

McGill University

May 1948

TABLE OF CONTENTS

Page



## LIST OF FIGURES

## ANATOMICAL CONSIDERATIONS

Before discussion of the physiology of the gastro-intestinal motility it would be well to review briefly the anatomy of the region. The parts are: esophagus, stomach, small and large intestine.

The esophagus or gullet is, with the exception of pylorus, the narrowest and one of the most muscular parts of the whole alimentary tract. In the neck anteriorly lies the trachea and in the groove at each side, between the trachea and esophagus, the recurrent laryngeal nerve ascends to the larynx. The two vagus nerves, after forming the posterior pulmonary plexus, descends to the esophagus, where they form, with each other and with branches of the sympathetics, the esophageal plexus. From this plexus two nerves pass downwards, one on the front and one on the back of the esophagus, through the opening in the diaphragm. Each of these nerves contains fibers from both vagi, and they are termed the anterior and posterior gastric nerves. The sympathetics reach the esophagus by way of the thoracic sympathetic trunks passing to the esophagus mainly through the esophageal branches of the greater splanchnic nerve. Histologically, the epithelium of the mucous layer is thick and stratified. The muscularis mucosa is very wide. It is a layer of longitudinal smooth muscle fibers, which is thrown into longitudinal folds when the esogus is contracted. The muscular layer consists of an inner

circular and an outer longitudinal layer as elsewhere in the digestive tract. It is interesting to note that there are considerable differences in the musculature of the esophagus in different species (64) (182). The esophagus, for instance, in the rabbit and dog is composed almost entirely of striated muscle; in the cat two-thirds of the upper part is striated muscle. In man the upper third consists of striated muscle, middle third of mixed, and lower third of smooth muscle. This striated muscle is peculiar in that it does not atrophy when its nerve supply is cut, but maintains its tone. Another peculiarity is that, though striated, one has no control over it.

The stomach is composed of a serous coat and three layers of muscle fibers - longitudinal, circular and oblique from without inward. The mucous membrane has an abrupt transition at the junction of esophagus and stomach from a stratified squamous epithelium to a simple columnar epithelium which is thrown into elevations and depressions called rugae. There is a well marked muscularis mucosa. The pyloric part consists of a proximal chamber, the antrum, and the pyloric canal through which the stomach communicates with the duodenum. The notch at the lower end of the lesser curvature formed by the bending of the pyloric part upon the body is known as the incisura angularis. The pyloric canal is a narrow passage around which the circular coat of the stomach is thickened to form the pyloric sphincter.

The musculature of the stomach is almost completely se-

parated from that of the duodenum by a ring of connective tissue (40). Horton (213) made serial sections of the pyloric region of ninety human stomachs and found that, in most sections of the ring, the strong submucous fibrous layer of the pars pylorica runs outward to join the subperitoneal layer in such a way as to separate the muscle of the stomach from that of the duodenum. In one of the specimens he found a complete break between the muscle sheets on the two sides of the sphincter, but usually there were a few small bridges of circular muscle and some larger ones of longitudinal muscle. But even these bridges were broken up into little bundles by connective tissue or by spaces filled with blood vessels. Curiously, the Auerbach's plexus crosses over from stomach to bowel without much of a break; in fact, there sometimes is a duplication of the layer of nervous tissue at the pylorus (214). Interesting to the spread of carcinoma of the stomach will be the fact that in no one of thirty-five specimens of pylorus injected by Horton (215) with India ink was there any connection between the submucous lymphatics of the stomach and those of the duodenum. In a few cases there were some connections between the subserous lymphatics on the two sides of the pylorus. This break may account, at least in part, for the tendency of gastric carcinoma not to spread across the pylorus. A considerable degree of separationbetween the blood vessels of the pars pylorica and duodenum was shown by Williams (455).

The wall of the small and large bowel is composed of an outer longitudinal and an inner circular coat. The latter

is considerably thicker than the former. These two coats are arranged in a spiral fashion (95) (96) (97) (98). As elsewhere in the gastro-intestinal tract the myenteric plexus of Auerbach is situated between the two muscular sheets. The plexus of Meissner lies in the submucosa. These two plexuses are connected with one another by nerve filaments which pass between the circular muscular fibers. Auerbach's plexus contains numerous ganglion cells which are scare in Meissner's plexus. Its extrinsic innervation is through the vagus and the sympathetic.

Innervation. Following the analysis of many anatomical pathways in the so-called sympathetic system (366) (257) and the functional influences on the gastro-intestinal tract and various visceral structures it became apparent that there were two more or less antagonistic patterns in the motor innervation of viscera. There were found to be preganglionic efferent fibers in the thoracic and upper four lumbar nerves passing by way of white rami communicantes to the sympathetic trunk and ganglia; and other preganglionic efferent fibers in cranial nerves ninth, tenth and eleventh and sacral nerves second, third and fourth, passing directly with these nerves to peripherally located ganglia. The visceral efferent fibers of the thoracic and lumbar nerves when stimulated were found to have effects upon gastro-intestinal tract that were different from, and in many cases opposite to, those of the visceral efferent fibers of cranial and sacral nerves. These two different outflows were known respectively as the sympathetic

and parasympathetic innervations of the gastro-intestinal tract.

The motor innervation of these structures, in contrast to the innervation of the skeletal muscle in which a single neuron extends from the central nervous system to the muscle fiber, is by a two-neuron chain, made up of a preganglionic neuron with its cell body in the central nervous system and a post-ganglionic neuron with its cell body located in some autonomic ganglion. The axon of a preganglionic neuron synapses with one or more postganglionic neurons in a ganglion; the axon of a postganglionic neuron ends in relation to muscle or gland cells. Such is, in brief, the principle of gastro-intestinal innervation on its motor side. The usual term autonomic, for instance, does not include the sensory side of gastro-intestinal innervation by definition. The digestive tube like other viscera are well supplied with afferent nerve fibers, the arrangement of which is essentially like that of somatic afferent fibers.

Afferent fibers are found in the ninth and tenth cranial nerves and in many of the spinal nerves, specially in those associated with the white rami ( thoracic and upper lumbar nerves ) and in the second, third and fourth sacral nerves. These afferent fibers take origin from cells in the cerebro-spinal ganglia. From these ganglia the fibers run through the corresponding cerebrospinal nerves to the autonomic nerve and ganglia, through which they pass without interruption to end in the viscera. These fibers are of all sizes, including large and small myelinated fibers and many which are unmye-

linated (114) (365).

The afferent impulses mediated by these fibers serve to initiate visceral reflexes, and for the most part remain at a subconscious level. Such general visceral sensations as we do experience are vague and poorly localized. Tactile sensibility is entirely lacking in the gastro-intestinal tract and thermal sensibility almost so, although sensations of heat and cold may be experienced when very warm or cold substances enter the stomach or colon (102). Pain cannot be produced by pinching or cutting the thoracic or abdominal viscera. Acute visceral pain may, however, be caused by disease, as in the passage of a stone along the biliary tract or ureter. Tension on visceral structures is an adequate stimulus for pain and tension may be produced by overstretching or by excessive muscular contraction-when tissues are inflammed or edematous the threshold for pain is lowered.

Efferent fibers of the cerebrospinal nerves take origin from cells located within the cerebrospinal axis. They do not run without interruption to the structures which they innervate; instead, they always terminate in autonomic ganglia, whence the impulses they carry, are relayed to their destination by neurons of a second order. This important information we owe to Langley (258) (259), who showed that the injection of proper doses of nicotine into rabbits prevents the passage of impulses through the autonomic ganglia, although an undiminished reaction may be obtained by stimulation of the more peripheral visceral nerves. By a long series of experiments

Langley has shown that there are always two and seldom, if ever, more than two neurons concerned in the conduction of an impulse from the central nervous system to smooth muscle or glandular tissue. The neurons of the first order in this series are designated as preganglionic, those of the second order as postganglionic, with reference to the relation which they bear to the ganglion containing their synapse.

Preganglionic neurons have their cell bodies located in the visceral efferent column of the cerebrospinal axis. The cells are smaller than those of the somatic motor column and contain less massive Nissl granules. From these cells arise the fine myelinated visceral efferent fibers which run through the cerebrospinal nerves to the autonomic nervous system and terminate in the autonomic ganglia.

Postganglionic neurons have their cell bodies located in the autonomic ganglia. In fact, these cells with their dendritic ramifications and the terminal branches of the preganglionic fibers synaptically related to them are the essential elements in the ganglia. Their axons for the most part remain unmyelinated and run through the visceral nerves and plexuses, to end in relation with involuntary muscle or glandular tissue. A very few postganglionic fibers acquire delicate myelin sheaths.

Knowledge of the final terminations of autonomic fibers upon the effectors they supply is not complete (366). Smooth muscle is supplied with small knobbed endings which make contact or, according to Boeke (57), become embedded in the

muscle cell near the nucleus. It is probable that not all smooth muscle cells are directly innervated, for although this appears to be so in the intrinsic muscles of the mammalian eye, no such profusion of endings has been demonstrated in the smooth muscle of the gut wall (157).

The action of visceral effectors in most instances is that of large groups of cells, and, in the absence of direct innervation to each unit cell in gland and muscle there is implied a method of spread of influence to the units not in contact with nerve endings. This need is supplied in some instances as postulated by the release of humoral substances in the tissue juice and other body fluids which activates or prolongs the action of visceral effectors. Epinephrine produced by the cells of the medulla of the adrenal gland is the best known example of such a substance. The cells which produce it, incidentally, are homologous with neurons of autonomic ganglia. That is, they are both derived from the same embryological source and are supplied by nerve-fibers arising from visceral efferent neurons of the spinal cord. This type of innervation of the chromaffin tissue is the one known exception to the rule that a two neuron chain intervenes between central nervous system and visceral effector.

There are three important branches of the thoracic portion of the sympathetic trunk known as the splanchnic nerves. These run through the diaphragm for the innervation of the abdominal viscera. The greater splanchnic nerve is usually formed by branches from the fifth to the ninth thoracic sympathetic gang-

lia and after piercing the diaphragm joins the celiac ganglion. The smaller splanchnic nerve is usually formed by branches from the ninth and tenth thoracic sympathetic ganglia and terminates in the celiac plexus. The lowermost splanchnic nerve arises from the last thoracic sympathetic ganglion and terminates in the renal plexus. These splanchnic nerves, although they appear to be branches of the thoracic sympathetic trunk, are at least in major part composed of fibers from the white rami, which merely pass through the trunk on their way to the ganglia of the celiac plexus (258) (365).

The celiac plexus ( solar plexus ) is located in the abdomen in close relation to the celiac artery. It is continuous with the plexus which surrounds the aorta. Subordinate portions of the celiac plexus accompany the branches of the celiac artery and the branches from the upper part of the abdominal aorta. The celiac plexus contains a number of ganglia which in man are grouped into two large flat masses, placed one on either side of the celiac artery and known as the celiac ganglia. These ganglia are bound together by strands which cross the median plane above and below this artery. Somewhat detached portions of the celiac ganglion, which lie near the origin of the renal and superior mesenteric arteries, are known respectively as the aorticorenal and superior mesenteric ganglia. In addition there is a small mass of nerve cells in the inferior mesenteric plexus close to the beginning of the inferior mesenteric artery. This is known as the inferior mesenteric ganglion.

Preganglionic fibers reach the celiac plexus from two sources: namely, from the white rami by way of the sympathetic trunk and splanchnic nerves and from the vagus nerve. Most if not all of the preganglionic fibers contained in the splanchnic nerves terminate in the ganglia of the celiac plexus. Preganglionic fibers, arising in the dorsal vagal nucleus, leave the medulla in the ninth, tenth and accessory part of the eleventh cranial nerves. They constitute the major portion of the vagus nerve in the neck and through it reach the heart, bronchial tree, and gastro-intestinal tract, as far down as the transverse colon. At the lower end of the esophageal plexus the fibers from the right vagus nerve become assembled into a trunk which passes to the posterior surface of the stomach and the celiac plexus. The fibers of the left vagus pass to the anterior surface of the stomach and to the hepatic plexus. It is probable that the preganglionic fibers of the vagus do not terminate in the ganglia of the celiac plexus, but merely pass through that plexus to end in the terminal ganglia, such as the small groups of nerve cells in the myenteric and submucous plexuses of the intestine.

The myenteric plexus ( of Auerbach ) and the submucous plexus ( of Meissner ), located within the walls of the stomach and intestines, receive filaments from the gastric and mesenteric divisions of the celiac plexus. They also receive fibers from the vagus either directly, as in the case of stomach, or indirectly through the celiac plexus. Unfortunately, very little is known concerning the synaptic relations established

in the ganglia of these plexuses. According to Langley, the postganglionic fibers from the celiac ganglia run through these plexuses without interruption and end in the muscular coats and glands of the gastro-intestinal tract. The preganglionic fibers from the vagus probably end in synaptic relation to cells in these small ganglia; and the axons of these cells serve as postganglionic fibers, relaying the impulses from the vagus to the glands and muscular tissue.

The enteric plexuses must also contain a mechanism for purely local reactions, since peristalsis can be set up by distention in an excised portion of the gut. These purely local reactions are known as myenteric reflexes of Cannon (81) and depend upon a mechanism entirely contained within the enteric wall. But as yet we are entirely ignorant as to what that mechanism may be. With this exception the evidence strongly indicates that all visceral reflex arcs pass through the cerebrospinal axis. It seems certain that no reflexes occur in the ganglia of the sympathetic chain (58) (183); but the possibility cannot be ruled out that the collateral ganglia may serve as reflex centers, controlling to some extent the viscera which they supply (255). From time to time various authors have suggested (390) that some visceral afferents have their cell stations in the sympathetic ganglia instead of the dorsal spinal nerve roots. Kuntz (254) has showed evidence of local sympathetic reflexes which do not involve the spinal cord at all. He speculated on the autonomic nervous system as a collection of reflex arcs involving both afferent

and efferent fibers, some of which were strictly local with cell stations in the walls of the particular organs innervated. Schwartz (383) further supported the concept of extraspinal sympathetic reflexes by cutting the dorsal roots of the entire limb distal to the dorsal root ganglia. After time had elapsed for degeneration, he was still able to obtain galvanic reflexes from the skin; nicotine abolished the reaction, which suggests true synaptic transmission quite separate from an axon reflex (432). Fulton also mentioned that there is some evidence that true reflexes can occur through peripheral ganglia whose connections with the centrak nervous system have been severed (255) (383) which would mean that cell bodies of certain visceral afferents may lie peripherally and their processes form synaptic connections directly with postganglionic neurons in sympathetic ganglia. Recent attempts with unquestionably decentralized ganglia have, however, failed to corroborate this evidence.

The visceral branches of the sacral nerves supply motor fibers to the colon and rectum. Preganglionic fibers arising from cells of the lateral gray matter pass out of the spinal cord in ventral roots of sacral third and fourth ( sacral second and fifth occasionally participating ). They leave the corresponding spinal nerves, and run forwards as separate nerve bundles ( pelvic nerve or nervi erigentes ) on each side of the rectum. They form synaptic connections with cells in ganglia of the pelvic plexuses or within the walls of the rectum and bladder, from which postganglionic fibers arise

to supply the hind gut, bladder, and blood vessels of the generative organs.

## THE MOTILITY OF THE ESOPHAGUS

It is noted that there are considerable differences in the musculature of the esophagus in different species. The muscle lining the esophagus is interesting in that at least in the upper part of the tube it is striated. In rabbits and dogs this semivoluntary muscle extends a little way onto the stomach; in the goose it is absent, and in man and in cats, it lines the upper two-thirds of the tube. This striated muscle seems to be a little different from other striated muscles in that it does not atrophy when the nerves are cut. In this regard it resembles that of the external sphincter of the anus. Its physiologic peculiarities have been described by Goodall (170).

Regarding the peristalsis of the esophagus the earliest investigation reported by Wild (83) in 1846 showed that if the esophagus is divided or simply tied about it with a thread, the peristaltic wave is definitely blocked at the point of interference. From this observation he drew conclusion that esophageal peristalsis is due to a series of reflexes starting in the mucous membrane of the esophagus itself - a series at once stopped by any interruption of the continuity of the tube. Mosso (83) placed a small wooden ball in the esophagus below the point where the tube had been transected. When a wave started by a swallowing movement had traversed the upper

section it did not stop at the point of incision but in due time appeared below and carried the ball on into the stomach. Mosso concluded that esophageal peristalsis is originated in the central nervous system. The experiments of Wild and Mosso were repeated by Meltzer (311) (312). According to Meltzer's results Wild observed conditions which appear in deep anesthesia and discovered the reflex peristalsis which can originate in the esophagus itself. Mosso on the other hand who studied the conditions in light anesthesia discovered the central origin of the procession of esophageal peristalsis which normally prevails. Meltzer and many others pointed out that any one who wishes to study the mechanisms underlying the process of deglutition must avoid the use of anesthetics because they interfere so markedly with the proper working of the many reflexes which are involved. Cannon (79) prepared cats for double vagotomy by the Pavlov method. He observed paralysis of the whole esophagus immediately after operation and noted recovery of the lower end which corresponds to the smooth musculature. From these investigations the differences between the nervous mechanisms responsible for main types of esophageal activity have been made out, since Mosso's observation revealed an esophageal peristalsis of central origin, distinguished by Meltzer as primary peristalsis; whereas Wild's studies disclosed a reflex esophageal peristalsis of peripheral origin and is called the secondary peristalsis of Meltzer. The peristaltic activity in the

lower smooth end of the esophagus, capable without vagus support to clear the esophagus of food, is denoted as the tertiary peristalsis of Cannon. These experiments repeated on the monkey gave identical results as in cats; but when tried on the rabbits, no tertiary peristalsis was present, since the esophagus of rabbit, unlike that of cat and monkey, is composed wholly of striated muscle (235).

The normal activity of the esophagus is largely dependent on the integrity of the vagus nerves. When they are cut or damaged, the part of the wall of the tube that is supplied by striated muscle becomes paralysed and the chain of reflexes that normally carries food into the lower end of the esophagus is broken. According to Jurica (235), double vagotomy results in paralysis of the entire esophagus, but soon ( 9 to 24 hours ) there are signs of recovery of function in the lower end where the muscle is involuntary in type. The upper end of the tube with its voluntary muscle remained paralysed. The food swallowed by vagotomized cats lodges in the upper part of the esophagus, but it is moved downward by subsequent swallows and also by gravity. The column of food is pinched off by a wave when it reaches the segment supplied with smooth muscle. Interestingly, the striated muscle usually regains some of its motility after three months; it does not degenerate after double vagotomy and it does not lose its tonus. Cannon showed that in those animals in which the lower end of the esophagus is supplied by involuntary muscle, there

is a certain amount of return of activity within a few days after the vagi have been cut; but in those animals, like the rabbit, in which the entire tube is lined by striated muscle, the paralysis that follows the operation is likely to be permanent. Evidently the esophagus is more dependent on the function of the extrinsic nerves than is the stomach and bowel.

Stimulation of the vagus nerves on either side is said to produce tetanic contractions of the muscle throughout the esophagus. In Jurica's experiment, double splanchnicotomy did not affect the motility of the cat's esophagus, and most investigators agree that the sympathetic nerves have little to do with the movements of this part of the digestive tube. Carlson (103) (105), May (307), Veach (433) and others (182) took exception to this view. Kure et al (256) noted that after section of the sympathetic nerves to the esophagus, a barium meal stuck to the mucosa, which indicates that there was a stoppage of the secretion of the mucus. Vineberg and Komarov (434) under the direction of Babkin, demonstrated in dogs that there is a close relationship between the esophageal secretion and stimulation of vagi. Rhythmic stimulation of the vagi in the neck activates a secretion of mucoid fluid emanating from both the upper and lower ends of the esophagus. In addition there are typical changes in the chemical composition of the esophageal secretion which indicates that the vagus is a secretory nerve to the esophageal mucosa and the action of the vagus produces a true secretion from the eso-

phageal glands. The part played by the vagus in the esophageal secretion is important experimentally whenever the influence of this nerve on the gastric secretion is studied since the possibility of admixture of the esophageal secretion with the latter must be excluded.

The mucous membrane of the esophagus is not very sensitive to irritants, but painful sensations can sometimes be felt and are usually referred upward into the neck or downward to the epigastrium (59). According to Hurst (220) (224) fairly strong solutions of hydrochloric acid are not felt in the lower end of the tube; but, according to clinical experience, they may sometimes be felt, particularly, perhaps, in highly sensitive individuals. The fact that food often regurgitates into the esophagus and that its acidity ordinarily is not perceived would indicate that the esophagus is normally rather insensitive. The pharyngeal end of the tube is sensitive to acid, as anyone knows who has ever regurgitated or vomited. In some persons the esophagus responds painfully to the presence of strong alcohol.

Reverse peristalsis in the esophagus of man has been observed usually in the presence of disease (101). Frequently, during roentgen-ray examinations, specially in cases of spasm at the cardia, ripples of reverse peristalsis are readily visualized and sometimes the barium mixture shooting even as far as the mouth, but this might be caused by the powerful contractions of the lower end of the tube. Ripples of reverse

peristalsis running up the esophagus are probably common, specially in persons who suffer from indigestion. If very shallow, they may be perceived by the subject only as little gurgles. When these wavelets are strong and deep they produce true belching and acid regurgitation.

It is commonly believed that the esophagus is far removed from voluntary influence. Roentgen-rays and kymograms used by Jacobson for studies of esophageal spasm made this belief open to question (231). He presumed that the tonus of the esophageal musculature may vary with that of the skeletal system and it would seem that esophageal relaxation can be carried through diminution of spinal impulses from relaxed muscles. Individuals with esophageal spasm had been trained in this way to relax their skeletal muscles and it was found that the esophagus could be voluntarily relaxed.

The normal esophagus generally contains some air and it may be seen to dilate a little with each inspiration. The pressure in the esophagus is generally a little less than atmospheric about -3.5 mm. of mercury. It may that this helps somewhat in allowing the food to be shot through from the mouth (20).

The main function of the esophagus is to share the act of swallowing. This is a complicated reflex movement which may be initiated voluntarily but is, for the most part completed quite independently of the will. The classical description of the act given by Magendie divides it into three

stages, corresponding to the three anatomical regions - mouth, pharynx and esophagus - through which the swallowed bolus passes on its way to the stomach. The first stage, which is voluntary in nature, consists in the passage of the bolus of food through the anterior pillars of the fauces. The masticated food is formed into a bolus by the action of the tongue against the palate and at the same time lubricated by mixing with saliva, then moved towards the back of the mouth by elevation of the front of the tongue. Moistening of the food by the saliva is very important: it is extremely difficult or impossible to swallow dry material. Mosher (327) made an interesting and detailed roentgenologic study of swallowing. According to him, the barium-containing mouthful was first gathered in a space between the tip of the tongue and the back of the incisor teeth. From there it flows into a space formed by the hollowing of the dorsum of the tongue. The tip of the tongue was then carried to the roof of the mouth and against the teeth so as to prevent the mouthful from escaping forward. The tip of the tongue rose, the base was depressed, and the mouthful was pushed back against the posterior pharyngeal wall. The base of the tongue then darted upward and backward like a piston, and the mouthful was forced downward. The tip of the epiglottis was at first separate from the base of the tongue, but as the tongue moved upward and backward, it forced the epiglottis back against the pharyngeal wall. If a person swallows only a small mouthful containing barium it can be

seen to accumulate in the valleculae at the sides of the base of the tongue. The epiglottis acts as a watershed which divides the material into two streams, each of which runs into a pyriform sinus. Below the pyriform sinuses the two streams unite. The shadow of barium is seen to be narrow back of the cricoid cartilage, but below this the esophagus widens out. During the continuous swallowing of barium water, the material can be seen to run not only on either side of the epiglottis, but also over it. From a study of serial roentgenograms, Barclay (45) concluded that a large element of suction enters into the process of swallowing. Negative pressure in the pharynx is produced, first, by a raising of the larynx and a backward movement of the tongue which for a fraction of a second obliterates the pharyngeal space; and second, a reopening of the pharyngeal space due to a lowering of the larynx and a forward movement of the tongue. Barclay felt that, except in the case of fluids, gravity plays a minor part in swallowing. The larynx appears to be closed off during swallowing by a dragging up of the anterior wall of the lower part of the pharynx to form contact with the epiglottis. It is evident that any factor which interferes with these movements of the tongue or the moistening of the bolus by appropriate secretion of saliva can operate to produce dysphagia in the first stage of swallowing.

The second stage of swallowing is a purely involuntary process, fundamentally a complicated coordinated reflex act

by which the bolus is passed through the pharynx into the esophagus. The whole act is very rapid as well as complex, so that not more than about one-fifth of a second elapses between the beginning of the contraction of the mylohyoids and the entrance of food into the upper end of the esophagus. The nervous mechanisms involved in this reflex are sensitive receptors located in various parts of the pharynx and back of the mouth. Pommerenke (348) studied the sensitive spots on the posterior wall of the pharynx from which the swallowing reflex can be started. In the dog and cat the chief spot is on the posterior wall of the pharynx and is supplied by the glossopharyngeal nerve. Accessory spots on the upper surface of the soft palate are supplied by the glossopharyngeal and the second branch of the trigeminus; others on the epiglottis are supplied by the superior laryngeal nerve. These spots can be mapped by touching the mucous membrane here and there until the reflex appears. After these spots have been cocainized, swallowing may for a time be impossible. According to Pommerenke, the anterior pillars are the most sensitive regions in starting the swallowing reflex, and after them come the posterior pillars. The uvula and soft palate are relatively insensitive. In man the most important spot, at least for the swallowing of solids, is at the side of the posterior wall of the hypopharynx. This region is innervated by the glossopharyngeal nerve. The margins of the epiglottis are very sensitive and much concerned in directing the swallowing of liquids.

This region is innervated by the superior laryngeal branch of the vagus nerve. There is a swallowing center located in the medulla oblongata just above that of respiratory center. These centers are doubtless connected because during swallowing the respiratory center is inhibited for a moment. The effectors are located in various muscles of the pharynx and larynx. When food is passed through the pharynx into the upper esophagus, it is important that certain openings into other passages be closed. The mouth cavity is shut off by the position of the tongue against the palate and by the contractions of the muscles of the anterior pillars of the fauces. The opening into the nasal cavity is closed by the elevation of the soft palate and the contraction of the posterior pillars of the fauces and the elevation of the uvula. The soft palate, uvula, and posterior pillars thus forming a sloping surface shutting off the nasal chambers and facilitating the passage of the food backward through the pharynx. The respiratory opening into the larynx is closed by the adduction of the vocal cords and by the strong elevation of the entire larynx. If the elevation of the larynx is prevented, by fixation of the thyroid for example, the act of swallowing becomes impossible. The movements of epiglottis during this stage of swallowing have been much discussed; authorities do not agree on the details concerning this matter. Formerly it was believed that the epiglottis is pressed down upon the laryngeal orifice like the lid of a box, thus effec-

tually protecting the respiratory passage. Most recent observations incline to the view that it is not necessary for the protection of the larynx that the epiglottis be actually folded down over it by the contraction of its own muscles. The forcible lifting of the larynx, together with the descent of the base of the tongue, effects the same results by mechanically crowding the parts together, and the larynx is still further guarded by the approximation of the false and true vocal cords, thus closing the glottis. According to Mosher (327), however, the epiglottis does turn down to cover the larynx. It is well known that the upper half of the epiglottis can be removed without causing trouble, but Mosher stated that the base or cushion of the epiglottis must not be interferred with if difficulty in swallowing is to be avoided. Any factor that interferes in the operation of this reflex act can obviously cause dysphagia in the second stage of swallowing. Injuries to the nervous and muscular elements involved in the reflex are common causes. As is well known clinically, the mechanism of swallowing is often thrown out of order by injuries to the cranial nerves and to the nuclei in the floor of the fourth ventricle. Such disturbances are seen commonly with intracranial thrombosis, diphtheria, myasthenia gravis, balbar palsy and botulism. They result in the regurgitation of food into the nose and in its penetration into the larynx, with resultant spells of coughing and, sometimes, aspiration pneumonia. Such dysphagia

can also be the result of the application of anesthetics to the areas in the back of the mouth and pharynx provided with the receptors, and mechanical failures of various passages to close because of loss of tissue through operation.

The third stage of swallowing deals with the passage of the food bolus along the esophagus and through the cardiac sphincter into the stomach. Meltzer (310) and Greving (20) showed that when the food is liquid or very soft, it is shot through the whole length of the esophagus as a powerful squirting by the force of the initial act of swallowing, arriving at the lower end of the esophagus in about 0.1 second, and may pass immediately into the stomach or lie some moments in the esophagus, and then peristaltic waves clean up what is left. When, however, food is solid or semi-solid, as was shown by Cannon and Moser (89), it is forced down the esophagus by a peristaltic movement of the musculature. The upper portion of the esophagus contains cross striated fibers indicating rapid contractions; the lower end consists of smooth muscle only, while the intermediate portion is a mixture of the two varieties. The circular muscle is constricted from above downward by an advancing muscular wave. The peristaltic wave takes about five or six seconds to reach the stomach, and on its arrival the cardiac sphincter, which ordinarily is contracted, relaxes and permits the bolus to pass into the stomach. There are some species differences in the respect. For example, in the dog cross-striated muscle fibers are found throughout the entire length of

the esophagus, and therefore the peristaltic wave moves much more rapidly and at an uniform rate all the way. In those species that drink with the head down it is evident that both the squirting action in swallowing and the peristaltic mechanism play important roles even against the force of gravity. In man gravity plays a role because Schreiber (20) showed that when the persons being studied tried to swallow while standing on their heads, the barium mixture could not be passed into the stomach; it merely lodged in the esophagus and the upper edge of the column approached the cardia but it did not pass through. Paluglay (20) showed that when patients are put in the trendelenburg position material passes through the esophagus seven times more slowly than normal. The afferent nerves for initiating the peristaltic wave are the sensory fibers to the mucous membrane of the pharynx and esophagus, including the branches of the glossopharyngeal, trigeminal, vagus, and superior laryngeal division of the vagus. Artificial stimulation of the last nerve in the lower animals is known to produce swallowing movements. The motor fibers concerned in the reflex comprise the hypoglossal, the trigeminal, the glossopharyngeal, the vagus, and the spinal accessory nerves. Since the lower part of the esophagus is composed of smooth muscle, the wave of peristalsis moves along independently of extrinsic nerves as is the case in the intestines. The difference between the upper and lower parts is thus related to the difference in the type of muscular fibers

and their innervation. Any factor that can interfere in the passage of the bolus through the esophagus can cause dysphagia in the third stage.

The esophagus does not play an important role in the act of vomiting. The passage through the esophagus is effected mainly by the force of the contraction of the abdominal muscles. However, relaxation of cardia is an essential part of the vomiting act. After division of vagi, the animal retched but material was not expelled from the stomach.

## THE MOTILITY OF THE STOMACH

When the stomach is empty its cavity below the upper part of the fundus is completely obliterated by the apposition of the gastric walls. Food, after passing through the cardia, collects just above the obliterated portion; apparently simply of its weight it gradually separates the gastric walls, and passes downwards along the lesser curvature into the body and pyloric part of the organ. The fundus and usually the remainder of the stomach above about the middle of the body shows no peristaltic activity (83) (82). The muscle of this part of the organ is the seat of a weak tonic contraction which is immediately inhibited by the entrance of food into the stomach, or even by the presence of food in the esophagus. The pyloric part, on the other hand, constitutes a chamber wherein the food is fragmented and thoroughly mixed. Peristaltic waves commencing near the middle of the body of the stomach sweep downwards through the pyloric antrum. They are shallow and ill-defined at their commencement but become stronger as they descend. They also increase in strength as digestion proceeds and, when this is at its height, bite deeply into the gastric walls. Cole has studied the waves in human stomach by means of serial roentgenography and cinematographic projection (118) (119) (120). He described the peristaltic movement as a band of constriction which becomes well

marked in the region of the incisura angularis and ends a centimeter or two above the commencement of the pyloric canal. The gastric wave travels more rapidly over the greater curvature than over the shorter distance of the lesser curvature, and according to Cole the constriction on the lesser curvature upon reaching the incisura angularis " marks time ", while that on the greater curvature continues on through the antrum. The wave thus executes a sort of wheeling movement.

Two or more peristaltic waves may be seen at one moment. traveling through the lower part of the body and pyloric region; for this reason the roentgen-ray appearance of the actively motile stomach is irregularly convoluted. The waves in their downward journey show rhythmical variations in depth. They might be described as waxing and waning. At one intant they deeply indent the gastric wall and the segments between the annular constrictions are also reduced in diameter. There appears to be a general increase in tone of the gastric wall, the capacity of the entire pyloric region being reduced. At the next instant there is a general reduction in tone, the waves are less intense, the convolution of the stomach outline less pronounced, and the capacity of the pyloric region is increased. Cole compares these rhythmical alterations in the organ's shape to the cardiac cycle, and speaks of a gastric cycle. During the gastric cycles the stomach goes through a series of shapes and comes back to the original one. He was one of the first to point out that, at intervals, all the

indentations due to waves become deeper or shallower or systolic or diastolic changes take place in the whole organ. A complete gastric cycle occupies about two to three seconds and three or four cycles may occur during the passage of a wave. The time requires for the passage of a four cycle type of wave from its origin to the pyloric sphincter will be from eight to twelve seconds. The obvious result of these movements is to mix the food thoroughly.

It is well known, in the stomach of man there are about three large waves a minute, and this holds true for a number of laboratory animals. In the cat, there are generally five or six waves a minute (83). There is no definite or any constant relation between the frequency and intensity of the waves and intragastric pressure or acidity, or disease in either the stomach or neighboring organs (20). There is also no relation in man between the acidity and the motor activity of the stomach, however, in undernourished asthenic children the stomach tends to be inactive, and others found that the emptying time is somewhat prolonged (20). According to many observers, the frequency of the waves is lessened when fats are eaten. This will be discussed later.

Cole maintains that the peristaltic movement is a function of the muscularis mucosa and not of the regular muscular coats. Some support of this view has been furnished by Goldon and Singleton (20) who fastened steel beads to the outer surfaces of the curvatures of the stomach and studied the gastric movements by roentgenoscope, a barium meal has been first given.

Waves were observed at times which did not disturb the alignment of the beads. They conclude that the stomach wall exhibits two types of peristaltic movement, one, a vigorous peristalsis, which involves all coats of the stomach and another, a weaker movement, invloving the mucosa and muscularis mucosa only.

It is a remarkable fact that, with all the recent advances in knowledge, physiologists are still uncertain as to the exact way in which the waves of the stomach travel to the pylorus. In 1920, Wheelon and Thomas (447) reported having seen in dogs with the abdomen open, the fading out of some of the waves at the incisura, the apparent pausing of waves there, the dissociation between the activities of the two parts of the stomach, the systolic type of contraction in the pars pylorica, and the waves of relaxation. They concluded, however, that the continuous type of peristaltic wave was the normal one for the moderately-filled dog's stomach, and never saw a systole of the whole pars pylorica. Evidence obtained with the eletrogastrograph was shown by Alvarez in 1922 (10) (11). He found that although some of the waves that seemed to begin a little above the incisura had really come as ripples all the way from the region of the cardia, others semmed to be starting here, there and everywhere on the surface of the stomach and traveling in different ways to the region of the pylorus. Not infrequently, he found signs also of a dissociation between the activities of the body and the pars pylorica; sometimes there was a blockage of one or more waves but,

occasionally, there was a complete independence of the rhythmic activities in the two regions, with the body contracting about three times to the pars pylorica's once. According to Alvarez the highly rhythmic muscle found on the lesser curvature next to the cardia may perhaps serve to some extent as a pacemaker to send off the waves that course over the body of the stomach. Under some circumstances another highly rhythmic band of muscle near the incisura may serve as a pacemaker for the pars pylorica. It is probable that waves can originate in any part of the wall of the stomach. McCrea et al (286) used cats, rabbits and dogs and either watched the movements with the abdomen open, or else gave barium meals and used the roentgenoscope. They described waves which began near cardia and spread downward, producing a contraction ring at the incisura, then a bulging of the pyloric portion, and finally a concentric contraction of this region. This contraction relaxes as a new wave arrived at the incisura. In the pars pylorica of the cat, McCrea and his colleagues observed about equal numbers of the two main types of contraction, the peristaltic and the systolic. Occasionally they saw pulsation in a contraction ring at the incisura when the rest of the stomach was quiet. In dogs, about 75 per cent of the waves changed into systoles at the incisura. Their impression was that in the rabbit, dogs, and in man, the systololic type of antral contraction is predominant. Klein (247) described his experiments with dogs which were anesthetized with

ether and then opened from seven to ten days after subdiaphragmatic vagotomy. He saw the two main types of contraction, with certain variations. He saw ripples coming from the region of the cardia, contractions that did not move forward, stomach blocks, systoles of the pyloric antrum, and occasional reverse waves. Groedel (20) described peculiar waves that he saw in diseased stomachs or in stomachs that were nearly empty. In his serial roentgenograms there sometimes were signs of disturbances in the rhythm, frequency, size and direction of the waves along the middle of the greater curvature, and also small, shallow, multiple wavelets running either caudad or craniad, perhaps in the muscularis mucosa. Alvarez and Zimmermann (10) (11) (12) (32) have recorded these small rapid wavelets in the dog's stomach and found rates running usually between twelve and twenty-four a minute. Todd (430) also appears to have seen them in man after giving milk. The presence of this food caused, at first, a decrease in amplitude of the normal waves. Sometimes they disappeared, to be replaced by puroseless wavelets, which appeared and disappeared locally. He spoke of the phenomenon as shimmer. Such wavelets are easily differentiated from the powerful contractions of the muscularis mucosa.

The exact mode of conduction of the wave of contraction over the stomach is still not clearly understood. Patients with either an ulcer somewhere in the stomach or the scar of a V-shaped excision on the lesser curvature, in whom the

two sides of a wave failed to meet exactly at the pylorus and hence caused delayed emptying of the stomach. It is known to our surgeons that in the old days, when a V-shaped piece was sometimes taken out of the lesser curvature to get rid of an ulcer, this disproportion between the length of the curvatures was exaggerated, the emptying of the stomach was then much interferred with. Another reason for the poor emptying of such a stomach may be a lessening of activity in the part below the line of excision, and the fading out of the waves before they reach the pylorus. If a sleeve resection is made and a complete ring is removed, all observers agree that the stomach will empty satisfactorily. According to Klein (247), after such a sleeve resection has been made, the lower portion of the stomach contracts independently of the upper half. This was to be expected from the studies (5) (6) with excised strips which showed that the muscle on the proximal edge of the pars pylorica has a high degree of rhythmicity, sufficient perhaps to assume the function of pacemaker for the gastric segment distal to it. However, Cannon showed years ago that waves traveled normally over the stomach after the healing of several encircling incisions made through the muscle down to the mucous membrane (82). Similarly, Gordon-Taylor et al (173) found no change in the motility of the human pars pylorica after circular gastric resection.

The mechanism producing conduction of the waves over the stomach is different from that in the bowel has been

indicated by a number of observations. For instance, Thomas and Kuntz (423), Cannon (81), and Alvarez (19) have found that the gastric waves keeping running after the giving of nicotine in amounts large enough to stop the intestinal rush waves.

The ability of the stomach to adapt itself to large amounts of food has been shown to be remarkable. When food enters the stomach, the organ expands sufficiently to accomodate the mass and maintains fairly steady tonic contractions on which are soon superimposed the peristaltic waves already described. This slow tonic contraction of the whole muscular wall which increases the intragastric pressure is probably the one of the most important factors in determining the gastric emptying time. It appears that this tonic type of contraction is independent of the caudally traveling waves. What really happens is that the stomach expands sufficiently to accomodate the mass without at the same time appreciably increasing the pressure exerted on it. According to Grutzner (20), as the stomach fills, the muscle fibers slip over one another so that there is little if any increase in intragastric pressure. Others have stated that the pressure rises up to a certain point and then falls or remains unchanged no matter how much is eaten (163). Grey (178) made measurements of the intragastric pressure when the stomach of the living animal is distended by fluid and observed that even when the organ was distended to the point of rupture, the intragastric pressure showed very little

change. The excised stomach was found to lose this adaptive power in considerable degree.

The stomach serves as a reservoir into which a large amount of food can be placed at once, or within a short period, there to be reduced to a liquid or semiliquid condition, partly by digestion, partly mechanically, and then periodically discharged into the intestine in small amounts. Evidently one important function of the stomach is to protect the intestine from receiving too large quantities of material at any one time. Grutzner (20) succesively fed to rats morsels of food of different colors. After a short period the animals were sacrificed, and the stomach frozen and sectioned. The colored materials were found to be in layers for which a simple explanation is at hand. Each swallowed bolus, when entering the stomach, tends to lodge in the center of the material already there, however, there is little tendency to stratification in the stomach of man (20). It is evident that the material at the fundic end may remain undisturbed for a long time and thus escape mixture with the acid gastric juice, so far at least as the interior of the mass is concerned. This explain the observation that salivary digestion of the starchy foods can proceed in the stomach for approximately half an hour after the food has been swallowed. As the outer layers of food are digested, the food is forced slowly into the more active pyloric antrum from which it soon is moved on to the pylorus and then into the small intestine. These phenoemna seen in experimental animals have been also observed in man. Studies have been made of the time required

for colored material, giving after the swallowing of a test meal, to appear in the pyloric region as revealed by removal through a stomach tube. Approximately twenty minutes were required. Furthermore, material removed from the cardiac end was lumpy whereas that from the pyloric end was semifluid and homogeneous in nature.

The gastric furrow or " magenstrasse " which runs from the cardia down one side of the lesser curvature and up the other, contracts when fluids are swallowed, and makes a furrow through which they can pass into the pyloric region as is the case in some of the herbivora. The longitudinally directed folds of mucous membrane along this furrow in man may suggest and represent a short path for fluids similar to that which is found in animals. This might be consistent with the condition as used to be reported in the literature that when small amounts of corrosive poisons are swallowed, most of the destruction of the mucous membrane takes place along the lesser curvature. According to McLanahan (290) however, the worst burns are found usually around the pylorus, but they may be anywhere. The same is true according to Alvarez's observation (20). The studies of Gianturco and others (164) have shown that when semifluid food is given to a man or woman who is standing, it can be seen with roentgen-rays that, although it tends to follow the lesser curvature for the first two or three inches, it then drops straight down to the bottom of the stomach. Furthermore, if fluids are given when the stomach is full of semisolid food, they

do not follow the gastric furrow, but make many small channels around the mass and down to the pylorus. The question of a " magenstrasse " is of some interest because it is usually claimed that the frequent appearance of ulcers and tumors along the lesser curvature is due largely to the greater traumatization of this pathway by hot and otherwise irritating foods. There may be something in this idea, but Cannon (83) however, has pointed out that the mucous membrane of the pars pylorica as the part of the stomach most likely to be traumatized. All of the trituration and mixing of food which gastric juice takes place in this short segment, and in it solid particles have to be pushed forward and backward for some time before they can get through the pylorus. The greatest objection to all these explanations for the site of predilection for peptic ulcer is that they fail to account for the fact that the commonest site is just below the pylorus, outside of the stomach.

In his studies of hundreds of students, Todd (430) noted that when a meal is swallowed, the gastric bubble is elevated together with the cupola of the diaphragm. He believed that he could see the stomach enlarge with the inflow of gastric juice. He found also that, as regards its tonus and its rhythmic activity, the stomach is less active and reliable in February than in October. This observation is of interest perhaps in connection with the tendency for symptoms of ulcer to flare up in the spring and fall. Todd also found that painful emotion and anxiety in students was associated with

hypotonus of the stomach. Depression mental conditions appeared to reduce the amplitude of the waves. Similar abnormalities of gastric activity were found in students who had recently donated blood for a transfusion or who were coming down with a cold. Girls showed a hypotonic stomach and weak waves after the first day of menstruation. Mental disquiet slowed the emptying of the stomach. Tenseness and apprehension in the roentgenoscopic room usually cause spasm of the pylorus which is hard to overcome by pressure of the hand over the stomach.

It is believed that in many instances the discomfort or distress which follows shortly after a meal has its origin in one or other of such nervous factors as those just mentioned. When food is taken while one is fatigued, anxious, agitated or hurried, disturbances of the normal motor mechanisms of the stomach give rise to unpleasant gastric sensations. The precise manner in which these are set up is not clear, but it is not unlikely that, in some instances at least, with the inhibition of the normal descending waves of peristalsis, reverse waves arise which lead to heartburn, belching and a feeling of discomfort. But whatever the mechanism, the relation of psychic factors to gastric symptoms is clearly evident. This so-called nervous dyspepsia is, to quote Alvarez (15) (16)

> " the disease of the mother who prepares the meal and then wrangles with children or husband at the table; it is disease of business men and women who gulp down some food at a counter and rush back to work; and it is the disease of the president of a luncheon club, or of the traveling sales-manager who gives pep talks at luncheons and dinners ".

As mentioned before there is a mechanism for adjusting the tonus of the gastric wall to the quantity of food taken, and some indigestion appears to be due often to eating so fast that this mechanism hasn't time to work. Consequently, as a result perhaps of abnormal tension in certain parts of the gastric wall, there is a dislocation of the pacemaker, with the production of abnormal and distressing types of waves. Occasionally, also, intracranial thrombosis in an aged person will injure the vagal center and produce such hyperirritability of the muscle of the stomach or such a failure in the fiber-slipping mechanism that the patient suffers from cramps everytime he or she eats or drinks. The fact that drinking even water will bring the distress shows that the essential stimulus is distention of the stomach. Another important point to remember is that in many persons subject to indigestion, drinking considerable amount of fluid, either on an empty stomach or with a meal, seems to dislocate the pacemaker and produce an uncomfortable type of gastric activity which can be avoided best by eating dry meals.

That the muscular activity of the stomach can be affected by food derivatives which have been absorbed into the blood was shown by Ivy and Farrell (146) (270) when they transplanted a pouch of the stomach into the abdominal wall of a dog and found that within five minutes after fats were put into the stomach, the movements of the transplanted gastric pouch were inhibited. They could show that this was not due to the absorbed fat itself since the effect was not abolished by draining the chyle to the exterior and so preventing absorbed fat

from entering the general circulation. In 1930, Kosaka and Lim (250) (251) noticed that a certain sample of cholecystokinin was contaminated with a substance that inhibited gastric secretion. From this they got the idea that they might be able to extract an inhibiting hormone from the intestinal mucosa after subjecting it to contact with fat. Actually their first attempt was successful, but later, Kosaka, Lim, Ling and Liu (252) found that the new hormone could be obtained from mucosa which had not been in contact with fat. In 1934 some steps in the purification of the substance were taken by Lim, Ling and Liu (269) (271) and it was given the name of enterogastrone. Later it was purified still further by Gray, Bradley and Ivy (174). This substance is free from depressor ( vasodilator ) activity, and does not contain secretin nor cholecystokinin. It is capable in maximal doses causing complete supression of gastric secretion for from one to five hours and of gastric motility for thirty minutes. It also inhibits the hunger contractions. Recently Ivy and his associates (175) have split it into two fractions: one which inhibits secretion and the other motility.

A substance known as urogastrone and having effects similar to enterogastrone upon gastric secretion and motility have been extracted from normal urine by Ivy, Gray and their associates (174) (175). Urogastrone was thought at first to be most probably excreted enterogastrone but certain differences have since been demonstrated which indicate that they are separate and distinct substances.

Crider and Thomas in 1938 (126) noted that ten to twenty c.c. of five per cent proteose obtained from the products of the protein digestion in the living animal, placed in the upper small intestine of dogs caused inhibition of the gastric tonus and peristalsis comparable to that caused by the commercial peptones (419). Acidity of the material used was found to be a minor factor unless it was more acid than pH 3.0. They found the peptones and proteose used had no inhibitory effect on the gastric peristalsis after double vagotomy in dogs and they concluded that the inhibitory effect is the result of a reflex dependent on the vagi and is, therefore, a manifestation of the enterogastric reflex. In another paper Thomas (418) used sixteen different amino acids to determine whether they caused gastric inhibition when placed in the small intestine of unanesthetized, fistula dogs. He found that only the monoamino-monocarboxy acids caused gastric inhibition regularly when administered in neutral solution. The inhibitory effect of these acids was roughly proportional to their molecular weights. The dicarboxy acids and the diamino acids caused gastric inhibition when administered as free acids without neutralization but were ineffective in neutral solution.

In 1916, Carlson (100) presented evidence indicating that the gastric motility may bear some reverse relation to the blood sugar level. Quigley et al (354) (353) (356) failed to modify the gastric motility in normal or vagotomized dogs by the intravenous administration of glucose. The spontaneous hypoglycemia occurring several hours after the glucose adminis-

tration was without constant effect on the motility of the stomach. On the other hand when glucose, cane sugar and lactose introduced directly into the stomach produced the gastric inhibition in the normal and vagotomized dogs. This inhibition was apparently not related to the production of hyperglycemia but appeared to be a reflex from the duodenum. Carbohydrates introduced into the duodenum lead to a similar gastric inhibition. This reflex is not mediated over the vagus fibers since it can occur in the vagotomized animals. It is probably induced through the medium of enterogastrone.

Cannon (83) found that under a number of conditions the presence of a certain amount of free acid on the gastric side of the pylorus tends to facilitate the departure of solid foods from the stomach. Quigley et al (359) used normal trained dogs and direct observational methods showed, however, that hydrochloric acid in the stomach exerts little or no physiological action on the motor activities and the pressure changes in the pyloric sphincter region or on the process of gastric evacuation. The presence of hydrochloric acid in the duodenum slows the emptying of the stomach. The acid does not weaken the waves traveling over the gastric wall.

According to Weitz and Vollers (20), sleep does not much change the gastric activity in man as it is recorded with two balloons. The reference regarding the influence of sleep is extremely rare in the literature.

The nature of the testmeal affected the appearance of the stomach was first noted by Todd (430). Milk and barium

produced a picture different from that seen with water and barium. He found also that the giving of sodium bicarbonate or peppermint temporarily halted gastric waves. After this only one or two waves at a time went over the stomach, and they were slow, deep, steady, and regular. This effect lasted about twenty minutes. These deep waves had little if any effect upon the expulsion of a fluid meal from the stomach. According to Klein (247), slight ether anesthesia does not have much effect on gastric activity.

Reviews of the gastric activity in infants were made by Carman (108) and Rogatz (373). The latter recognized two main types of infant stomach: one in which the viscus looks like a fairly long narrow pear, and the other in which it looks like a globe. Usually, after a liquid meal, the air bubble represented from a fourth to a third of the area of the gastric shadow in the roentgenograms. When Rogatz gave an infant thick gruel or mashed potato, the stomach always contracted and became more globular and the air bubble became small. This observation has clinical value because it offers an explanation for the fact that infants with congenital pyloric stenosis do better on semisolid than on liquid meals. Apparently, with the increase in tonus in the gastric musculature, the stomach is better able to push the food past the obstruction.

From the roentgenologic observation the infants have more trouble getting gas out. Perhaps because of the round-

ness of the baby's stomach, gas is more likely to be trapped at a distance from the cardia so that it can not be got rid of by belching. For this reason a baby should be placed in the upright position for a few minutes after each meal.

The emptying time of the infant's stomach is usually from one to four hours. Mother's milk, half milk, and malt soup leave comparatively early, while whole cow's milk and buttermilk leave rather late. Just as in adults, so in infants, small amounts of food leave more slowly than do large ones, and fats tend to slow the emptying of the stomach.

Gastric evacuation. It is well known that a large meal which distends and stimulates the stomach will generally leave faster than will a small one, and a second one will hurry the emptying of the first (268). Marbaix (20) found that 250 c.c. of water left his stomach much faster if he put 250 c.c. of air on top of it. The radiologists sometimes tell their patients to swallow some mouthfuls of air after the ingestion of barium mixture in order to hasten the gastric evacuation particularly in patients with some sort of pylorospasm. There is little doubt about the rapid emptying of carbohydrates as compared with proteins. It was shown by a number of investigators (77) (80) (192) (191) (457) (165). In a general way it was demonstrated by Beaumont even in 1833, when he found that St Martin could digest starches in from one to three hours and meats in from three to five hours. Cannon concluded that the carbohydrates leave promptly because, unable to combine with the acid, they allow it to appear early in a free state;

proteins, on the other hand, may leave late because they combine with acid and keep it from becoming free until gastric digestion has continued for an hour or two. This is an example to show a good explanation but another point might be counted in is that the food leaves about this time because much of it is becoming so liquid that it can be squirted through the sphincter.

The consistency of the food should, then, much to do with the rate at which it leaves the stomach; and theoratically, if the carbohydrates were difficult to liquify as meats, they should go out as slowly as meats. This may explain why raw white of egg, which is semiliquid, leaves the stomach promptly like water and not slowly like solid protein. When eggs are hard boiled they leave slowly. Actually much evidence indicates that main work of the stomach is accomplished when it has liquified its contents or at least turned them into a pap, and when this done, the material can go on into the duodenum no matter what its acidity. In support of this view is the fact that inert liquids generally run out of the stomach, when the stomach is empty, within a few minutes after they are ingested, and also that when carbohydrates are fed in the form of dry hard masses they leave much more slowly than when fed as gruel (192) (37). It is quite logical to make the conclusion that the consistency of the food, which determines the rate at which it becomes liquified in the stomach, is the big factor affecting the rate of gastric emptying. As soon as some of the material is liquified it squirted through the pylorus and the solids are left behind. Maile and Scott (299)

found that a concentrated carbohydrate such as sugar left the stomach much more quickly than more complicated carbohydrates such as banana and potato. Cooking shortened the digestive time for some foods and increased it for others. They observed the usual slowing of gastric emptying with fat. Using rats , Menville, Ane and Blackberg (313) found that starch, casein and cream all left the stomach about the same time. Gianturco (163) was able to confirm Cannon's result with different foods. By using the roentgenologic method he showed that the stronger the solution of an irritant, the longer the delay in the emptying time of the stomach. Solids leave more slowly than fluids, that fats and oils leave very slowly, and that gastro-enterostomy and pylorectomy have little effect on the rate of gastric emptying.

Food eating with pleasure is said to leave the stomach faster than when it is put in with a stomach tube (221) (166) apparently because of appetite there is a psychic increase in the tonus of the gastric muscle. However, Gianturco (165) could not confirm this. On the other hand, disgust, worry, and fear, which perhaps weaken gastric activity or tonus, will block for hours the emptying of the stomach. It is claimed (448) that the thirst of an animal has much to do with the rate at which fluids leave the stomach, and sham drinking will greatly speed up the process.

Distention of the duodenum by a balloon, by food, by strong saline solutions, or by mechanical irritation, will

retard emptying of the stomach (408). Four per cent solutions of sodium chloride and magnesium sulfate if put through a fistula into the upper part of the bowel ~~and~~ thereby will produce marked slowing of gastric emptying, with nausea and even vomiting. Shay and Gershon-Cohen (387) found that the farther down the intestine one applies a stimulus, the weaker the effect on gastric emptying. Acid placed even in the middle or lower third of the small bowel would slow the emptying of the stomach. It is doubtless this holding back effect of intestinal activity that keeps the food from pouring out of the stomach after a gastro-enterostomy or pyloric resection. According to Crider and Thomas (125) the stomach does not empty any faster when a tube is placed in the pylorus to keep it open.

The fats have a particular tendency to slow the emptying of the stomach when placed in the duodenum. According to Babkin (37), the latent period for the closing reflex is the same with fat as with acid, but the effect of the fat lasts longer. The fat reflex can be obtained from almost any part of the small bowel, but it becomes weaker the greater the distance between the pylorus and the point of stimulation. The fact that mineral oil has little if any effect on gastric emptying indicates that the action of fat is not due to its physical properties. All observers agree on this point (37) (297) (457) (163). Roberts showed a relation between the viscosity of various fats and the slowness with which they

leave the stomach, and he also found a relation between the chemical composition of a fat and the amount of gastric stasis produced (371).

McSwiney and Spurrell (297) thought that the fat exerted its inhibitory effect while still in thestomach, but most investigators were satisfied that the effect came from the jejunum and indicated that there was little effect from contact of the fat with the gastric mucosa (443) (360). According to most observers (357) (457) (324) (163), the delayed gastric emptying as caused by the fat is due to a weakening of the gastric muscle. The peristaltic waves are slowed and made shallow and that the tonus of the muscle is lowered. In accord with these changes, with fat in the duodenum, the intragastric pressure is lowered by three or four cm. of water. It seems that the effect on the pylorus is unimportant as was shown by Crider and Thomas (125) who demonstrated the slowing effect of fat in the case of animals with a tube holding open the pyloric canal. A number of observers have concluded that the muscle of the duodenum is also relaxed by fat. Some thought that the pylorus became more or less closed (443), while others thought it was relaxed as the rest of the gastric wall (357) (417). It is also believed that in man, much of the delay in emptying was due to a sort of sphincteric action by the muscle beyond the duodenal cap. In some cases the barium was held in the cap for an hour in spite of the observer's efforts to push it out. Waugh (443) using dogs

with a jejunal fistula and watch the stomach with roentgenoscope, he found that the skimmed milk put into the jejunum caused an average delay of 6.8 minutes in the first passage of material from stomach to duodenum. Then cream was placed in the jejunum, and immediately the gastric wall became atonic and the waves disappeared for periods ranging from thirty to ninty minutes. Gianturco observed with fat were long periods in which the gastric waves were shallow, followed by short periods of normal activity. Emptying occurred only during periods of activity.

There is no clear cut evidence to show which fraction of fat is held to be responsible for this inhibitory effect exerted upon the gastric musculature. Quigley, Zettleman and Ivy (360) found that the stomach was not inhibited by the intravenous injection of sodium oleate or glycerin. Gianturco (163) made some studies with roentgen-rays on cats and found that both fatty acids and glycerin had a slowing effect, but soap had little effect. Dickson and Wilson (132) who introduced one or two c.c. of bytyric, valerianic and caproic acid into the stomach of volunteers, saw an intensification of muscular activity with more rapid emptying. Acetic, malic, propionic, and lactic acids had no effect. Wilder and Schultz (456) found that a number of fatty acids had little effect on gastric activity in the dog.

In the old days people considered the possibility that free acid in the stomach opens the pylorus, but they saw that

the theory did not fit well with a number of facts. Later, the closing effect of acid on the duodenal side was demonstrated to the satisfaction of almost every one. The presence of a from 0.2 to 0.5 per cent solution of hydrochloride acid in the duodenum would slow the emptying of the stomach. The weak concentrations had little if any effect, and this is important because several workers (277) (42) noted that the material coming through the pylorus often contains no free acid. Consequently, Thomas and Crider (420) wondered if there is normally enough acid in the chyme to close the pylorus, and if the usual temporary inhibitions of emptying may not be simply due to the presence of any product of digestion in the duodenum. Thomas and Crider (419) and Crider and Thomas (126) thus concluded that, when it comes to the control of the pylorus, the products of protein digestion are more important than is hydrochloric acid. Strong concentrations up to one per cent of acid placed in the duodenum generally produced so much back pressure that vomiting followed (230). Interesting was the observation of that the preliminary cocainization of the duodenal mucosa would prevent the acid from slowing the emptying of the stomach. This indicates the existence of a nervous form of transmission, and this was also suggested by experiments in which the vagus or splanchnic nerves were cut (417) (358). One point should be pointed out here is that the so-called acid-reflex from the duodenum is not so easily demonstrable in anesthetized dogs. Perger (20), using a dog with a duo-

denal fistula, noted the length of time in which the stomach failed to empty after injecting into the duodenum 40 c.c. of decinormal solutions of several acids. Hydrochloric acid restrained all emptying for thirteen minutes, acetic acid for five minutes, and lactic acid for from ten to twenty minutes.

The fact noted by Morse (326), that tobasco sauce in water did not slow the emptying time of the stomach suggests that pepper is irritating only to taste-buds in the mouth and not to digestive mucous membranes in general.

Many workers have wondered if the inhibitory stimulus from the duodenum lowers the tonus of the gastric muscle, weakens the contractions, or closes the sphincters. Because deep waves continue to course over the stomach after food has passed into the duodenum and jejunum, Cannon (83) concluded that the main effect must be on the sphincter. Others felt that in addition there must be some weakening effect on the gastric activity because, after the pyloric ring has been resected, the placing of acid in the duodenum still retards the emptying of the stomach. Perhaps a better explanation as offered by Alvarez would be that the irritant causes so great an increase in intra-duodenal pressure that the stomach cannot empty.

Barsony and Egan (20) found that 15 c.c. of a 0.36 per cent hydrochloric acid put into the duodenum of a man depressed the tonus of the stomach and stopped the waves. Carlson

and Litt (106) found that any stimulus, acid or alkaline, in the duodenum would cause the pylorus to contract on a balloon in its lumen. Stimulation from the gastric side had no effect. Brunemeier and Carlson (69) found also that any stimulus from the duodenal mucosa depressed the tonus of the fasting stomach and stopped hunger contractions. According to Thomas (417), acid and other irritants placed in the duodenum caused first, contraction of the pylorus and then relaxation. The pars pylorica relaxed. Relaxation of the sphincter was seen only in unanesthetized animals with intact vagus nerves. The impression gained was that gastric evacuation is regulated more by changes in gastric motility than by changes in the tonus of the pyloric ring. In dogs, a decinormal solution of hydrochloric acid left the stomach very slowly in spite of the fact that the pylorus was not contracted. Mogan and Thomas (324) found that stimulation of the duodenum of anesthetized dogs produced marked contraction of the pylorus which lasted for from ten to fifteen minutes. In unanesthetized dogs, they found only a momentary contraction of the pylorus, followed by relaxation and then a quieting or complete inhibition of the gastric waves. As stimulants to the duodenum they used fats, water, dilute hydrochloric acid, solution of acid phosphate or sodium chloride, and normal gastric contents. The inhibiting effect was demonstrated more easily in the empty stomach. The threshold for the inhibition of the gastric waves was lower than for the contraction of the pyloric sphincter.

From what mentioned above, there was no doubt about the ability of hydrochloric acid to close the pyloric door behind it, but it was questionable if it could open the door ahead of it. When Cannon presented evidence indicating that acid in the stomach does open the door ahead of it, the theory of acid control of the pylorus was accepted. The following paragraph is quoted from Cannon's book, page 106, to see on what evidence he based his rule:

> " Moistening carbohydrates with $NaHCO_3$ retards their normal rapid exit from the stomach; feeding proteins as acid proteins remarkably hastens their normally slow exit; observations through a fistula in the vestibule show that an acid reaction closely precedes the initial passage of food through the pylorus, that the introduction of acid causes pyloric opening, and that delaying the acid reaction causes retention of the food in the stomach, in spite of strong peristalsis; and, when the stomach is excised and kept alive in oxygenated Ringer's solution, the pylorus is opened by acid on the gastric side ".

We must know that even Cannon himself as well as his predecessors had seen defects in the theory and some instances in which it would not work. Cannon saw that it did not explain the behavior of liquids, which run through the empty stomach without waiting to be acidified; he saw that it did not account for the rapid passage of white of egg, and it did not account for the slow emptying of fats. It failed also to explain some observation. It did not account for the rapid gastric emptying seen in cases of achlorhydria, the slow emptying in many cases of gastric ulcer, and the initial rapid emptying in cases of duodenal ulcer. Neither did it fit well with the fact that the stomach continues to

empty intermittently and almost normally after pylorectomy (86) (234) (150). One would hardly expect so intricate a mechanism to work well after the removal of its most important part. Unfortunately, also, when experimenters attempted to demonstrate the acid control of the pylorus from the gastric side they failed.

The effect of giving acidified or alkalinized food should be mentioned here. Nearly all workers agree that fluids tend to leave the stomach immediately unless their reaction is remarkably acid or alkaline, the same is true on the other side beyond the pylorus. As one would expect from what is now known about the refusal of the bowel to accept any irritant material coming from the stomach, almost every one has found that entrance of strong solutions of acid into the duodenum delays gastric evacuation until the irritant has been largely neutralized (192) (42) (407) (326). As one would expect also, strong solutions of alkalies are just as effective in retarding gastric emptying as are strong solutions of acid (407) (106). The idea of an acid control of the pylorus is dependent to some extent on the belief that the duodenal contents are normally alkaline and that this alkalinity is upset for a moment by the arrival of acid contents from the stomach. It was disturbing, therefore, when many research workers found that the duodenal contents are not so alkaline as they were formerly assumed to be. In man, the hydrogen-ion concentration seems to range from pH 3.0 to pH 8.0, with the average usually on the acid side (322) (303)

(298) (16) (237). For the small bowel of man, Miller and Abbott (322) obtained figures between 6.6 and 7.3. Mann and Bollman (303), using dogs, found usually a slightly alkaline juice with a pH between 7.0 and 8.0, but the reaction often was acid for a while after a meal specially if the gastric contents were highly acid. According to McWhorter (298) the pH of pure gastric juice ranges between 1.0 and 1.5 and that of ordinary gastric contents ranges around 2.1.

Because the rate of disappearance of acid in the duodenum should be an important factor in gastric emptying, it is interesting that Ivy (227) found that a segment of duodenum or jejunum 35 cm. long can, in an hour, neutralize half of the free acid in 150 c.c. of N/10 hydrochloric acid.

The osmotic pressure also plays an important role in the gastric emptying. There is much evidence to show that just as the stomach protects the bowel from irritating by too great a concentration of acid or alkali, so it will protect it from insult by fluids with too great an osmotic pressure. The physiological salt solution leaves the stomach a little faster than water, and sodium chloride and glucose can act in the duodenum much as acids do, keeping the pylorus closed until the osmotic pressure of the gastric contents is brought nearly to that of the tissues. Isotonis solutions ran out rapidly, hypotonic ones more slowly, and hypertonic ones still more slowly. There was also a specific effect from the substance used because isotonic solutions of glucose left the stomach more slowly than did isotonic solutions of

sodium chloride. McSwiney and Spurrell (295) found that hypertonic meals produced a delay in gastric emptying in proportion to the degree of the hypertonicity. Hypotonic meals left the stomach more rapidly than did the isotonic ones. Using the roentgenologic technic, they came to the conclusion that the osmotic pressure of a liquid suspension of a foodstuff is of more importance in determining the rate of passage through the pylorus than is the nature of the food. Karr and Abbott (237) found that, in man, an isotonic solution of sodium bicarbonate left the stomach rapidly; a strong five per cent solution left more slowly. Apperley (36) also came to the conclusion that the osmotic pressure of the gastric contents must be brought nearly to that of the tissue fluids before material can leave the stomach. That the osmotic pressure does not have to be brought exactly to normal is shown by the fact that water can pour out of the stomach rapidly. The opinion against the importance of these observations might seem to be the tendency for water to run rapidly out of the stomach, but one must always ~~to~~ distinguish between what happens with the first few swallows on an empty stomach and what happens when fluids are taken on top of a meal. The holding back effect from the bowel cannot be expected to appear until some material has been in contact with the mucosa for a while. At the beginning of a meal there is nothing in the bowel to serve as a stimulus to keep the pylorus closed. For this reason it would be a good policy in the fluoroscopic room to instruct persons with a so-called

dumping stomach, as after gastro-enterostomy or partial gastrectomy, to begin the meal with a little solid food like toast which will go a little way into the jejunum and there serve to hold back more food put into the stomach. Usually this helps the patient to avoid the unpleasant effects of a too rapid progress of unwarmed, unneutralized and undigested liquid material through the jejunum. Some can help themselves also by lying down for a while after a meal, and others are helped by avoiding sugar. Sugar probably irritates the bowel because of its dehydrating effect.

The gastric emptying can be delayed due to an upset in the balance between the intragastric and intraduodenal pressures. Now that it is known that the stomach can empty almost normally after pylorectomy or gastro-enterostomy. When material moves from the stomach into the duodenum it must be because the pressure in the stomach became greater than that in the duodenum. Similarly, when duodenal contents regurgitate into the stomach it must be because the intraduodenal pressure has become greater than the intragastric, and when, so often happens, the roentgenologist sees deep and active gastric waves, an open pylorus, and no material leaving the stomach, he must assume that the pressures in the stomach and duodenum are equal. It is the roentgenologist's common experience that in cases of so-called gastric stasis often the pylorus seemed actually to be relaxed, and the least pressure applied to the stomach by the hand caused the barium meal to run out of the stomach on into the duodenum.

Especially when the waves in the stomach appeared to be normal, it made one ~~to~~ think that there was not enough excess of pressure in the stomach, as compared with that in the duodenum, to force the food onward. Schmidt (20) described his experiments and found that the waves traveling down the stomach do not change the intragastric pressure. At intervals, the pressure in the stomach as a whole rose by little steps until it was from 4 to 8 cm. of water higher than normal. Then the stomach began to empty. At times each step-like increase in pressure was associated with the passage of a wave over the stomach. From this it seems that the stomach empties much as does the urinary bladder because the internal pressure has increased and the sphincter has relaxed.

Gianturco (165) increased intragastric pressure in cats by removing most of the fundus and the greater curvature side of the body of the stomach, and found as he expected, that this increased intragastric pressure has brought about a more rapid emptying of the organ. Spurrell's experiments on cats (250) also showed how much gastric emptying depends on the difference between the pressures in the stomach and duodenum. The upset of the pressure balance can also be shown by the experiments of Kreidl and Muller (20) who produced gastric stasis in dogs by removing the muscle from the wall of the stomach. Connell (122) removed from eight dogs the fundus and much of the body of the stomach on the greater curvature side. After eight weeks the emptying time appeared to be slightly shortened. The stomach gradually increased

in size after the operation and in about six weeks regained most of its original capacity. In three weeks the acidity was back to normal. It is assumed that after these operations the tonus and activity of the stomach are somewhat increased since any increase in the tonus and activity of the stomach tends to hasten its emptying. Studying men and women with the roentgen-rays, Shay and Gershon-Cohen (387) came to the same conclusion that the tonus of the gastric muscle is important in producing gastric emptying.

A good proof of the fact that the essential factor in the production of gastric emptying is an increase in intragastric pressure as compared with the intraduodenal pressure is to be found in Crider and Thomas' observation (125) that the stomach empties no differently when a mechanical device is fitted into the pylorus to keep it open.

Ulceration in the pars pylorica tends to produce hypertrophy of the pylorus. Ulcer on the duodenal side does not ordinarily produce such hypertrophy. The initial rapid emptying seen in some cases of duodenal ulcer is due probably to the marked increase in the tonus of the muscle lining the stomach. Later, when most of the food has left and the stomach has lost this stimulus to contraction, the spasm at the sphincter produced by the ulcer, or the hypertonicity of the inflamed duodenum is likely to delay the egress of what material remains in the stomach.

It has been shown by a number of workers that, as one might expect, the stomach emptying time is more rapid when

a man lies on his right side (331)

The influence of heat and cold has been studied by many workers, all of whom agree that there is not much difference between the rates of egress of warm and cold fluids but the warm ones probably go out a little faster (37) (192). A few claimed that hot or cold fluids are held back for a while until their temperature is brought nearly to that of the body. The differences observed by Neilson and Lipsitz (331) were not striking. So far as animal experiments go, there seems to be no justification for the way in which many surgeons deprive their patients of cold water.

Kasabach (238), Neilson and Lipsitz (331), and others found that exercise seems to accerlerate the emptying time of the stomach. The stomach appears to empty somewhat more slowly in women than in men.

Using cats, Gianturco (165) found that anesthesia of various types quieted gastric activity and greatly lengthened the emptying time of the stomach. Emptying is likely to be delayed for as long as two days by trauma to the bowel such as occurred in many operations. Atropine is commonly used by phycisians to relax the pylorus, Cerqua (113) found that, in dogs, large doses produced spasm of both pylorus and fundus, and Herrin (201) found that it delayed evacuation of the human stomach.

The nervous influences also play an important role in gastric evacuation. Anxiety, fear, discomfort, pain, disgust,

or uneasiness and excitement would close the pylorus for some time and the emptying time is slowed down, and it is not uncommon that complete stoppage of digestion may occur. Minor degree of this sort of thing are seen by the roentgenologist when patients are particularly apprehensive about the examination; and many of the functional disturbances of digestion are almost certainly due to these psychic inhibitions of all the functions of the stomach. This has been discussed before.

Hunger contractions. In 1912 Cannon and Washburn (90) showed that there is a relationship between the contractions of the balloon filled stomach and the pangs of hunger. These hunger contractions apparently travel down the stomach much as do the normal waves, but there are some differences between the two types of activity. The hunger contractions tend to come in groups, with fairly quiet intervals in between. In 1912, Carlson began the long series of studies that threw light on almost every phase of the hunger mechanism (100). According to Carlson when a recording balloon on the end of a tube is put into the stomach of a fasting man, the tracings made on the kymographic drum will generally show alternating periods of quiet and activity. After a period of rest, which may last for from $1\frac{1}{2}$ to $2\frac{1}{2}$ hours, the first contractions probably will appear at intervals from two to five minutes; these intervals then shorten, the contractions become more powerful, and finally there may be short periods in which the stomach remains contracted. In a strong built man, the cycle of activity usually lasts from thirty to thirty-five

minutes. According to Carlson the hunger contractions move down from cardia to pylorus. They resemble the waves of the digestive period, and the digestion contractions of the filled stomach pass gradually over into the hunger contractions of the empty stomach. In 1919 (100) Carlson presented evidence indicating that gastric hunger motility may bear an inverse relation to the blood sugar level. In 1924, Carlson and Bulatao (104) reported that the intravenous injection of glucose to the normal dogs was followed by a marked gastric inhibition, while the insulin hypoglycemia was associated with gastric motor augmentation. In 1928, on the contrary, Stucky and Cowgill (410) under the conditions of their experiments to study the effect of insulin on gastric motility in vitamin B deficiency showed that there was no direct relationship between the blood sugar level and the gastric motility. Quigley and Hallaran in 1932 (354) presented a paper and obtained experimental evidence which was not in agreement with Carlson's theory. They failed to modify the gastric motility either in the normal or vagotomized dogs by the intravenous administration of glucose solution. Such injections were also without effect on the motility of the terminal ileum or colon. The spontaneous hypoglycemia occurring several hours after the glucose administration was without constant effect on the motility of the stomach, ileum or colon. They used glucose, cane sugar, and lactose, introduced into the empty stomach, produced the gastric inhibition both in normal and vagotomized dogs. This inhibition as pointed out by them,

was apparently not related to the production of hypoglycemia, but appeared to be a reflex from the duodenum, and such reflex probably is not mediated over the vagus fibers since it can occur in vagotomized animals. More work is needed to review this theory. Todd (430) concluded from experiments in which he gave only a few mouthfuls of barium containing food that there is always a wave-like activity in the empty stomach which is made visible when the first mouthful of food enters the stomach. His view was that after the stomach is markedly distended, this activity ceases, and later a new type starts up. Martin and Rogers (304) made roentgenograms of an intragastric balloon during the progress of hunger contractions and observed deep contractions only in the pars pylorica. These contractions moved caudad a short distance and, at the same time, there was often some shortening of the whole gastric shadow. As is well shown, one of the most characteristic features of hunger contractions is the way in which they are inhibited by the taking of food or alkalies; according to Rogers and Hardt (374), they are more susceptible to inhibiting influences than are the digestive waves. It should be pointed out that the recording balloon placed in the stomach serves to bring out and make visible the hunger contractions. When one studies under the roentgenoscope the really empty stomach of a cat, with the outlines marked by lead shot placed under the serous coat, one cannot see any contractions or waves. Contractions are sometimes present, but they are so shallow that they can be detected only by taking roentgen

motion pictures and then measuring and plotting the distances between the markers in successive frames. Only when a little air has been swallowed or when a balloon has been inserted, do the tiny contractions deepen enough to make visible to the unaided eye. For this reason, McSwiney and Spurrell (296) after outlining the stomach with silver sutures, also found waves going over the fasting stomach of the dog. That there is some activity of the fasting human stomach which does not contain a balloon was indicated by the work of Templeton and Johnson (414), when they obtained records of the pressure in the usual gas-bubble by passing a tube down to the cardia.

Carlson found in one patient who had a fistula in the stomach that sugar, quinine, sodium chloride, or weak solutions of acetic acid or hydrochloric acid put into the mouth caused a prompt inhibition of the tonus and activity of the empty stomach. The chewing of indifferent substances had only a slight depressing effect on the movements of the empty stomach. The chewing of tasting palatable foods had a stronger inhibiting effect. When the stomach was strongly contracted, swallowing movements seemed to have no effect on the tonus of the muscle.

The contractions are not always inhibited by the presence of food metabolites in the blood because they start up sometimes when absorption is still taking place from the bowel. Emptiness of the stomach, alone, will not always bring on hunger pain, as can be shown by washing out the gastric contents during the course of digestion. The pains are inhi-

bited for some time after giving water, dilute hydrochloric acid, alkalies and food, but they are only slightly affected by the presence of air or carbon dioxide. They are inhibited also if some gastric juice or dilute hydrochloric acid is introduced into the bowel. These long distance effect persist after the section of the vagus and splanchnic nerves, but the latent period is longer, the degree of inhibition is less, and the effects are more transient. The same observations have been made in the case of other inhibitions of the digestive tract, all suggesting that the usual pathway is along nerves in the mesentery, and that when these are gone, the impulses must travel slowly through Auerbach's Plexus. Smoking will cause some inhibition of the hunger contractions. Tightening of the belts, contrary to what one might expect from popular belief, does not inhibit the hunger contractions. The effects of a number of drugs on the mechanism have been studied (167), the bitters commonly used in medicine with the idea of increasing appetite have no effect on the hunger contractions except perhaps a depressant one. These two things, appetite and hunger contractions do not go together all the time. The hunger contractions may disappear entirely during the course of infections, such as common colds.

Vomiting is a complicated act which can be started in a number of ways and from many parts of the bowel. As is well known, in most persons vomiting can be induced by stimulating the pharynx with the finger. Another efficient trigger zone seems to be located in the semicircular canals

of the inner ear, and another is the duodenum. Vomiting can be induced by pressure on the brain, by irritation of the common bile duct, and by distention or irritation of any part of the bowel or of the genito-urinary tract. Curious is the observation of Franklin and McLachlin (155) that in the cat, ligation of the mesentery vein produces vomiting while ligation of the splenic vein does not. The suggestion was made that in some cases of unexplained vomiting, the cause might be spasm in the mesentery vein. Influences from the bowel are more effective in producing emesis than are influences from the stomach. This is suggested not only from animal experimentation but by the fact that vomiting is often absent in cases of gastric ulcer and carcinoma without obstruction, while it is often severe with acute appendicitis and intestinal obstruction.

Regurgitation of material from the esophagus in the case of cats in which the abdomen had been so widely opened that not the slightest pressure could be exerted on the stomach by voluntary muscles; but, as Hatcher (189) pointed out, the stomach of such animals does not entirely empty itself, and one should speak more of a regurgitation from the esophagus and the upper end of the stomach. It is noted also that curarized animals, which can not vomit on account of the paralysis of the abdominal muscles, will regurgitate if given certain emetics.

Magendie was one of the first to show that vomiting can take place in the absence of the stomach. He substituted

for it a pig's bladder. Far more striking, however, is the remarkable experiment of Eggleston and Hatcher (140) who in some dogs removed the whole digestive tract, from cardia to anus, and showed that typical retching, with some regurgitation from the esophagus, could still take place. Mann (20) showed that dogs from which he has removed every bit of stomach vomit if given coarse food, and Hartman found that a man could vomit from total gastrectomy.

Gold and Hatcher (168) found that retching consists of a series of spasmodic and abortive respiratory movements with the glottis closed, during which an inspiratory effort of the chest muscles and diaphragm occurred simultaneously with an expiratory contraction of the abdominal muscles. Although the diaphragm moves downward violently with each retching movement, it remains in a low position throughout the period of vomiting. Barclay made the same observation (46). The more nearly empty the stomach is, the greater the amount of retching required to empty it entirely. A number of observers have observed the stomach of men and women during vomiting and have seen abnormal contractions similar to those seen in animals. Rarely was there any reverse peristalsis. A striking picture on the fluoroscopic screen is the jerking of the stomach brought about during retching by the contraction of the abdominal muscles. Inregard to the cardia, Openchowski came to the conclusion that it is relaxed reflexly by stimuli coming from any one of the numerous parts of the body from which vomiting can be started, and recently many of his view

have been confirmed by Carlson and Hatcher. The esophagus helps in vomiting by moving orad material that it receives from the stomach. Its activity is not essential, however, because animals will continue to vomit after the esophagus has been replaced by a glass tube.

It is claimed that there is a vomiting center in the medulla oblongata in which the afferent impulses are received and through which a coordinated series of efferent impulses is sent out to the various muscles, however, this has not been satisfactorily determined. According to Hatcher the vagus is probably the most important path for afferent emetic impulses, because Miller (317) has shown that its destruction interferes with the production of vomiting more than does the cutting of the splanchnics. Vagotomy, for instance, interferes also with the production of the deep respiratory movements and salivation that precede the act of retching. Cutting the vagi may make vomiting more difficult also because then the cardia may not relax properly. Walton, Moore and Graham (437) found that, to stop vomiting in experimental peritonitis, they had to cut both the vagus and splanchnic nerves. Because these nerves are sopposed to supply only the visceral peritoneum, the inference was drawn that it is the only irritation of this part of the peritoneum that produces vomiting. Herrin and Meek (470) found that when Thiry Vella loops in dogs were distended, the animal became nauseated and depressed and occasionally began to retch or vomit. If the pressure was maintained, the animal refused to eat

and went on downhill and died. When, however, the loop was denervated, the animal stood the distention indefinitely without symptoms of intestinal obstruction. Obviously, then, some or all of the nausea and vomiting associated with disturbances in the bowel is produced by stimuli which travel along nerves to the brain.

Nervous control on gastro-intestinal motility. Before review the nervous behavior of the gastro-intestinal tract, one must bear in mind that, apart from species differences, which are considerable, the effects of the sympathetic and parasympathetic excitation vary according to the physiological state of the tissue at the time of experiment. Thus in the cat, the effect of vagal stimulation on the stomach is increased peristalsis if the tonus of the organ is low at the time of stimulation and relaxation (294). Obviously every reaction of an organism or of its parts, to a new stimulus, is superimposed upon a fluctuating base line of activity, which is a reflection of the organism's response to an ever changing environment. If these fluctuations are small in comparison to the artificially produced response, as they are in skeletal muscle, then the relation of the experimental observations to the particular stimulus can be more readily elicited. If, however, as in smooth muscle, the experimentally produced responses are superimposed upon a widely fluctuating base line, interpretation is considerably more difficult, and always impossible. Furthermore, many nerves contain both motor and inhibitory fibers to the same organ. The effect

of stimulation of the hypogastric nerve in the monkey, for example, is an initial excitation followed by a period of inhibition of all activity, and the two responses can be separated by nicotine, which in suitable doses blocks the excitatory response but leaves the inhibitory phase intact (393). With these qualifications, and bearing in mind that autonomic regulation in the intact animal takes place through reflex mechanism, dependent upon afferent stimulation and integration at higher levels of the central nervous system, we can review the effects of nerve excitation and section in the gastrointestinal tract.

Both splanchnic and vagal nerves contain motor and inhibitory fibers and the effect of nerve stimulation varies according to the physiological state of the organ at the time of experiment. Broadly speaking, however, during sympathetic activity, tonus and peristalsis are reduced and the sphincters closed throughout the entire gut. Digestive juices are generally reduced and mucous secretion abundant. Babkin et al (39) showed that ~~by~~ stimulation of the cervical sympathetic trunk, however, produces a slight flow of thick saliva, and splanchnic stimulation causes some external secretion of the pancrea. The processes of digestion are thereby inhibited and the emptying time greatly prolonged. Stimulation of any afferent nerve, e.g., the central end of the sciatic, produces reflex inhibition of gastric and intestinal motility. Injury, particularly to the head, is frequently followed two to three days later by vomiting of undigested food partaken just before

the accident. Parasympathetic activity, on the other hand, promotes digestion and aids in the passage of the food through the gut. Peristalsis is increased, the sphincters relaxed and the production of digestive juices, including salivary and pancreatic, is stimulated. Digestion, however, can proceed adequately following bilateral section of the vagi at the level of the diaphragm and bilateral section of the splanchnic nerves, and the preoperative tonus and peristaltic activity are soon re-established.

Wolf and Wolff (461) have recently made important studies in this connection on a patient with a large gastric fistula. Hyperemia of the gastric mucosa accompanied increased motor activity and secretion. Such a state, manifesting parasympathetic activity, accompanied intake of food and periods of emotional stress characterized by supressed resentment and agression. If the emotion is accentuated small hemorrhagic erosion of the mucosa appeared. Pallor of the mucosa, decreased gastric motility and secretion occurred at other times, more particularly when the patient was in a psychological state of fear and the sympathetic system apparently dominant.

The relation of the hypothalamus to the gut has been little studied until 1932 when Cushing published his Balfour lecture on peptic ulcer and the midbrain (129), in which he attributed the severe gastro-intestinal disturbances which often follow surgical procedures involving the base of the brain to hypothalamic injury. Inhibition of gut motility by hypothalamic stimulation was mentioned by Karplus and

Kreidl in 1910 (158). Evidence for a hypothalamic center for gastric movements has been obtained by Beattie and Sheehan in 1934 ( ). Beattie and Sheehan under the stimulus of Cushing's work, found in fasting cats under chloralose anesthesia that stimulation of tuber region caused increased intragastric pressure and augmented peristaltic movements of the stomach, the effect being abolished by vagal section; whereas excitation of the posterior hypothalamus caused a fall of intragastric pressure and complete obliteration of all gastric motility. This has been confirmed by Masserman and Haetig (305) and many others (391).

The effects of hypothalamic lesions upon the gastro-intestinal tract did not draw enough attention until in recent time, thus, following diencephalic lesions in a series of 17 monkeys, profound gastro-intestinal disturbances were encountered, accompanied by gastric and duodenal erosions, bleeding and, in two instances, perforation of the stomach (442). In another series of 16 monkeys with more restricted hypothalamic injury, five showed multiple hemorrhagic foci in the gastric mucosa, and in all five the lesion was restricted to the tuber nuclei (211). In a series of several hundred control observations, with the lesions elsewhere in the nervous system of monkeys, few corresponding gastric disturbances were encountered, except occasionally following simultaneous bilateral removal of the motor and premotor areas of the cerebral cortex (245). Keller and D'Amour (244) found corresponding gastric disturbances in dogs following tuber lesions. If the dogs are previously

sympathectomized, the hemorrhagic lesions of the mucosa fail to occur, but ulcers with crater formation were encountered. Keller (242) (243) is, therefore, of the opinion that hemorrhage from the mucosa depends on the integrity of the sympathetic system and that ulcer formation occurs only when the parasympathetic ( vagi ) are intact. Death from acute gastric hemorrhage has occurred in a young and healthy chimpanzee following hypophysectomy and presumed injury to the hypothalamus (306).

Influence from the cerebral cortex is also important on gastro-intestinal motility. It is a fact that epileptic seizures caused by the lesions located at cortical levels frequently begin with a gastro-intestinal aura, i.e., with gastric sensory impressions and motor action of the stomach and intestines. Experimental analysis of the problem began with Bochefontaine in 1876 (159) as he observed that electrical stimulation of the dog's sigmoid gyrus caused contraction of the stomach, specially near the pylorus, but the pyloric sphincter itself was relaxed and there was usually increase in peristaltic movements of the small intestine and colon. The observation was confirmed by Hlasko and Bechterew. With dogs under curare Bechterew observed that faradization: a, of the anterior part of the sigmoid gyrus caused slowing of the rhythmic pyloric movements of the stomach with increase in general contractions of the walls; b, of the posterior part of the sigmoid gyrus gave active rhythmic movements of

the pylorus; c, and occasionally from the region just lateral to the two areas there were primary movements of the cardia. Bechterew concluded that the cortex contained centers for excitation and inhibition both of the pylorus and stomach walls, possibly also of the cardia. He also obtained increased peristaltic movements of the small intestine with similar stimulation (159). May (307) failed to confirm many of these observations and attributed the effect to the escape of stimulating current, the work accordingly was largely put aside.

Cushing's (129) emphasis upon the relation of cerebral trauma to the gastro-intestinal tract has caused the problem to be studied afresh. Watts and Fulton (442) observed changes in intestinal movement of monkeys under light ether anesthesia on stimulating various parts of the prontal lobes, the more excitable foci being in area 6. Sheehan (389) described marked inhibition in peristaltic movements of recently-fed monkeys when area 6 was stimulated, but there was little response of a definite character from the quiescent unfed stomach; from stimulation of area 13 much more conspicuous inhibiting effects can be obtained on the gastric musculature (41). There is also enough evidence indicating that frontal lobe lesions, specially when bilaterally located, cause disturbances of motility and possibly also of secretion of the gastro-intestinal tract. Watts and Fulton (442) have described three instances in which monkeys developed acute intussusception with fatal obstruction following bilateral ablations of the

frontal lobes or its parts. When intussusception does not occur, such animals are prone tobecome voraciously hungry, eating an abnormal quantity of food, and sometimes passing undigested food in their feces. The gastro-intestinal movements were studied by roentgen-rays and by measurement of the rate of transit of carmin before and after bilateral ablation of the frontal association areas, indicate that the motility is moderately increased following such lesions. The effects, however, tend to pass off with time. Evidence of this morbid hunger is more marked in animals with premotor ablation than in those with ablations restricted to areas 9, 10, 11, and 12 (203).

Bilateral ablation of the frontal lobes caused marked hyperactivity of the stomach, sometimes accompanied by pyloric spasm, lasting several days after the procedure. Complete removal of one or both cerebral hemispheres was followed by similar but more intense disturbance of motility. Ablations of the occipital lobes, even if bilateral, caused no appreciable change in gastro-intestinal movements. In some animals, erosions of gastric mucosa were noted at autopsy. Mettler and his associates (316) conclude that ulceration is only one phase of a much more extensive disturbance of the gastro-intestinal tract due to autonomic imbalance.

The clinical implications of these and earlier studies have been discussed by Watts and Frazier (441). The gastro-intestinal aura, which occurs in cases of localized epilepsy

coincides with vigorous and abnormal gastro-intestinal movements; they are initiated locally in the cortex by the irritating agent responsible for the subsequent epileptic seizures. The existence within the cerebral cortex of gastro-intestinal representation thus gives a rational basis not only for the gastro-intestinal aura of epilepsy, but also for the large number of gastro-intestinal disturbances known to accompany states of anxiety, unusual mental activity, etc. Little is yet known concerning the influence of the cortex on gastro-intestinal secretion, but it may pointed out that the psychic flow of gastric juice studied for so many years by Pavlov (339) depends upon the integrity of the cerebral cortex. Conditioned reflex salivation also depends upon the cortex, probably upon area $6_a$.

One of the cases of morbid hunger referred to by Bechterew was quoted sporadically in the literature. It was a child who suffered a depressed fracture in the midfrontal region from the kick of a horse. When the child recovered consciousness, he cried constantly that he wanted more food. The splinters of bone which compressed the frontal lobe were removed surgically and four days thereafter the symptoms of abnormal hunger ceased. Another case from Paget's series (337), was that of a young woman 24 years old who was knocked down and fell striking her head on a step; she had concussion with vomiting followed by fever which lasted about a week. She then began to have a voracious appetite so that she would

not leave the house even to go a short distance without taking a supply of food in her pocket. The abnormal hunger lasted for about three months, varying from time to time in its intensity. This pathological hunger is also encountered in Pick's disease in which bilateral degeneration of the frontal lobes occurs. The voracious hunger of certain idiots and general paretics is also well recognized in psychiatric institutions and schizophrenics are likely to pass through a period of polyphagia some time in the course of their disease. Unfortunately the gastro-intestinal motility of these cases has not been studied. P.Levin (266) reports increased gastro-intestinal motility in a group of children with cortical diplegia who also showed morbid hunger. M.Levin (265) has described an interesting new syndrome of periodic somnolence and morbid hunger due possibly to cortico-hypothalamic derangement. It seems probable that involvement of the orbital surface of the frontal lobe is responsible for morbid hunger.

## THE MOTILITY OF THE SMALL INTESTINE

The most important part of the digestive tract is the small bowel. It is the organ of digestion, and most of the symptoms of indigestion appear to arise in abnormalities in the motor functions of this tube.

Four types of muscular movements are usually described as occurring in the small intestine: namely, peristalsis, rhythmic segmentations, pendular movements and movements of the intestinal villi.

Peristalsis. The peristaltic movements when they first start, is a slow gentle wave which moves sluggishly along the bowel at the rate of from two to four cm. per second, but they travel faster the farther they go, so that by the time they reach the lower ileum, they are often covering from 7 to 25 cm. a second. This swiftly moving peristaltic wave appears from time to time and moving down the bowel for longer or shorter distances, sweeping all food before it and then disappears. The food is left for a later wave to carry it further and is thus conveyed along the bowel in relays. This type of movement is spoken of as the "peristaltic rush." The length of bowel traversed by any wave varies with the general state of activity of the bowel at the time and with the strength of the stimulus. After a strong cathartic or as the result of some intense stimulation of the gastro-intestinal tract as by an irritant poison, the wave may sweep with great rapidity from pylorus to anus, com-

pleting the entire journey in a few minutes. In rabbits suffering from diarrhea, an occasional rush is seen run from pharynx to anus (20), and there is no doubt, in man, the same phenomenon occurs. Particularly in cases of diarrhea in children or nervous women, a few swallows of food or water are commonly followed by a series of gurgling sounds through the bowel and then a call to defecation.

Experiments made upon animals (26) show that a rush may be initiated by conditions within the stomach or even by an act of swallowing and one of the most effective means of producing such a movement in the intestine is to have the animal drink, or simply squirt some water or Locke's solution into the duodenum if the abdomen is opened under warm saline solution (20). In some instances the rush is evidently started by the passage of material through the pyloric region into the duodenum, but in many instances a peristaltic wave of the stomach does not reach the pylorus before a rush commences in the duodenum. Such facts indicate that the mechanism is essentially reflex in nature.

Swallowing movements alone are not likely to be so effective in starting rushes as is the swallowing of food or fluid (124). In rabbits, the presence of fluid in the bowel is very helpful in producing rush waves. Alvarez (26) squirted water into the first segment of duodenum but kept it from going on down by placing a band of tape around the gut 25 cm. distal to the oral end, found it was hard to start a rush. Similarly, electrical or mechanical stimulation of the duodenum was less effective

than quick distension by fluid. At times, after the duodenum has been segmenting actively for a while, it seems to become highly irritable, so that the slightest stimulus will be enough to start a rush. After that, for a while, the bowel will seem to be fatigued or refractory, so that rushes can not be started.

Rushes can begin anywhere in the bowel. What usually happened is that the tonus of the segment rises, and the amplitude of its rhythmic contractions increases; the material within is thrown backward and forward more and more forcibly by the two ends of the segments, and from time to time it looks as if any minute it would succeed in emptying itself. Eventually the segment either succeeds in emptying itself caudad or else it tives up and quiets down. Commonly a ripple or a rush will come down from the stomach to upset the balance, or the balance may be disturbed sufficiently by the emptying of a segment lower down, or by movements of defecation.

Most of the rush waves in the rabbit's small intestine stop in the lower ileum, but some go on down the colon. When the wave stops in the lower ileum it either fades out in this sluggish region or else is blocked by powerful contractions, or perhaps by a marked rise of tonus in some segment. Occasionally a rush strikes the closed ileocecal sphincter and is reflected and caused to run back up the bowel for some 20 or 30 cm. It is not difficult to understand that one of the most important functions of the ileocecal sphincter and of the thickened muscle in the bowel just orad to it is probably to stop the rushes. It is fortunate for us human beings that so many of the waves

are thus stopped, because otherwise we might suffer with diarrhea.

Liquids will run long distances through the small bowel without the help of any peristaltic contraction (26) (17). Unfortunately this mechanism fails when there is much gas present to distend and kink the bowel, as in cases of paralytic ileus.

Carey mentioned (95) (96) (97) (98) that the longitudinal and circular muscles of the small intestine are arranged in a spiral manner and bolus moves in a counter-clockwise spiral path as viewed from the cephalad end in an excised intestinal loop. Reid, Ivy and Quigley confirmed Carey's work and similar conclusion has been reached from roentgenologic studies (368). Quigley and associates have shown that a bolus is propelled along the bowel in a spiral fashion (355) (368). They inserted a bolus of cotton to which two long threads of different colors were attached and found that the rotation occurred in an anticlockwise direction. The length of bowel traversed in making a full rotation - 360° - was from 23 to 35 cm. The bolus was propelled along the intestine at an average rate of 9 cm. in 8 or 9 minutes at the ileal region.

Antiperistalsis. Occasionally an antiperistaltic wave arises in the duodenum below the cap. It is a normal occurrence and the reverse waves can be seen during roentgen-ray examination of the human subject passing orally and conveying material to a higher level of the duodenum, into the cap or through the pylorus into the stomach (46). For a variable distance above

the ileo-colic valve, antiperistalsis also occurs, and appears to serve as a check to the too rapid passage of ileal contents into the cecum (26). With these exceptions peristalsis normally travels caudad. That the small intestine for the most part is incapable of transmitting peristaltic waves in the opposite direction was demonstrated by Mall (300) (301). He resected a segment of small bowel and then restored the continuity of the tube by suturing the resected portion in the reverse position. Peristaltic waves travelled from below upwards in the reversed loop, and obstruction occurred due to the accumulation of food at the upper suture line. Cannon in a similar experiment (85) also observed that the reversed loop offered a barrier to the passage of the food. He saw, in addition, the food carried towards the pylorus in the normal segment of intestine above the loop. This important observation made by Cannon is in accord with the belief that reversed peristalsis can hardly be called normal and occurs only in pathological conditions, for example, intestinal obstruction, and is responsible for the passage of fecal material into the stomach. However, if the reversed loop is short or if the animal survives the operation for a sufficient length of time (several weeks), the reversed segment may adapt itself to the altered conditions and move the food downward by true peristalsis.

From a study of the peristaltic wave in the bowel, Bayliss and Starling (49) (50) (51) claimed that food goes down the bowel simply because, "if cerebrospinal reflexes be excluded,

excitation at any point of the gut excites contraction above and inhibition below; this is the law of the intestine." Such was the conclusion of Bayliss and Starling when, in 1899, 1900, and 1901, they published their three classic articles on the movements and innervation of the bowel. The law of the intestine as formulated by Bayliss and Starling, states that a stimulus applied to a given point in the intestinal wall initiates a band of constriction on the proximal side and relaxation on the distal side of the stimulated point. The two phases contraction and relaxation - excitation and inhibition - were described as travelling down the bowel at the same rate, making a wave which swept the intestinal contents before it. Henderson (195) and many others (161) were unable to demonstrate the phase of relaxation in the intestine of either the guinea pig or rabbit, a simple contraction ring being the only movement observed. Alvarez and Zimmermann also mentioned the absence of inhibition ahead of peristaltic rushes (13) (33) (27), and suggest the need for restating the law.

Rhythmic segmentations. These movements are brought about by localized rhythmic contractions of the circular muscle, generally in the duodenum and jejunum. The annular constrictions do not progress along the bowel and cause little or no transition of the food at all. According to Cannon (85), the segmenting movements appear in groups of simultaneous constrictions spaced regularly along the bowel. One group succeeds another rhythmically at the rate of from 20 to 30 per minute. They divide the intestinal contents into numerous small sections

which are redivided by the next group which follows. The halves of adjacent segments so divided flow together to form fresh masses which are reformed by the fusion of the divided parts. This process is repeated over and over again and results in a thorough mixture with the digestive juices. It also encourages absorption by continually bringing the chyme into contact with fresh mucous surfaces, and by the massage-effect of the movement upon the bowel wall, the flow of lymph and blood is hastened.

The segmentations are well shown in animals if the abdomen is not opened and the barium-filled bowel is studied with the roentgenoscope. The kneading usually continues in one place for twenty minutes or so, causing only a moderate amount of downward progress of the material, and then the segment either quiets down for a while or a rush wave comes along to carry the contents onward for a short distance. In the animals, with the possible exception of man, the rate of these rhythmic contractions varies with the distance from the pylorus. It is interesting that the actual rates in dogs, cats, and rabbits are about the same. They are faster in the white rat and guinea pig. The segmenting movements in the human intestine by roentgenoscope occur at a rate of about 8 per minute (46).

Pendular movements. In the rabbit, and to a certain extent in other animals and in man, a local mixing of the intestinal contents with digestive juices, similar to that produced by the segmenting contractions, is brought about by swaying or pendular movements. These are also simply annular constrictions. They travel up and down short length of the bowel in a to and

fro fashion at a rate of about 5 cm. per second. They have the effect of carrying the chyme alternately from one to the other end of a loop of bowel. Their frequency is from 20 per minute in the duodenum to about 10 per minute in the lower ileum. They afford another factor contributing to the thorough mixing of the food, they have no direct effect upon the movement of the food but exert a purely local churning action.

Movements of the intestinal villi. The intestinal villi are in constant motion - swinging from side to side, shortening and elongating alternately, or lashing to and fro, either singly or in groups (246). The movements are due apparently to rhythmical contractions of smooth muscle fibers situated within the villi. By constantly stirring the fluids which bathe the surfaces of villi, these movements undoubtedly aid the digestive and absorptive processes.

There are also tonus waves which are to be found in many of the records made of intestinal activity. Early in 1911, Cannon noticed the importance of tonus for the movements of the alimentary canal (84). Usually these waves have, superimposed upon them, the more rapid rhythmic contractions, but occasionally they appear as simple curves. They do not seem ordinarily to travel along the bowel, but under abnormal conditions as in the presence of intestinal obstruction in the rabbit, these tonus contractions were moving slowly caudad and resembled the waves of the stomach and colon. It should be remembered that fluids commonly spread out and trickle through long segments much as they would spread out through

a piece of hose lying on the ground. Some of this transport of fluid may be due to large tonus changes in long segments of bowel; contractions which cause a narrowing of the lumen together with much shortening of the affected segment.

From what described above, there are two main types of activity in the small bowel; one, the rhythmic contractions, segmentations and the probably closely related swaying or pendular movements, and the other, the peristaltic rushes. In some animals and in man most of the forwarding of intestinal contents is effected by peristaltic rushes, but some part is effected by rhythmic segmentation. In addition there are tonus waves which may perhaps, in the face of an obstruction, turn into slow, powerful travelling contractions. It is well known that aided perhaps by big tonus changes in the wall of the bowel, fluids spread out and trickle through long segments even when the muscle lining them is paralyzed or incoordinated by drugs or anoxemia.

The rhythmical contractions - segmenting and pendular - are myogenic, that is, they are dependent solely upon the rhythmical property of the intestinal muscle itself. They are not abolished by such nerve poisons as cocaine and nicotine. A segment of excised intestine beats rhythmically when immersed in a 1:4,000 cocaine solution. Furthermore, the contractions of the circular coat of the bowel have been shown by Gunn and Underhill (180), Alvarez and Mahoney (28), and many others (422) (423) (162) to continue after it had been stripped from the longitudinal layer, and from the mucosa as well; all ganglion cells, they believe,

are in this way removed. The peristaltic contractions, on the contrary, are dependent upon the integrity of the intrinsic nervous plexuses. They are readily influenced through the extrinsic nerves - the vagus and sympathetic. It was shown by Bayliss and Starling that section of both these sets of nerves does not abolish the peristaltic movements, whereas the application of cocaine to the bowel wall does (49) (50) (51) (246) (13). The extrinsic nerves also influence the tone of the intestine, the vagus increasing, the sympathetic diminishing this property. The sympathetic exerts a continuous inhibitory action upon the bowel movements which are therefore, augmented after section of the sympathetic fibers. The vagus on the other hand, does not appear to exert any continuous augmentor effects upon intestinal motility, for section of this nerve does not essentially affect the movements (112). According to Alvarez, degenerative section of the nerves to the small bowel interferes somewhat with some forms of conduction. There is marked slowing in the rate of rhythmic contraction, particularly after splanchnicotomy. The bowel also becomes extremely irritable - so much so that the animal often dies of diarrhea. The removal of the celiac plexuses is a serious operation and one that commonly leads to the death of the animal. It leaves so irritable a bowel that the animal often dies of diarrhea. In man, surgeons have cut both vagus nerves, apparently without doing much harm, and today, both splanchnic nerves are commonly being cut for the relief of hypertension, apparently without producing any lasting disturbance in digestion.

The metabolic gradient theory of Alvarez is very interesting and suggestive (31) (9) (24) (124). He believes that the fundamental factor determining the polarity of intestinal peristalsis is the gradual diminution in the metabolic activity of the intestinal muscle that occurs from the duodenum downwards. A parallelism was found between the magnitude of the energy exchanges of the bowel at different levels and its muscular activity. Rhythmicity, irritability and force of contraction and tone are graded from above downwards, being high in the duodenum and low in the ileum (112). The length of the latent period of the muscle also shows an increase as the intestinal tract is descended. The carbon dioxide production and oxygen consumption exhibited a corresponding decrease from the duodenum to the lower reaches of the intestine. The frequency of the rhythmical contractions, eg, segmentations, is 17 per minute in the duodenum but only 10 in the lower ileum. Warming a strip of ileum raises its metabolism; its rate of beat is increased to equal that of the duodenum while the latent period is shortened. The decline in the metabolic rate from duodenum to ileum is spoken of by Alvarez as the metabolic gradient; to it are ascribed the progressive diminution of the other physiological activities of the muscle. Upon the difference between the intensities of the latter between any two levels of the digestive tube, the direction and swiftness of the peristaltic waves are supposed to depend. Alvarez suggests in illustration of his conception, water flowing between two regions of unequal pressures. When the gradient has the normal slope, peristalsis

is active and downward in direction. An inflammatory or irritative lesion, however, according to this observer, may raise the metabolic rate at a certain point to that it approaches, equals, or rises above that at a point nearer the pylorus. In such a circumstance the gradient would become reduced, annulled or even reversed. Sluggish peristalsis, stasis or antiperistalsis, respectively would result (23). Reversal of the gradient and the production of antiperistalsis as the result of mechanical blockage of the lumen, or injury and inflammation of a region of the bowel are advanced to explain the passage of fecal material into the stomach in intestinal obstruction and paralytic ileus. This theory is very suggestive. It accords with many experimental and clinical observations, but cannot be said to have been completely established.

Activity in the small bowel of man is easy to be watched with the roentgenoscope, such as pendular movements, rhythmic segmentations and peristaltic rushes. According to Alvarez, the rate of travel of the rush waves is about the same in man as in rabbits. As in the animals, so in man, rushes are likely to occur immediately after taking food; and in persons with diarrhea, they are likely to continue down the colon to the anus where they produce a call to defecation. As one would expect, the best time to look for the rushes that lead to defecation is in the morning after breakfast, when the bowel has been quiet for some time. In man, as in animals, food sweeps rapidly through the upper jejunum and travels more slowly in the lower ileum. It is only in the lower ileum that the

progress of material is slowed to such an extent that the barium can gather into dense sausage-like masses. While studying a man with an umbilical fistula, Hines and Mead (206) saw waves travelling at the rate of 3 cm. a second. They also saw reverse waves. The bowel usually became more active during the periods when there were hunger contractions in the stomach.

Many factors influence the rate of progress of food along the intestine, for example, the chemical and physical character of the food, individual variations in the activity of the intestinal musculature and the state of fulness of the alimentary tract. The transit period of different foodstuffs in the small bowel will be discussed in another separate chapter.

Nervous influence has much to do with the motility of the small bowel. It has been discussed in gastric motility. Emotional states according to general opinion, tend to increase the intestinal activity (112).

It is also generally claimed that muscular exercise increases the rate of movement in the small bowel. Hellebrandt and Miles (193) made a particular study of the influence of exercise on the rate of passage of material through the digestive tract of man and could not see that it made much difference.

The motility of the human small intestine is generally believed to be unaffected by sleep ( Cannon (76) ), Barcroft and Robinson (47), Douglas and Mann (133), Alvarez (14), and Hines and Mead (206). In fasting subjects studied with a balloon kymograph method, however, Helm et al (194) have noted a definite reduction of intestinal motility occurred in 12 of 16 human subjects who fell asleep spontaneously. This finding suggests

that motility may be similarly inhibited by sleep in any fasting person, and that cerebral activity is capable of affecting the motor functions of the small bowel. It also follows that the effect of sleep must be taken into consideration when the action of drugs on intestinal motility is studied. If the subject falls asleep, any coincident decrease in motility may be non-specific, or may be the result of hypnotic rather than antispasmodic properties of the drug in question.

Fats, through the production of glycerine and soaps, stimulate the movements of the small bowel; sugars are mild stimulant. Acetylcholine, pilocarpine, eserine and sodium bicarbonate given intravenously are powerful stimulants (112) (406). Pituitrin is also excitatory, whereas adrenalin is inhibitory (411). The depressant action of $CO_2$ is due to acidification and the degree of depression will be the same when it is produced by $CO_2$ or by HCl. Serious depression begins when the perfusion fluid is about PH 6.4 and complete arrest of the intestinal motility generally between 6.2 and 6.0 (406). Atropine reduces the tone of the musculature of the small and large bowel and relieves intestinal spasm. Morphine increases intestinal tone, the rhythmical movements are increased in frequency but reduced in amplitude. The propulsive movements are profoundly depressed or abolished, constipation results (253).

It is generally held that the intestinal muscle is resistant to anoxemia to some extent. Cannon (87), Scandola (380), and Alvarez (18) found that intestinal peristalsis returns to

normal after the mesenteric blood vessels have been obstructed for from 7 to 12 hours. Alvarez showed that the synapses cease to function in from 30 to 50 minutes after the stoppage of the circulation, but that the nerve fibers conduct well for at least 5 to 6 hours and often for some time after the rhythmic activity has begun to fail. Berkson (53) found that in his experiments that the action currents and the rhythmic movements seemed usually to fade out together as the tissue became fatigued or toxic. Ellis made some conclusion (142) that in the case of frog intestine, the local nerve cells are if anything more resistant to anoxemia than is the muscle. She cut segments, from 1 to 2 cm. in length, from the upper portion of the small bowel and kept them in Ringer's solution. In one set of experiments on sixteen frogs the minimal survival time, as judged by the faculty of rhythmic activity, was 143 hours, the average was 180 hours, and the maximal was 239 hours. After 72 hours, histologic studies showed degenerative changes in the nuclei of the muscle cells. These nuclei shrank and wrinkled, so that by the end of 150 hours most of them were pyknotic and many showed signs of fragmentation. After about 180 hours they gradually lost their staining power and disappeared. Since most of the segments stopped contracting after from 150 to 200 hours, Ellis concluded that the nuclear degeneration probably had something to do with the cessation of activity. One segment kept going, however, for 239 hours. Curiously, degenerative changes appeared more slowly in the nuclei of nerve cells than in the nuclei of the muscle cells; they began to

come after about 100 hours.

The view has also been held that bile plays an important role as a stimulator of intestinal peristalsis. The idea is found on two facts; first, those individuals who have biliary obstruction are often constipated; second, bile when given in considerable quantities by mouth or when introduced into the colon usually acts as a laxative. According to Schmidt (381), the first statement is not conclusive since the effect of the absence of bile from the intestine on intestinal peristalsis is not a direct but an indirect one. The presence of undigested fat, together with putrifactive products in the intestinal tract undoubtedly influences the tonus, particularly in those individuals with a low intestinal gradient. The experiments of Young (463), Ott and Scott (336) show that bile exerts but little influence in stimulating peristalsis of the small intestine. Schupbach's work (381) indicates that it may even have a slight inhibitory action.

A number of investigators have suggested that the motility of the gastro-intestinal tract is controlled by a hormone mechanism. Weiland reported that if the intestine of living animals were bathed with warm Ringer's solution, the intestine gave off something to the solution which excited isolated intestinal strips to contract and which was antagonized by atropine (228). Le Heux confirmed Weiland's experiments and came to the conclusion that the active principle was either cholin or some closely allied substance (228). He found free cholin in the intestinal wall and proposed the theory that

cholin is the gastro-intestinal hormone and acts by sensitizing Auerbach's plexus, atropine decreasing motility by antagonizing cholin. Clinically, cholin has been tried in post-anesthesia cases and gastro-intestinal disorders with negative or variable results. Carlson, Smith and Gibbins (107), using barbitalized dogs, observed that the action of cholin on the motility of the stomach and intestine was quite variable, and concluded that it was difficult to interpret their results on the theory that cholin is the normal stimulus to motility. If there is a gastro-intestinal motor hormone, it is going to be very difficult to demonstrate conclusively its existence. Ivy, Farrell and Lueth (229) were unable to observe any definite increase in the motility of a subcutaneously transplanted jejunal loop after the ingestion of a meal, although the transplanted loop manifested a spontaneous motility at irregular intervals and became very active when its mucosa was mechanically or chemically excited. According to Ivy, gastrin (crude) given subcutaneously in doses sufficient to cause copious gastric secretion does not affect gastric motility. The effect of purified secretion on motility has not been convinced (228).

Effect of endocrine glands on gastro-intestinal motility. Carlson (99) found that in severe tetany following removal of the parathyroids, any deviation from the normal in the motility of the stomach and intestine is in the direction of depression or paralysis. Dragstedt (135) on reviewing the literature concluded that the disturbances in the digestive tract are therefore an effect of the tetany and are not directly due to a decrease in the amount of parathyroid hormone liberated

In regard to the thyroid, it is a matter of common knowledge that patients with hyperthyroidism may have gastro-intestinal motor complaints, and that the feeding of the thyroid extract to man and animals frequently causes diarrhea, and markedly hastens the gastric emptying. However, the mechanism that is involved in these effects is not known, a number of factors is probably concerned, e.g., the toxemia, increased metabolic activity of the intestinal musculature, the direct exciting effect of the active principle on the nervous mechanism of either the extrinsic or intrinsic nerves, the disturbance of digestive secretions, etc.

The effect of adrenalectomy on gastro-intestinal motility has not been thoroughly studied. The anorexia that is known to result suggests depression of gastric motility, and the hemorrages into the mucosa of the bowel that occur would certainly greatly disturb intestinal motility. Hoskins and McClure (20) found that intravenous epinephrine in etherized dogs causes depression of intestinal motility in doses smaller than those required to raise the blood pressure. This was confirmed by Durant (137) for dogs and cats, but in rabbits it was found that the blood pressure could be raised by epinephrine without significant effects on the intestine. Dragstedt and Huffman (135) found that in dogs under anesthesia epinephrine caused the effects on the intestine noted by the above workers, but that in normal dogs under morphine or paraldehyde small doses of epinephrine would cause slight rises in blood pressure without inhibiting intestinal motility, which shows

that one of the objections to the old tonus theory of medulli-adrenal function, namely, that blood pressure effects could not be obtained except at the price of intestinal paralysis, could no longer be maintained.

The effect of insulin on gastro-intestinal motility has been discussed before.

Bozler made some electrophysiological studies on the motility of the gastro-intestinal tract (63). He showed that in contrast to the great diversity of motility, the action potentials of the gastro-intestinal tract were found to be remarkably simple; they consist of bursts of brief spike potentials which vary only in duration, frequency and amplitude. The action potentials of the stomach and intestine were recorded during the normal muscular activity, pendular and segmenting movements and peristalsis. The movements of these organs are accompanied by a discharge of brief action potentials. In the light of some experiments on isolated muscle (61) these electric changes must be interpreted as impulses conducted within the syncytial muscle tissue, since several facts disprove the assumption that the responses are due to stimulation of motor nerves. First, only inhibitory nerves are present, for instance, in the uterus of some of the species used like the cat; second, cocaine 1:200 does not abolish excitability or conduction; third, chronaxie and refractory phase are much longer than in the slowest type of nerve fibers; fourth, muscle fibers oriented at right angles to the direction of flow of an electric current are not stimulated, proving that a diffuse nervous plexus is not

responsible for excitation. Consequently the excitatory phenomenon of smooth muscle is not due to nervous structures it must be assumed that excitation can be conducted from muscle cell to muscle cell.

Usually each contraction is accompanied by a repetitive discharge and is, therefore, analogous to a tetanic contraction of skeletal muscle. The frequency of discharge ranged from about one per second during peristalsis of the stomach to 10 per second during a peristaltic rush in the small intestine of the rabbit. Grading of the contractions is possibly by a variation in the number and frequency of impulses. In addition the size of the impulses varies with the strength of the contraction, probably because only part of the musculature is active during weak contractions. The peristalsis in the small intestine of the cat and dog consists of rhythmic contractions on the oral side of a bolus, whereas the peristaltic rush in the rabbit is a continuous wave of contraction.

## THE TRANSIT PERIOD OF THE DIGESTIVE TRACT

If any one wants to study the intestinal activity related to the transit period he should know something about the behavior and properties of smooth muscle particularly the smooth muscle of the digestive tract.

As is well known, smooth muscle is made up of spindle-shaped cells which vary in size, shape, number in nuclei, and other details, in different animals and in different parts of the same animals (289). As a rule it contracts more sluggishly than striated muscle does; it takes longer to get started, and it is slower in recovering its original length. Incidentally, the greatest difficulty in working with this type of muscle arises from the fact that one can never be sure what its original length was because of the constant changes in tone even when isolated from the central nervous system. After a number of strong stimuli, or sometimes after only one, the muscle may become refractory (462), but after a long rest it will respond powerfully and explosively to a slight stimulus. That is the condition of the digestive tract after a night's rest, and it probably has much to do with the fact that most of us have the daily bowel movement in the morning, immediately after the breakfast. With an animal's abdomen open under a bath of salt solution, one can often start a rush wave down the bowel by pinching the duodenum. For some time afterwards similar pinches will have no effect, but if one waits long enough the bowel will again become so sensitive that the slightest stimulus will

start a wave.

Another characteristic of smooth muscle is its ability to maintain a firm and lasting contraction without fatigue. It is a fact that some muscles in man like the glutei and back muscles are carrying much heavier loads all day and they do not complain (395). One learns from this that there are all kinds of muscles, all suited to different purposes. Some workers believe that there are differences between, for instances, the muscle in the cardiac and pyloric ends of the stomach (5 ) (6) (7), and between that in the small intestine and that in the cecum (30) and colon (8). The muscle on the lesser curvature near the cardia is soft to the touch like coagulated fibrin; that in the pars pylorica is tough and has a different color. If one stimulates the two with an electric current or with a pinch, one gets two entirely different contraction curves; and if they are put into warm oxygenated Locke's solution they show two different types of rhythmic activity. These differences should be expected when it is remembered that the upper and lower ends of the stomach have different kinds of work to do. The upper end serves largely to hold the food, the lower as the mill to do the heavy work.

Another characteristic of smooth muscle in hollow organs as its responsiveness to tension. Most of the motor activities of the stomach and bowel are brought about and regulated largely by the internal pressure due to the presence of food or gas. Cannon (83) showed that during rhythmic segmentation in the small intestine the muscle fibers that are stretched tend to contract. Their contraction increases the pressure in neighbor-

ing segments, and so the process goes on. Cannon showed also that the waves in the stomach tend to appear at those places where the internal pressure balances the local tonus of the muscle. If the pressure is too little or too great there may be no waves (83) (460). When a man has been purged, his bowels are not likely to move for a few days. There is considerable evidence to show that this is due simply to the lack of tension in the colon. The bowel has to fill to a certain point before the muscle fibers will be stretched enough so that they will contract well. As Cannon has pointed out, these reactions to stretching are purely local and are not brought about by nervous reflexes.

Smooth muscle usually shortens under the influence of direct irritation. Thus one finds spasmodic contraction of the cardia, pylorus, ileo-cecal sphincter and anus when there is ulceration or inflammation near by. Hourglass contractions of the stomach appear opposite ulcers on the lesser curvature, and a shrunken and irritable cap is produced by ulcers of the duodenum. From the point of view of physician anxious to make an early diagnosis of cancer of the digestive tract, it is unfortunate that carcinomatous growths commonly fail to stimulate the adjacent muscle to contraction in the way that benign lesions often do.

It has been discussed briefly in the first chapter of this thesis that some peculiar way in which stimuli are transmitted from nerves to smooth muscle. In striated muscle every little fiber seems to have its motor nerve supply; some fibril which

brings the stimuli necessary for contraction. But most workers suggest that there is no such thing as a direct electric transmission of nerve impulses to smooth muscle; instead there is transmission through chemical substances which are formed at the ends of the nerves (376) (377). As a result, in smooth muscle, a stimulus arriving by way of any one nerve fiber can touch off contraction of a fairly large mass of muscle.

The studies of Rosenblueth (375) indicated that, when smooth muscle is stimulated through a nerve, a quantal nervous impulse liberated a quantal amount of a chemical mediator which may be called "M". This "M" combines with some substnace, H, in the muscle according to the reaction, $M + H \rightleftarrows MH$. Free M is destroyed locally, and as it disappears, the muscle relaxes. Because the process of destruction of M takes place slowly, there often is time for some of it to diffuse into the surrounding structures. With this new conception the problems of spatial and temporal summation of effects can now be attacked more intelligently. One can now understand why the type of response of a smooth muscle can depend on the number of nerve impulses delivered in a unit of time, regardless of the number of nerve fibers stimulated.

Bozler (63) (61) ( 60 ) ( 62 ), however, has brought forward some evidence in favor of the view that smooth muscle is directly excitable by an electric current. He argued that if it were influenced only indirectly through a nerve net, it would not make any difference how the current went through, but actually, Bozler found the threshold for electric stimuli more

than twenty times higher for a current passing at right angles to the fibers than for one passing longitudinally in the direction of the fibers. Actually some histologists have demonstrated a fine nervous network, fibers from which reach every muscle fiber in the wall of the bowel.

Evans (143) stated that there is no drug which has an action on smooth muscle like that of curare on striated muscle. In order to block the effects of vagal stimulation, atropine has to be used in doses so large that it probably then injures the muscle. According to Alvarez the nicotine even in fatal doses had no effect on motor nerve endings in the bowel, and according to Evans, cocaine actually increases the sensitiveness of smooth muscle to sympathetic excitation.

More needs to be learned about the metabolism of smooth muscle. Prasad (349) (350) found that isolated intestinal muscle in the presence of oxygen oxidized about 1 mg. of carbohydrate per gram per hour. In the process lactic acid was produced. Sodium iodo-acetate in a 1:10,000 concentration interfered with the utilization of glucose by the muscle. A slowing up of the movements of a bit of intestinal muscle did not appear to be due to an accumulation of acid but to an exhaustion of the labile carbohydrate store. Fatigue in smooth muscle appears to affect first the contractile tissue and not the myoneural junction as in striated muscle.

The literature contains conflicting statements as to the relation between the activites of longitudinal and circular layers of muscle of the bowel. Some writers (195) concluded

that the layers act independently; others (209), (210) (182) (361) thought that one coat contracts while the other relaxes; and others, as Bayliss and Starling, and Cannon said that they often contract together. Trendelenburg (20), using guinea-pig bowel, found the contractions of the two layers of muscle slightly out of phase. Forster and Hertzman (154) noted in an exteriorized segment of human ileum that the longitudinal and circular coats sometimes contracted together, while at times the longitudinal coat contracted first. On analyzing motion pictures of rabbit bowel Alvarez found that although the two coats often contract together, they also contract independently, and he could not get much evidence in favor of the view that commonly one relaxes because the other contracts.

It has generally been assumed that the residues from any one meal leave the body within 24 or 48 hours, and this is the conclusion that one might draw from observing the progress of a barium meal through the bowel of an average person. Unfortunately, it did not occur to any one that the addition of several ounces of indigestible material like barium to a small meal of gruel or milk must modify the passage of that meal or its residues through the intestine. The added bulk must act like a large dose of agar or mineral oil and, as one would expect, patients who have just been examined roentgenoscopically for the study of constipation not infrequently find themselves temporarily relieved of their trouble, Furthermore, a little barium, according to Alvarez, is apparently absorbed, enough to act as a stimulant to intestinal activity. This

was the conclusion arrived at during the First World War when, on changing from bismuth to barium, roentgenologists found that the barium went through the bowel more rapidly than did bismuth. Childrey, Mann and Alvarez (115) found in dogs also that the addition of barium sulfate to a meal caused it to go unusually rapidly through the small bowel. This is the reason why the other means should be used for investigation of the transit period of the digestive tube besides the barium meal.

In 1904 Elliott and Barclay-Smith (141) observed the rate of progress of food through the bowel of rabbits by giving them the smallest colored beads which mixed well with the stools. Alvarez used the same method in human being. Different colored beads were given on each of three successive days, so that three rate-determinations could be made on each person without much extra work. The stools were passed into wide mouthed fruit jars and were brought to the laboratory where they were rubbed through a sieve under running water. The beads recovered were counted, and plotted daily as percentages of the whole number taken. Most of the persons studied seemed healthy, and they usually had a good bowel movement every day. It is found that normal young men with a good digestion and a daily bowel movement did not, in 24 hours, pass 100 per cent or anything like 100 per cent of the beads. There were two men who passed about 85 per cent in 24 hours, but most of the volunteers took four days in which to get rid of 75 per cent, and there were some who passed only 50 or 60 per cent in nine days. Most of them passed about 15 per cent on the first day and 50 per cent more on the

second. It is also an interesting fact that the beads given on the second day nearly always came through a little faster than those of the first day; and those given on the third day came through even faster. It would appear that the first set of beads must get off into the haustra and out of the central column, and once there, they seem to keep the later ones from coming in. Another interesting fact is that the addition of even 60 gm of barium sulfate to the meal and beads given on one day caused these beads to go through faster than did the other control sets. 84 per cent appeared in two days as compared with 62 ppr cent of the other set of beads given without barium. Furthermore, it is well known to roentgenologists that even after purgation of a patient who has had a barium meal, small masses of the barium will usually remain for a week or more to interfere with the interpretation of films of kidney or gallbladder. In order to measure this residue Freedlander (22) gave 60 gm. of barium in milk to a number of students, collected their stools, and recovered the drug quantitatively. He found that by the third day, when barium could perhaps no longer be seeing in the stools as white particles, only 75 or 80 per cent of the material had been passed. After that it kept coming away in small amount for days, just as the beads did. Wallace et al (436) studied the evacuation of a barium meal and decided that in 10 per cent of the persons tested the material was out in 24 hours. In 66 per cent it was out in the next day or two, and in 24 per cent it was passed after four or five days. The fallacies in all work done with

this technic are first, that in many persons the barium tends to act like a laxative, and second, that long after the stools have lost their white color there is barium in them and in the colon.

The fact that most of the stools are mixtures of food residues - some like meat and starch which are easy to digest, and others like seeds and skins which are hard to digest, indicates that the bowel has little or no ability to pick and choose between those materials which are ready for extrusion and those which might with advantage be held over for further action by the digestive juices.

Food residues are constantly flowing into the cecum where a mixture of new and old must take place. Beyond this region, in men and women whose feces are formed, there seems to be little if any mixing. From the studies made with the beads it appears that, each day, about one-sixth of the material that arrives from the ileum goes straight on down the colon, and with it goes about half of the contents of the cecum.

The essential point for the clinicians to remember is that when the colon is well cleaned out by a purge or by a large bowel movement, no new movement should be expected or demanded for another 24 or 48 hours. It can come only if the colon is so sensitive that it can respond to the distention brought about by the residues from the three meals eaten on one day. Occasionally, of course, a chemical irritant without much bulk is able to produce defecation, but ordinarily, a certain amount of distention seems to be the necessary stimulus for colonic

emptying. Furthermore, if very little food is taken, as after an operation or during an illness, or if the colon is unusually long or large in diameter, or if it is exceedingly thrifty, the period of normal waiting may be several days or a week or more. To give purgatives during this time is unjustifiable and should be condemned except in those cases in which the patient or his relatives become sick with anxiety over the dangers of auto-intoxication, or in which headaches and distress actually develop. It is questionable, therefore, whether purgatives that produce copious movements should ever be given oftener than two or three times a week. Certainly, one who has been purged and who wishes to get back to normal must be content to wait a day or two for his first movement.

Burnett (70) used as a marked for the stools 30 c.c. of millet seed taken in half a tumbler of water. In one individual tested about forty times, the seed usually began to appear in stools passed from 40 to 73 hours after the ingestion of the markers. They continued to appear usually for from five to six days after ingestion. Burnett concluded that a rather slow rate of passage through the bowel was associated with the best digestion and health. In 1923, Burnett (71) reported the study of sixty persons with normal daily bowel movements. Again he found that in the average person the initial appearance after about four days. In persons with a slow rate of passage the seeds appeared in 62 hours and disappeared after six days.

Mulinos (329), who gave carmine, found that a third of his

patients passed most of it with the first stool from 6 to 48 hours later. Half of the patients passed most of the dye with the second stool, from 9 to 98 hours after ingestion.

Hellebrandt and Miles (193) repeated Freedlander's experiment and found a somewhat more rapid passage of beads. They confirmed the fact however, that there is a marked variation in the rate of intestinal passage in normal persons. Regarding the beads used by most workers the only objection is that of their specific gravity, somewhat greater than that of the residues from food, probably lagged slightly behind those residues.

David (20) made an extended study of the rate of progress in the digestive tract, but he used water as a test meal with 50 gm. of bismuth subcarbonate. The stomach was empty usually in from 2½ to 3 hours. The cecum began to fill in from 2 to 4 hours, and the ileum was empty in from 6 to 8 hours. The results of his observations in 124 persons are here tabulated:

The cecum began to fill:

Before 2 hours in.....36 cases

Between 2 and 3 hours in.....38 cases

Between 3 and 4 hours in.....35 cases

After 4 hours in.....15 cases.

The ileum was empty:

Before 2 hours in..... 5 cases

Between 2 and 3 hours in.....16 cases

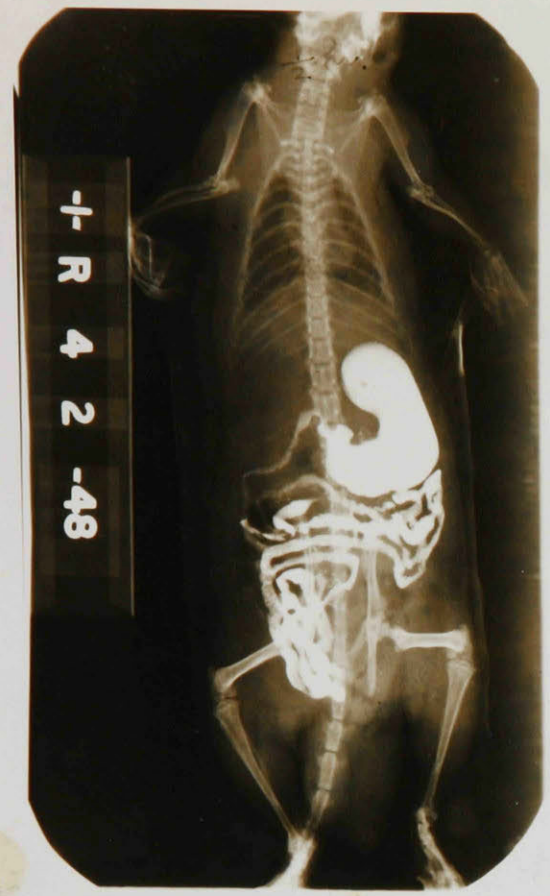
Between 3 and 4 hours in.....27 cases

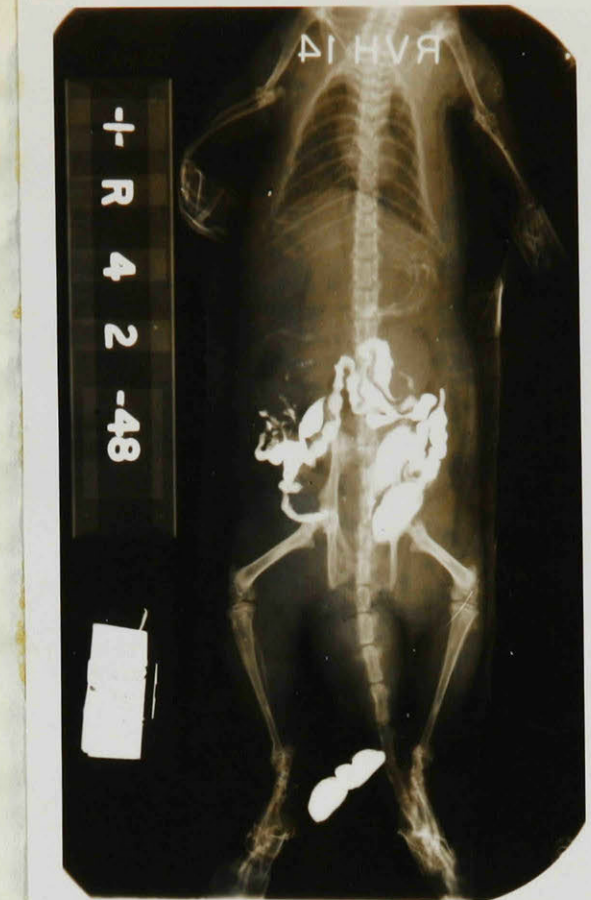
Between 4 and six and a half hours in.83 cases

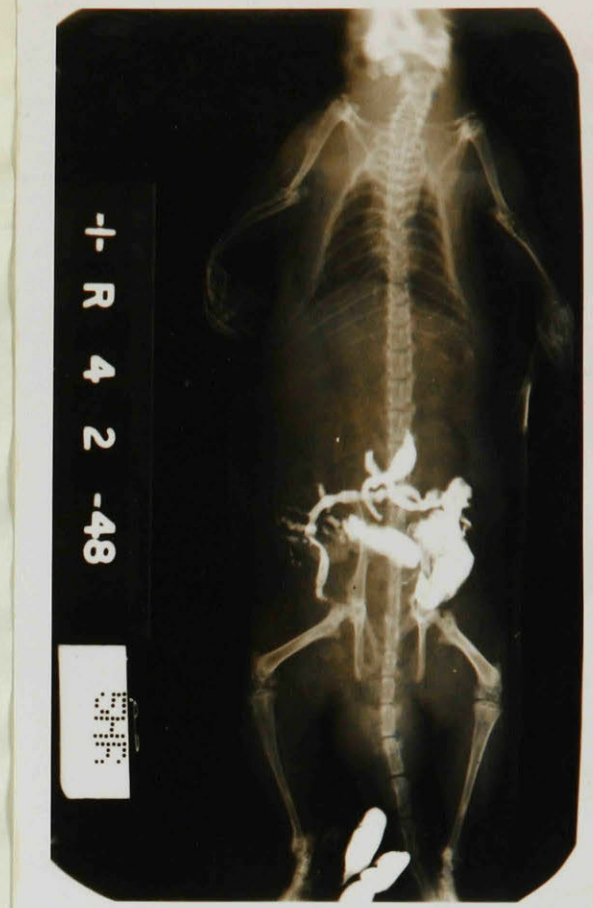
After six and a half hours in.....16 cases

In Todd's experience with 400 students (430), usually all the barium had passed out of the ileum in 8 or 9 hours, but with a hyperactive stomach and bowel it sometimes was all out in 4 hours. The passage of barium through the ileo-cecal sphincter began usually 2¼ hours after the meal was taken, but sometimes it began within an hour and a half. In 1936, Pendergrass and his associates (343) (367) made the similar observations and showed approximately the same results. They used the so-called Pendergrass standard barium meal, i.e. five ounces of barium sulfate mixed with five ounces of water.

In my own experiment eighteen normal and healthy albino rates were used for control to study the gastro-intestinal motility (Fig. 1 and Fig 2). Twelve c.c. of standard barium meal was given to each rat and found that the stomach of all the rats was completely emptied at the end of 3 hours. The cecum began to fill usually about one hour after the ingestion of barium and, the ileum was empty at the end of 5 hours. At the time when the gastric evacuation was completed, all the rats started to have bowel movement with white colored barium feces, however, the barium usually was retained in the colonic tract for two or even three days as observed either by roentgenoscope or as checked daily by watching the white colored feces excreted in the cage. It is interesting to compare these findings with the observations made in man as mentioned above. The emptying time of the stomach and ileum in rats is practically the same as that in humans. The transit period through the small bowel, however, is definitely faster in rats. In spite of all the rats starting to evacuate the barium at the end of 3 hours, the barium is usually



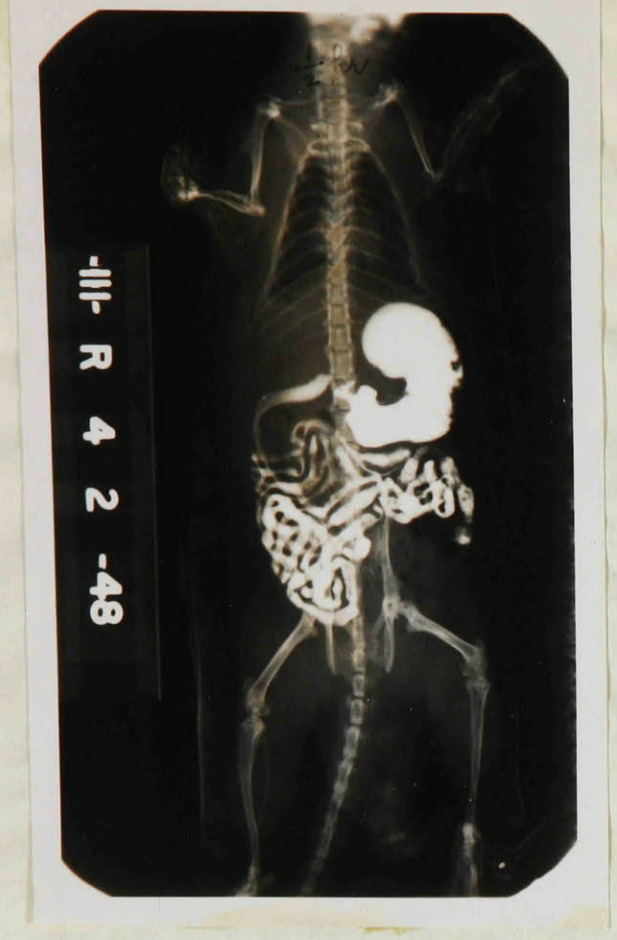




( half hour ) ( 3 hours ) ( 5 hours )

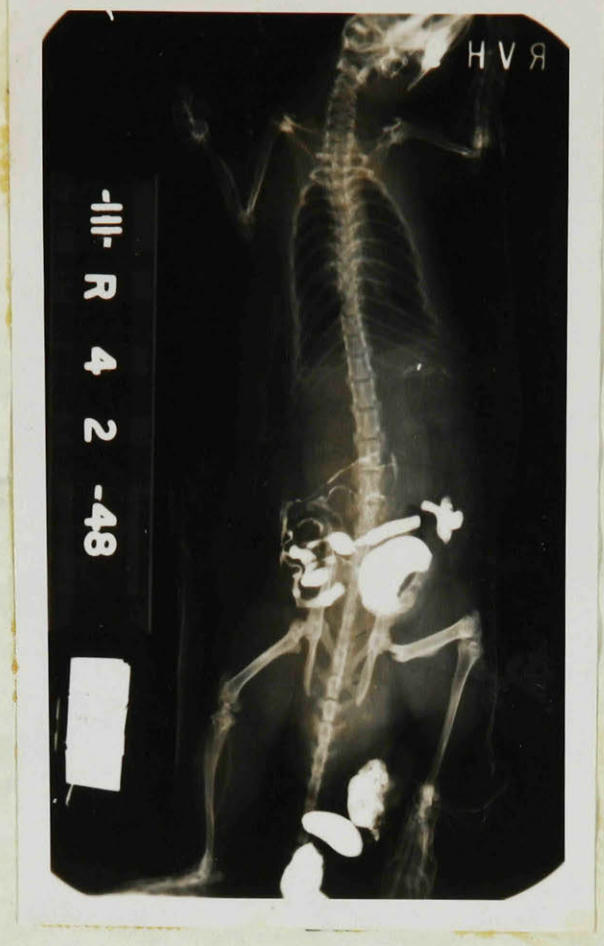
Fig. 1. Roentgenograms of rat No. 1 ( normal barium series )

Serial film s were taken at the time about half hour, 3 hours and 5 hours after the ingestion of barium:

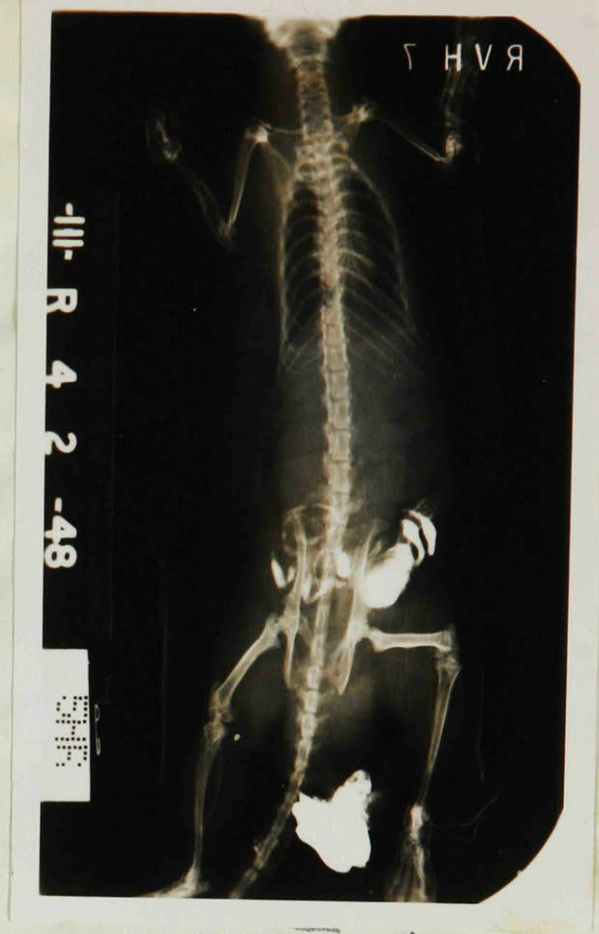
(1) Half hour film shows the jejunum is well filled. The head of the column of the barium has reached the proximal ileum.
(2) 3 hours film shows the stomach is practically completely emptied. Most part of the barium is accumulated in the colonic tract and the rat starts to evacuate barium feces. The segmenting movements are demonstrated very nicely on this film.
(3) 5 hours film shows the small bowel is nearly cleared up of the barium.




( half hour )




( 3 hours )




( 5 hours )

Fig. 2. Roentgenograms of rat No. 3 ( normal barium series )

Serial films were taken at the time about half hour, 3 hours and 5 hours after the ingestion of barium:

(1) Half hour film shows the small bowel is well filled. The peristaltic movements of both the stomach and small bowel is active.
(2) 3 hours film shows the stomach is completely evacuated. The rat starts to excrete the barium feces.
(3) 5 hours film shows most of the barium has been evacuated from the digestive tract. There is only some trace of barium retained in the colon.

retained in the colon for two or three days which is consistent with the observations made by Freedlander and others when beads or seeds are used in humans.

So much for barium meal in the study of the transit period through the gastro-intestinal tract, nevertheless, the barium holds definite disadvantages on this subject as pointed out before. In 1930 and 1932, Menville and Ane (313) (314) made a contributory investigation by x-ray study of the passage of different foodstuffs through the digestive tract of both man and rats. The observations are the results obtained from x-ray examinations of healthy normal individuals, divided into three groups and each group was fed with carbohydrate, protein and fat respectively. The carbohydrate is in the form of cream of wheat, protein in the form of casein, and fat is in the form of pure cream. They fed each group 170 gm. of food stuffs in the proportion of three parts of food to one part of barium sulfate. The results as tabulated on the next page are in accord with that of McClure, Reynolds and Schwartz (282) and Pendergrass and his associates (343) (367). They represent the results of observations upon the emptying time of the stomach, transit period of small bowel and cecum appearance of both individuals and rats fed different foodstuffs. In comparing the two tables they find that in both rats and humans the rate of passage of protein through the small intestine is fastest, carbohydrate only slightly slower and fats are decidedly slowest of all. Rats were the animal of choice because the character of their diet is closely related to that of the human

Table 1 - averages, ( Human )

| Foodstuffs | Number | Weight | Height | Age | Ate gm. | Cecum appearing time | Stomach emptying time |
|---|---|---|---|---|---|---|---|
| Protein | 6 | 154 | 5, 8 | 30 | 170 | 2' 18" | 2' 38" |
| Carbohydrate | 5 | 162 | 5, 8 | 30 | 176 | 2' 42" | 2' 37" |
| Fat | 6 | 164 | 5, 10 | 30 | 170 | 3' 45" | 5' 6" |

Table 11 - averages, ( Rat )

| Foodstuffs | Number | Weight | Ate gm. | Cecum appearing time | Stomach emptying time | Small intestine emptying time | Colon emptying time |
|---|---|---|---|---|---|---|---|
| Protein | L8 | 245 | 6.8 | 4' 26" | 13' 9" | 15' 1" | 63.4 hrs |
| Carbohydrate | 15 | 204 | 5.3 | 5' 5" | 7' 5" | 10' 24" | 51.15 hrs |
| Fat | 6 | 235 | 5.3 | 8' 35" | 16' 44" | 29' 10" | 61.3 hrs |

species.

There are many occasions when physicians and surgeons wish to slow the current in the intestinal tube or to prescribe a diet with the least possible residue, as in the treatment of diarrhea or during the preparation for operations on the colon, or in caring for patients who have just had an operation about the anus. If in the last-named group of cases the fecal residues can be made small enough, defecation can be postponed for a week or more and the patient can be spared much distress. Heile (20) studied dogs and patients with a fistula into the lower end of the bowel found that with the dogs on a mixed diet, undigested material began to appear at the fistula at the end of an hour. Most of it came through in the third and fourth hours, and by the fifth hour the bowel was empty. With a diet of lean meat the time of extrusion was about the same as that of the mixed diet. With carbohydrates and fats the extrusion began earlier and it ceased after three or four hours. When Heile gave 126 gm. of well chopped meat to a dog, only 20 gm. of material came from the fistula, but when he gave a liter of milk which contained 130 gm. of solids, the fecal residues amounted to 250 gm. He was impressed with the desirability of giving protein when the colon is to be spared work. He found that a dog could absorb 98 per cent of a meal ~~meal~~ even when this food was given in large amounts. 100 gm. of rice was also absorbed completely. F. Muller (20) also showed that meat is almost completely absorbed in the small bowel. He found that, in man, the eating of from 500 to 600 gm. of beef a day resulted

in only two gm. more of fecal material than is seen during starvation. Babkin (37) confirmed the observations in regard to the large residue which is left with a diet of milk. He found also that the addition of milk to other foods which otherwise would have been well digested greatly increased the fecal residues. Harley and Goodbody (184) also noted the tendency of milk to increase the bulk of residues. Rubner (20) fed many foods to healthy young men and found that those that were best used were meat, eggs, rice, white bread, noodles and macaroni. The largest residues were found with milk, cheese, cabbage, black bread, and carrots. When a low residue diet is desired, Cammidge (74) advised the use of white bread and butter, white of eggs, lean meat and well cooked rice. When a small residue in the lower ileum and colon is desired, as in the case of diarrhea, milk would seem to be one of the worst foods to use (109). Hosoi, Alvarez and Mann (216) studied fecal residues in dogs from which the colon had been removed and found, as others had done, that milk left large residues. Their studies indicated that a good low-residue diet should consist mainly of lean meat to which might be added rice, hard-boiled eggs, sugar with the exception of lactose, and perhaps small amounts of fruit juices, tea and black coffee. All the experiments suggested then that milk is the first food to be held in cases of diarrhea. Raw egg-white taken by itself ran right out of the stomach and down the small bowel without being digested at all. It was well digested, however, when it was mixed with some other food, and even an almost indigestible

one such as raw starch; if this served to keep the egg from leaving the stomach rapidly, then both the foods were well handled. These studies were continued by Childrey, Alvarez and Mann (115) and again it was found that the best digested foods were meat, rice, dextrose, and a little fat. Again, the combining of certain foods, such as bread and milk or raw egg and milk, improved the digestion of both substances. Lactose, cheese, and lard given with other foods not only interfered considerably with the digestion of foods given with them but also of foods given on the following day. Meat and cheese were better digested when given in lumps than when given in small pieces, and several foods were handled better when given in one large amount than when given in fractions at half-hourly intervals. Apparently each feeding tended to rush onward the residues from the food previously given, and thus interfered with digestion and absorption. Krzywanek (20) who followed the progress of barium meals through the bowel of animals, was also impressed with the fact that the rate of travel is speeded up by giving food at frequent intervals. He also noticed that giving water with food tended to handicap digestion by washing the material too rapidly through the bowel. This washing of food through the small bowel by added water appears to interfere with digestion and may give rise to troublesome diarrhea. It is unjustifiable by ordering people to drink an extra ten or more glasses of water a day. It often injures patients by causing polyuria at night and thus

interfering with sleep and rest. Senna leaves, phenolphthalein, and small doses of calomel caused the food to go through the small bowel in from 2 to 2½ hours, but cascara had little influence on the rate of passage. Solutions of sodium and magnesium sulfate went through in half an hour. With morphine or tincture of opium a mixed diet went through in ten and half hours. Morphine also caused the food residues to become more solid.

Opiates have been used for many years for their depressing effect on intestinal activity in diarrheal states and for the purpose of relieving pain of intestinal origin. Morphine is supposed to have a splinting effect and to produce constipation. The mechanism by which this is accomplished remains obscured in spite of many investigations (253). Pancoast and Hopkins (338) described roentgen observations on the gastro-intestinal tract in eleven humans after the administration of moderate doses of morphine. They claimed that practically all authors agree that morphine lessens motility in the small intestine. Unlike the stomach, delayed motility in the small intestine seems to result from lack of propulsion instead of spasm. They found no evidence of spasm of the ileocecal valve which had been previously reported. Abbott and Pendergrass (1) studied the effects of single doses of morphine on the small intestine in normal subjects by roentgen methods and by means of a balloon introduced into the intestine. After the injection of 15 mg. of morphine sulfate a prompt contraction in the upper part of the

second portion of the duodenum took place which persisted for an average time of about 20 minutes. This was followed by dilatation. With the rise in tonus, contraction waves as registered through the balloon were obliterated; if the pressure in the balloon was raised, small rhythmic waves of low amplitude appeared. With the fall in tonus the waves increased but averaged below normal in amplitude. After morphine the balloon records rarely showed an appearance suggesting peristalsis. About 5 to 15 minutes after the injection of morphine the barium shadows showed a segmenting effect due to areas of contraction with slight dilatation between them. Frequently disoriented movements occurred but little orderly movement was noted. These writers believed that the slow emptying of the stomach was caused by the spasm in the upper part of the second portion of the duodenum through the duodenogastric reflex; during the relaxation period the stomach seemed to empty more rapidly than normal. The upper part of the jejunum reacted similar to ø, but less than the duodenum, while the lower jejunal response resembled that of the ileum. The secondary depressant action may last for hours. These writers believe that these observations may be used as further evidence that small intestinal motility is primarily related to tonus differences rather than to contraction waves, and that the evidence is unfavorable to the use of morphine in conditions associated with intestinal distention. Some clinical workers (169) suggest that by increasing the tonus of the normal intestine, morphine prevents the onset of the vicious circle which culminates in paralytic ileus,

but the drug cannot interrupt the vicious circle after it is started. It would appear that morphine is an excellent prophylactic if used before distention begins and that it probably has little effect after distension has begun. Maintenance of tonus at a normal or a slightly increased level would prevent the disorders of secretion and absorption which follow stretching of the wall. Krueger (253) states that all workers report an increase in the tonus of the small intestine under the influence of morphine. He quotes Quigley, Highstone and Ivy (355) as having found a temporary increase propulsive activity, followed later by a decrease which lasted much longer; they found by using a bolus, that propulsion was actually decreased at a time when activity as shown by the balloon was augmented, showing that the balloon recordings cannot be taken as evidence of propulsive efficiency. The period of inhibition was earlier in onset in the ileum than in the jejunum. Tonus was increased throughout the earlier period of increased as well as the later period of decreased propulsion, showing that tonus is not the only factor. Evidence is divided as to whether morphine produced an increased or decreased rate of absorption from the small intestine.

A number of investigations of the effect of morphine on the substances concerned in neuromuscular physiology have been made. Bernheim and Bernheim (54) found evidence that morphine one part in 30,000 produced marked inhibition of choline esterase from animal brains in vitro. They interpreted their results

as suggesting that morphine in vivo may interfere with the normal destruction of acetylcholine in the brain. A given amount of morphine becomes more effective as the amount of acetylcholine decreased. Slaughter and Lackey (399) found that morphine sulfate added to blood in vitro produced no change in choline esterase activity. On the other hand serum choline esterase activity in the dog was consistently lowered followed injections of morphine sulfate. Slaughter and Gross (398) found that eserine (which inhibits the action of choline esterase) increased the effect of morphine in a number of tests on animals. On the dog's intestine they found that the combination of the two drugs did not eliminate peristalsis and that the effects did not last as long as with morphine alone. Slaughter, Parsons and Munal (401) reported excellent relief of pain from a combination of 0.5 mg. of prostigmine (which inhibits choline esterase) with decreased amounts of morphine. Prostigmine, they state, relieves tonic sontipation because it stimulates peristalsis. Slaughter and Munsell (400) found that physostigmine increases the effect of morphine on the intact dog's intestine and on the cat's blood pressure. On the other hand, atropine antagonizes the effect of morphine. These effects, they believe, indicate that morphine is a true cholinergic drug, but it is not clear whether it causes a liberation of acetylcholine. They found evidence that prostigmine diminishes addiction to morphine in dogs.

Atropine, according to Sollmann (405), antagonizes acetylcholine, which would explain the diminution in tonus observed by Puestow (352). It does not prevent the formation of acetylcholine following nerve stimulation but apparently keeps the acetylcholine from acting on the cell. Atropine relaxes intestinal spasm when it is due to parasympathetic stimulation but is not potent against other intestinal stimulation.

The barbiturates tend to decrease the general tonus of the intestinal musculature and the amplitude of rhythmic contractions in experimental animals. The therapeutic effects of these drugs in relieving gastro-intestinal symptoms is attributable to depressant action on the central nervous system (171).

Benzedrine sulfate in therapeutic doses, according to Myerson and Ritvo (330), caused an increase in the width of the lumen of both the small and the large intestine as observed by roentgen methods. Apparently because of this relaxing effect, they regarded benzedrine as a sympathicomimetic drug. Smith and Chamberlin (403) found that the average transit time of a barium water preparation through the small intestine of four normal subjects was 2½ hours; after therapeutic doses of benzedrine sulfate it was nearly 6 hours. Farah and Pinkston (145) studied the effect of benzedrine on isolated segments of the dog's intestine and on the living intestine in unanesthetized dogs with Thivy-Vella fistula. In the isolated preparation, benzedrine caused relaxation and decrease in the amplitude of pendular and peristaltic movements. The effect

in the intact animals was varied but usually a decrease in tonus was noted. These observers found that the colon reacted much more to benzedrine than the small intestine and showed definite inhibition of spontaneous movements. Goodman and Gilman (171) commented on the inconstancy and uncertainty of the effects of benzedrine on the intestine and stated that they cannot be predicted on the basis of sympathicomimetic properties. In short, as Krueger remarked (253) many gaps remain to be filled before the effect of morphine on the gastro-intestinal tract can be understood clearly. The same statement can be made regarding the other drugs mentioned above.

May and McCreary (308) and May, McCreary and Blackfan (309) showed that the injection of mecholyl bromide, a form of acetylcholine, improved both the intestinal movement and the absorption of glucose by the intestinal mucosa in celiac disease. This suggests that lack of this substance, which is necessary for the normal transmission of nerve impulses along the axon and at the nerve endings, apparently plays a part in the disordered function of the absorbing epithelium as well as the muscle.

Foods rich in cellulose go through the small bowel rapidly. Lehman and Gibson (263) found in a patient with a jejunal fistula that coarse foods would greatly intensify all the movements of the bowel. Jellies also tend to hurry the progress of food through the small bowel.

Schupbach (381) studied the influence of bile on the motility of the bowel and came to the conclusion that it has an inhibiting effect on the movements of the small intestine and an accerating effect on those of the colon.

The rate of progress of food through the bowel of infants was studied by Lesne, Binet and Paulin (20), using carmine. The rate lengthened slightly with age and with the increase in the variety of the diet. The carmine began to appear usually between 8 and 9 hours after ingestion, and it became too attenuated to color the feces after 18 or 20 hours.

Regarding the transit period through the digestive tube, some descriptive terms such as hypermotility and hypomotility, are commonly used by the roentgenologists. The barium shadow in normal cases is usually continuous and is not broken up into widely separated small boluses; after most of the barium has reached the lower ileum and cecum, the proximal or tail end of the column may show segmentation. In the average case, as mentioned before, the barium reaches the cecum in from 2 to 4 hours. If it reaches the cecum in less than one hour the intestine may be considered hypermotile. In some cases, without evidence of intestinal disease, the barium does not reach the cecum in 4 hours, but after the patient eats something the ileum promptly begins to expel the opaque material. This delay in the ileum cannot be taken as evidence of intestinal disorder. If, however, the barium does not reach the cecum in 5 hours with the stimulus of food, definite hypo-

motility is present and the cause of the delay should be looked for, particularly if the ileum is not empty at 9 hours. The borderline between the normal and the abnormal in transit time under the conditions of the small intestinal study is certainly not well defined as pointed out by Ross Goldon (169).

Influence of pathological conditions on transit period. Nutritional disorders. It may occur at any age, from the new born infants to the aged. The disorder may be the result of insufficient ingestion, disturbed digestive processes, incomplete absorption, or improper utilization after absorption. The vitamins which appear to be most important for the proper function of the digestive tract, as far as can be determined at the present time, are included in the B group and are found particularly in yeast and liver extract, rice bran and seeds. It is usually divided into the primary nutritional disorders in which arise without obvious anatomic cause, such as celiac disease and sprue, chronic deficiency in diet may be a factor, and included cases resulting from a low vitamin intake or to voluntary dietary restriction. The secondary group are those in which the condition is caused by, or is at least associated with, diseases which may interfere with the digestion or absorption of nutriment, e.g., peptic ulcer, carcinoma, primary disease of the small intestine such as tuberculosis or regional enteritis, primary disease of the mesentery such as lymphoblastoma, or biliary tract disease.

In all cases of the nutritional disorders show disordered motor function. Hypermotility is present in the earlier, less advanced stages as the barium may be passed rapidly through the jejunum and reach the lower part of the small intestine in a quarter of an hour; it may enter the cecum in less than half an hour. It may be propelled ahead so rapidly that the upper loops of the jejunum are never outlined satisfactorily. Hypertonicity is also present that the lumen is often reduced to one half, one fourth, or even less of its normal width. This is often most noticeable in the middle third of the small intestine and is usually associated with hypermotility. In the more advanced stages the movement of the barium through the intestine is slow; the opaque material may not reach the cecum in 6 hours or longer. Definite hypomotility is present. The lumen of the intestine in the advanced stages may vary from normal size to more than twice the normal width. The hypotonic, dilated loops are characteristically seen in the well advanced stages, usually called nontropical sprue and adult celiac disease.

Slow emptying of the stomach is frequently found in well marked primary nutritional disorders. A good sized 6 hour barium residue may be present with sluggish, ineffective peristalsis and often with antral spasm. This has been present in ~~of~~ early as well as ~~of~~ advanced nutritional disorders and has disappeared quickly after the beginning of vitamin therapy.

The effect of low blood protein on the motor function of

the intestine is well known. If the serum protein reaches the edema level (about 5.5) disturbances in the intestinal pattern occur which are promptly relieved if the serum protein is raised. The importance of the nutritional status of the surgical patient in the development of nutritional edema and the effect of edema of the intestinal wall was emphasized by Jones and Eaton (232). Small intestine disturbances are consistently present in nephrosis as was first pointed out by Pendergrass et al (343). One of the major manifestations of nephrosis is edema due to hypoproteinemia; the edema fluid in the intestinal wall is mainly in the submucosa, as described in deficiency states. When the patient loses the edema the intestinal picture improves. They also described disturbances in small intestinal physiology in diabetes insipidus, which is associated with a disturbance in water balance. Similar disturbances have been produced in dogs by experimental hypoproteinemia by Barden, et al (48) and are indistinguishable from those resulting from vitamin B deficiency as shown by Heublein, Thompson and Scully (204) in these animals.

Hypomotility and segmentation of the small intestine associated with icterus were reported by Gutzeit and Kuhlbaum (169); from experiments on dogs and observations on patients, they secured evidence interpreted as suggesting that the disturbance was due to a lack of bile in the intestine. Edema of the intestinal wall is present with cirrhosis of the liver and in some cases motor disturbances appear on roentgen examina-

tion. Healthy liver function depends among other things on adequate supplies of the vitamin B complex. The relation of the disordered intestinal physiology associated with biliary tract disease to vitamin B deficiency, if any, awaits further study.

Effect of allergy. Involvement of the gastro-intestinal tract by allergic reactions probably occurs much more frequently than is generally thought. The multiplicity of its clinical manifestations mades the diagnosis difficult. The reaction may be limited to one section of the gastro-intestinal tract, such as the stomach, the small intestine, or the colon. Allergy of the intestine is sometimes, but not always, associated with allergic reactions elsewhere, e.g., urticaria or asthma. Skin tests are of little help, as they may be negative in the presence of a food allergy, and if positive, may not indicate correctly the offending allergen. The association of the abdominal symptoms with other allergic manifestations, such as urticaria, suggests sensitivity to some food. Immediate and temporary relief of pain following the injection of adrenalin is likewise suggestive.

The symptoms usually encountered are abdominal pain, diarrhea, and nausea and vomiting. The pain may be mild or it may come in acute violent attacks and may lead to exploratory operation.

Very little information is available as to what might be expected on roentgen examination of the intestine, however,

three common manifestations of allergy are: edema, either localized to a small area or involving larger areas; spasm of smooth muscle, as in asthma; and inflammation, as in eczema. Walzer, Gray, Straus and Livingston (438) studied the reaction of the ileum of the rhesus monkey to allergens after local passive sensitization by the injection of reagin-bearing serum into the intestinal wall. Gray, Harton and Walzer (176) made similar studies on the exteriorized ileocecal region of two patients following ileocolostomy. The reactions in the two groups of experiments were the same. If the allergenic material was ingested or if it was injected directly into the intestine, pallor of the sensitized site appeared within 5 minutes. Edema followed quickly, obliterating the mucosal folds, and reached its maximum in from 15 to 20 minutes. The pallor was gradually replaced by congestion. Within an hour the reaction began to subside and in two hours the site appeared normal except for slight edema. The reaction was confined to the region of the mucous membrane which had been sensitized.

Many cases of apparent food allergy are present with marked hypertonicity of the lower third or half of the small intestine; the caliber of the lumen is reduced to a third or a fourth its usual size. This hypertonicity was usually associated with hypermotility. Pendergrass has found that hypermotility is associated with intestinal allergy. The reaction of the intestine in the presence of allergen is

quite different. Cooke (123) described the effect of a barium milk preparation on a milk sensitive patient as: (a) 6 hour gastric residue; (b) hypermotility, with the opaque material in the rectum at 6 hours; and (c) marked segmentation of the small intestine, resembling in this respect the disordered motor function seen in the milder vitamin deficiency states. A diagnosis of intestinal allergy cannot be made on the basis of the roentgen examination at the present time. However, if hypertonicity of the lower half or third of the small intestine appears, particularly when associated with a short transit time, it seems proper to mention the possibility of a food allergy as working basis for further investigation. A great many of cases in which this suggestion has been followed by the elimination of an offending food with relief of symptoms.

Constipation. Most writers on constipation have begun by dividing the cases into two groups; one with an atonic and the other with a spastic colon (260). From a clinical sense, the term atonic is not practical, for it is hard for any roentgenologist to recall that he ever has seen a constipated adult with an atonic looking bowel. It is also doubtful if that the colonic muscle is ever so weak that it cannot empty the rectum. It often fails to do so, but this may be due to the frequent failure of the person to answer the call, or to the absence of some stimulus normally present in the fecal material, or to the drying of feces into little hard balls which are hard to extrude. Muller and Hesky (20) presented

some fact against the idea that atony or weakness of the bowel is a common cause of constipation. They were able to remove the muscle from the colon of dogs without producing much disturbance in defecation. Apparently the small intestine was strong enough to force the material onward through the inactive segment.

It is claimed that the tonus of the muscle in the rectum is higher than that of the muscle in the colon immediately orad (29), which might be helpful in keeping material from packing up against the sphincter except at those times, as after a meal or after a peristaltic rush, when the pressure from above is great. Any increase in the tonus of the muscle of the rectum or simply a tightening of the sphincters such as one should expect to see with irritating lesions about the anus, might easily produce constipation, and actually this is the way in which the trouble seems sometimes to arise. It is frequent that constipated patients present a reddened, irritated and fissured anal ring, with hemorrhoids and inflammed crypts. If the local inflammation is cleared up, the constipation is sometimes cured.

It is a fact that thin, nervous, constipated persons often have a tight anal ring and it seems that the anal sphincters share in the increased tension which is to be found in all the muscles of the body. In this group of persons the constipation is decidedly a disease of nervous origin, and when, with increasing tension of all the muscles about the lower end of the pelvis, the rectum cannot empty against much resistance. Hurst (219) thought that a slowing of the progress of material

through the whole colon, and what he calls dyschezia, which is an inability of a man to empty the rectum. He also pointed out that constipation is practically always limited to the colon, and that there never is any large backing up of fecal material into the ileum.

One of the peculiar things about the rectum is its sensitiveness to slight increase in pressure. Zimmermann (20) found that changes of from 2 to 3 mm. of mercury could be perceived by the persons he studied, and that a rise of from 20 to 60 mm. caused distress. These observations were confirmed by Donaldson (134), who found in volunteers who restrained defecation for four days, an increase in blood pressure, nausea, loss of appetite, sweating, abdominal discomfort, mental depression, restlessness, and an inability to concentrate. Pearcy and Allen (341) distended the stomach and colon and obtained marked disturbances in vision, sweating, and feeling of drowsiness. Just as in cases of constipation, the person studied found it difficult to read; attention lagged, and the type seemed blurred. The power of accommodation was reduced, and an oculist could see changes in the ratina. According to Pearcy and Van Liere (342), distention of the rectum of the dog produces salivation, nausea and protracted vomiting. Loew and Patterson (276) found that marked distention of the rectum of dogs decreased gastric tonus, inhibited hunger contractions and sometimes caused much discomfort and restlessness. Smith and Miller (404), on studying patients, found an apparent-

ly reflex stimulation of the stomach from the colon, appendix, and gallbladder. On distending the colon there was an increase in the tonus of the stomach, particularly of the pyloric region, and an increase in the depth of the waves. The sensations produced in certain persons by such distention are sometimes those that are commonly ascribed to the presence of toxins re-absorbed from the colon: that is, mental haziness malaise and headache. That these symptoms are not always due to such absorption can be seen from the fact that they can sometimes be produced by stuffing the rectum with cotton, and they so commonly disappear within a few seconds or minutes after defecation. If they were due to toxins, relief would not come until next day when sufficient excretion had taken place to lower the concentration of poison in the blood. These results and symptoms due to distention also were not observed by Hines, Lueth and Ivy who, studying students, distended a toy balloon in the rectum (205).

Williams and Olmsted (454) (452) (453) found that of the three classes of substances that make up the effective portion of indigestible residues effective in the treatment of constipation, the hemicelluloses are most efficacious in increasing the bulk of the stool, and yet they constitute the most digestible fraction. Contrary to accepted belief, the effectiveness of indigestible residues did not appear to be due primarily to the mechanical stimulus of the distention but rather to irritating chemical substances which arise from the destruction of

hemicelluloses and celluloses by the bacteria of the bowel. Among the most stimulating of these products are the lower volatile fatty acids (454) (452) (453) (332) (333) (179).

As everyone knows, the treatment for constipation today is largely palliative, and consists as a rule in making the feces more irritant, chemically or mechanically. All treatment must be palliative as long as the main cause of constipation, which is the strain and hurry of civilization, goes on unchecked. Occasionally the removal of a diseased gall-bladder or appendix, or a large myoma of the uterus, or a painful anal fissure, or some hemorrhoids, or the short circuiting of an obstructed pylorus, will really free the patient from dependence on a nightly laxative or a daily dose of bran.

Following up some successes obtained in the treatment of megacolon in children, a few surgeons have cut some of the lumbar sympathetic nerves in badly constipated adults, the results, however, do not appear to have been encouraging. Hunter (218) believed that the severing of the white rami of the upper lumbar nerves would remove much of the inhibitory influence of the nervous system on the colon and would relieve constipation. Rankin and Learmonth (364) concluded that better results could be obtained in Hirschsprung's disease than in cases of severe constipation. They divided the presacral nerve. Trumble (431) and Adson (3) felt that in most cases resection of the hypogastric nerves or the presacral nerve would be sufficient to obtain the desired effect

in cases of Hirschsprung's disease or severe constipation.

The attempts to work out a surgical treatment for constipation have not yet been very successful. Constipation may be relieved but it is probably seldom curable as long as the patient has to go on living the strenous life which causes the colonic dysfunction. The fact is that even if some day a good operation is devised for the immediate relief of constipation, the bowel will, after a time, compensate in some way and return to its old habits.

## THE MOTILITY OF THE LARGE INTESTINE

The function and structure of the large intestine are quite different in herbivora from that of carnivora. In the herbivorous animals, it serves as a reservoir in which cellulose can be broken up by bacterial fermentation; it absorbs some of the final products of digestion and returns water to the blood. The meat-eating animal has a little need for a colon, because digestion is practically complete in the small bowel and about all that remains to be done is to retrieve the water that has been used in the chemical processes. This water has been pouring out by the glandular cells in the mouth, stomach, liver, pancreas, and intestine, and it is convenient to have the liquid returned to the blood. In man, it was shown by Welch and his associates (444) that some 400 c.c. of water reached the colon each day with about 30 gm of solids in a young woman with an ileostomy. Since the stools of a normal person contain about 70 c.c. of water and about 30 gm. of solids, it is clear that the colon must absorb about 330 c.c. of water a day. In man it serves also as a reservoir in which waste can be held until such time as it can conveniently be voided, and it serves perhaps as an excretory organ for certain substances such as the salts of the heavy metals.

The colon is a sluggish organ with a few and slow movements. Much of the progress of material in it seems to be due to the pressure exerted by new material coming down from above.

It is hard to stimulate and when it contracts, it does so slowly and perhaps only once or twice. Many observers have noted that the colon, with the exception of the rectum, reacts but little to moderate distension. Apparently, then, the muscular and nervous apparatus of the colon is designed, as it should be, for holding material quietly for hours at a time.

Peristalsis. The contents of the ileum after passing through the ileo-colic orifice collect in the blind end of the cecum. In the human cecum little or no movement can be seen, yet the material passes slowly into the ascending colon. Todd (430), studying hundreds of students, describes slow changes in the shape of the cecum but thinks such a movement inadequate for the propulsion of its contents. Cannon using opaque meals and enemata, found in cats that entrance of chyme from the ileum initiates strong antiperistaltic waves in the proximal colon. These waves occur in bursts of approximately 5 minutes duration and at intervals of from a quarter to half an hour.

In the large cecum of the rabbit peristalsis alternates with antiperistalsis. In the proximal colon the antiperistaltic waves are two to three times as frequent as the peristaltic waves and the haustra show continuous movement. This type of contractions, although it may occur anywhere in the colon, is usually confined to the proximal colon, so that the liquid chyme, newly received from the ileum, is passed to and fro over the surface of the colon where absorption of water occurs. The proximal colon of herbivora, in the intervals between

peristaltic and antiperistaltic contractions, shows marked segmentation.

Such antiperistalsis though not seen normally in the human cecum may, according to Todd, appear when the colon beyond is in a spastic state. The rest of the human large intestine as revealed by the roentgenoscope is usually free from antiperistaltic, segmenting or pendular movements, and peristalsis is absent or ill-defined (219). Todd describes slow weak peristaltic movements and alternate shortening and elongation in the transverse colon.

Post mortem in man, fecal matter is usually confined to the cecum and to the ascending and transverse colon. This disposition of the fecal matter is probably due to anti-peristalsis and to the normally high tone of the distal colon (161). The descending colon and sigmoid flexure are probably more sensitive than is the proximal colon because they are so often empty when the rest of the colon is full of barium-containing feces. According to Roith (20) these regions are found empty in 70 per cent of cadavers.

Alvarez (31) claimed that there is a metabolic gradient from the cranial to the caudal end of the colon, however, not all observations on the large bowel support this theory, due probably to the fact that normally the contents of the colon may move either caudad or craniad.

Templeton and Lawson showed that in the colon of the dog there commonly are large slow tonus contractions with

smaller contractions superimposed (415). In Alvarez's experiments, excised bits of muscle showed pronounced tonus contractions. Plant and Miller (347) put balloons into the colon of unanesthetic dogs and found from seven to fourteen small contractions a minute superimposed on tonus contractions which appeared about once a minute. Hines, Lueth and Ivy showed a regular tonus rhythm in the rectum of man when a balloon was left distended in the rectum. There were crises of pain associated with the contractions (205).

Mass movements. The mass movements in the colon occur only at long intervals, probably not oftener than two or three times in 24 hours. These were described by Hurst (225), Barclay (44), and Case (110). I have done seven hundred and fifty barium enemata in Royal Victoria Hospital and I never saw one by my stupid eyes. In animals, and probably in man, these mass movements in the colon are often secondary to a rush wave in the small bowel, and they not infrequently result in a call to defecation. It may occur immediately after the entrance of food into the stomach - gastro-colic reflex. Alvarez cited an instance of a subject with an incompetent anal sphincter in whom a bowel movement could be precipitated by purely psychic influences.

The movements usually start in the region of hepatic flexure. The haustral markings suddenly disappear and the bowel appears as a solid unsegmented column. A strong and rapid peristaltic wave then travels over the transverse and

descending colon carrying all before it. The descending colon is usually empty except during the time that the feces are being transferred by a mass movement. Feces after they have filled the pelvic colon may, however, extend upward into the descending colon and may even reach the splenic flexure. This phenomenon is called retrotransport, may be of some practical importance because it seems probable that when a person failed to answer the call to defecation, some of the material distending the rectum returns into the upper part of the colon where it no longer can be felt. In this way a habit of constipation may be started. Except preceding and during the act of defecation the rectum like the descending colon also is normally empty.

Gravity probably plays little if any part in the progress of material through the colon and, as time passes, clinicians pay less and less attention to the position of the colonic tube in the abdomen. The term "ptosis" is not justifiable anymore since quite common so-called ptosis is in persons with a normal digestion. As Moody, Van Nuys and Chamberlain (468) showed in their roentgenologic study of 600 normal college students, the colon is so frequently situated in the pelvis that this must now be regarded as its normal position. Another extensive study showing the great variability in the appearance of the normal colon was made by Davis (130). A similar condition is held true for the position of the stomach and an extensive study has been made by

Barclay (46). Barclay has also shown how much the position of the abdominal organs changes normally with the position of the body.

Defecation. The act is brought about by the passage of fecal material past the resistance of the pelvic-rectal junction. According to some observers (219), a definite thickening of the circular fibers of the colon (pelvic-rectal flexure or sphincter) exists in this situation and plays an important part in the function of the human colon, but this is not present in laboratory experimental animals.

The entrance of the feces into the rectum may result from a mass movement already described or simply from overloading of the pelvic colon and the gradual pushing of its contents downward. When the intrarectal pressure reaches to between 40 to 50 mm Hg, the defecation reflex occurs. The reflex consists of a strong peristaltic contraction of the colon, accompanied by shortening of its longitudinal fibers, and a coordinated relaxation of the anal sphincters, initiating the evacuation of the feces (219). This movement of the bowel is also accompanied and assisted by the contraction of voluntary muscles.

The defecation reflex is governed by a medullary center and a subsidiary center in the cord. The existence of the latter is evident in nervoud diseases associated with complete functional or anatomical division of the cord above the lumbar-sacral region, when evacuation is effected

automatically and in an almost normal manner. Also in animals after complete transection of the cord, though there is loss of control over the bowel movements and incontinence of feces for a time, the spinal center subsequently assumes control and automatically evacuates the bowel at regular intervals.

According to Fulton (158), immediately after the cord is cut, the anal and also the vaginal sphincters in dogs, may exhibit relaxation with tendency towards prolapse. The tone of the sphincters, however, generally recovers within a few days, and after several weeks the rectum begins to empty itself automatically. During the first days after spinal transection, there is generally great increase in peristalsis of the gut, and a tendency towards watery stools with a profusion of mucus; but the characteristics of the gastro-intestinal disturbances in spinal dogs have never been thoroughly analyzed. The great increase in peristalsis observed by Claude Bernard (1858) and others after spinal transection does not occur when the brain stem is severed above the vagus nucleus. Section of the vagus tends to cause stasis in the gut and impairment of digestive processes (469). Denny-Brown and Robertson (131) in their study of nervous control of defecation find that the act of defecation may still occur in man after complete destruction of the sacral and lower lumbar segments. The adequate stimulus for the act is a stretch of the wall of the rectum; this serves to initiate

peristaltic contraction that leads to relaxation of the anal sphincter. The nervous mechanism involved in the reaction lies in the peripheral nerve plexus surrounding the walls of the rectum. The mechanism, however, is subject to influence from the spinal cord and is depressed after spinal transection, during which time the anal sphincters abnormally relax. Cutaneous stimulation of the sacral dermatomes may serve to initiate reflex defecation in spinal man and bladder contraction may be accompanied by simultaneous defecation.

The spinal center is situated in the second, third and fourth sacral segments, but the destruction of this region in animals is not necessarily followed by complete and permanent fecal incontinence, for the rectum like the bladder is capable of controlling evacuation through its intrinsic nervous mechanism. Also in involvement of the sacral segments of cord in man there sometimes may be almost perfect automatic control of the rectum and anal sphincters as mentioned above.

The medullary center is situated in the floor of the 4th ventricle not far from the vomiting and respiratory centers. Hatcher and Weiss (190) have shown that a stimulus to defecation will exhibit vomiting and certain emetic drugs applied to the vomiting center cause defecation. They also found areas in the medulla which controls the tone of the sphincters. The well known fact that stimulation of the anal sphincter by forcible dilatation is an effective means

of stimulating respiration, suggests a close relationship between the respiratory and defecation centers.

The reflex as mentioned above is initiated under normal circumstances by the passage of feces into the rectum. The latter, however, soon adjusts its capacity to the bulk of the feces (postural tone) the pressure stimulus being then abolished. The rectum may therefore become unresponsive if defecation is voluntarily prevented.

In the cecum and the rest of the colon the fibers of the outer muscular coat are gathered into three longitudinal bands known as the taeniae of the colon, which being shorter than the underlying layer, draw into pockets known as haustra. The circular coat is thickened between the latter. Austoni (20) made a careful histological study of the taeniae of the colon in a number of species of animals and found that the muscle in them peculiar in that it was full of connective tissue and elastic fibers. The taeniae serve largely as a skeleton for the circular fibers. The intrinsic nerves of the colon have a distribution similar to that of the small intestine.

Learmonth and Markowitz (261) (262) showed that the sympathetic nerves exert a constant inhibitory action since increased colonic activity follows their section. The inhibitory impulses of the colon arise apparently within the lumbar cord, for if this region has been isolated previously from higher centers by spinal transection the full augmentor effect

upon the colon is obtained by sectioning the colonic nerves. Denny-Brown and Robertson made the same observation that the sympathetic nervous system is not essential for these reflex effects, although it is probably capable of depressing them.

Section of the pelvic nerve relaxes the wall of the distal colon and the animal subsequently experiences difficulty in emptying the bowel. Section the cord above the sacral segments also causes relaxation which indicates that the constant augmentor effect is due to impulses arising in higher centers. A subsidiary augmentor center apparently exists, however, in the sacral cord, for cutting the pelvic nerves some time after the spinal transection causes colonic relaxation. That is, the sacral segments acquired control during the time which had elapsed after their isolation from higher centers.

The colonic movements are inhibited by pain, fear and anesthesia (161). The movements of large bowel are also influenced by activity in other regions of the gut. Eating food increases colonic activity within a few minutes (208).

Adrenaline, in the dosage usually employed in experimental work, inhibits colonic movements and lowers the tone of the bowel wall. The action of acetylcholine given hypodermically or intravenously causes intense gut activity.

The idea that bile stimulates peristalsis is commonly taught since the oral administration of bile or bile salts is in common practice for relief in constipation. However,

no general agreement has been reached in the literature. Galapeaux et al (160) showed that the intracolonic injection of 10 and 20 c.c. quantities of tap water in divided quantities 15 minutes apart, had no appreciable effect on dogs, whereas injection of 10 and 20 c.c. quantities of dog's gallbladder bile into the colon was followed by a marked depression in colon activity lasting from 50 to 100 minutes. In all cases where the bile was injected into the colon defecation followed within a few minutes after the experiment and a marked tenesmus was usually manisfested.

## THE SPHINCTERS OF THE DIGESTIVE TRACT

It is generally believed that there is no true anatomical sphincter at the cardia in man. Lendrum (264) reported the study of 150 human cardias, in none of the specimens was there any special sphincteric band of muscle marked off by partitions of connective tissue. Usually there was no localized muscular thickening of any kind, but in a few cases there seemed to be a diffuse thickening of the muscle at the orifice of the stomach, or at the level of the diaphragm, or in both places. On examining several species of animals, Lendrum found what looked like a cardiac sphincter only in rodents. However, it seems no doubt that there is in man a functional sphincter of some kind at the point where the esophagus joins the stomach. There can be no question about the fact that there is a narrowing of the lumen at this point, with enough of a sphincter muscle to delay the passage of material from the esophagus into the stomach and to interfere with the regurgitation of the gastric contents. In some persons this sphincteric action is weaker than in others, and perhaps partly because of this they regurgitate or vomit with ease.

Regurgitation of gastric contents through the cardia is probably physiologic in certain animals and perhaps even in man. Because Cannon found that he could stop this process by acidifying the contents of the stomach, he suspected that the cardia must be under an acid control similar to that which he

thought existed at the pylorus. Later, the negative results of Carlson, Boyd and Pearcy (103) threw some doubt on the idea. Burnham (72) studied the type of regurgitation which can be seen sometimes in man, and concluded that it occurs most commonly in cases of disease of the gallbladder.

The muscle at the cardia shows at times a marked tendency to contract rhythmically (6) in the freshly excised stomach of the rabbit. This rhythmic indrawing of the lower end of the esophagus has sometimes been observed in man during the process of swallowing.

Cannon and Lieb (88) and Veach and others (433) showed with recording balloons that the upper end of the stomach and the cardia relax as an animal or man swallows. This receptive relaxation associated with swallowing apparently fails when a man eats too rapidly, and this may result in spasm and pain after eating.

The tonus of the cardiac muscle is constantly influenced by stimuli arriving from many parts of the body. Whether the effect of such stimuli is contraction or inhibition depends largely on the initial tonus of the muscle. When the tonus is high, stimuli tend to produce relaxation, and when it is low they tend to produce contraction. Probably because of this variability, authorities are not in agreement as to the effects of stimulation of the vagus and sympathetic nerves on the sphincter, (103) (433) (248) (256) (292) (287).

The motility of the pyloric sphincter has been discussed

in the section of gastric evacuation. Wheelon and Thomas (446) (447) (448) placed recording instruments in the pyloric antrum, pyloric canal, and duodenum distal to the cap, and obtained simultaneous tracings of the contractions in these three regions. The movements of the antrum and the sphincter were found to be related with those of the duodenum. During the contraction of the antrum the duodenum is relaxed, but about one minute after the commencement of the relaxation of the antrum the duodenum commences to contract. That is, relaxations of the antrum roughly coincide with contraction of the duodenum and contractions of the antrum with relaxations of the duodenum (receptive relaxation of the duodenum). Contractions of the sphincter were found to occur rhythmically from 3 to 5 times per minute, each contraction commencing while the duodenum was relaxed. The contraction of the duodenum commenced 2½ seconds later but the contractions in the two situations reached their maximal heights at about the same time. These movements of stomach and duodenum are correlated apparently through the intrinsic plexuses in the gastrointestinal wall. A connective tissue barrier exists between the muscle of the stomach and duodenum which must prevent the continuous spread of the wave independently of a nervous mechanism of some sort. This is of value to the organism. Perhaps without it the duodenum would receive so many stimuli from the stomach that it would become overactive and start off so many rush waves that the man or woman would suffer from

diarrhea. Similarly, too easy a passage of influences backward from duodenum to stomach might bring about much regurgitation up the esophagus.

Movements initiated in the duodenum have been shown, on the other hand, to influence the activities of the sphincter. When the duodenal mucosa was stimulated an ordinary peristaltic wave appeared which traveled down the bowel in the usual way, but a firm contraction of the sphincter also occurred, followed by a prolonged period of relaxation. A series of such stimuli produced a continuous contraction of the pyloric sphincter. Activity of the duodenum has been shown by several observers to have the effect of increasing the tone of the pyloric sphincter. The state of the duodenum in this way affects indirectly the emptying of the stomach, and the filling and emptying of the cap. When the duodenum is filled with chyme active movements are set up in its wall which have the two-fold effect of withdrawing material from the cap and causing reflex closure of the sphincter. When the duodenum becomes empty its activity subsides, the pylorus relaxes more fully and the emptying of the stomach is hastened. This effect of a full duodenum upon the emptying time of the stomach is shown by the fact that a meal taken after a period of fasting is discharged much more rapidly than if the duodenum is already deplete with chyme; gastric evacuation is then delayed. Distention of the bowel by a balloon or its irritation by chemical or mechanical means

increases pyloric tone. It had been shown repeatedly on the other hand that if the chyme as it issues from the pylorus be allowed to escape through a fistulous opening instead of permitted to fill the duodenum, the stomach empties with greater speed. It has been found by Thomas, Crider and Mogan (421) that a reflex effect of even greater importance than that upon the sphincter is exerted from the duodenum upon gastric peristalsis. Substances introduced into the duodenum markedly reduced the force of the peristaltic waves in the antrum, whereas draining the duodenum increased gastric motility and hastened gastric evacuation.

The pylorus was thought as "keeper of the gate" and had a remarkable degree of intelligence which enabled itself to recognize when digestion was complete. Then it would relax its wall and allow the chyme to run on into the bowel. Today we know that this is not true in every case, so far as liquids taken by an empty stomach are concerned, emptying begins as soon as the material is ingested. Solids are generally held back at least until the stomach has had a chance to soften or liquify them. According to Cannon (83), when protein, for example, is fed, peristaltic constrictions may press the food against the pylorus repeatedly for a half hour or more without forcing food through the orifice. Other experiments on dogs with duodenal fistulas indicated, however, that liquids tend to run out of the stomach with the arrival of every gastric wave at the sphincter. Todd (430) found

on examining hundreds of students that, with water as a test meal, the pylorus remains practically open, while with milk or other food, it is rhythmically opened or closed. Hurst and Briggs (223), Cole (117), McCure, Reynolds and Schwartz (282), Wheelon and Thomas (446) and Klein (247) all mentioned that the pylorus of man relaxes as each gastric wave approaches. Some of these observers were impressed by the fact that in so many roentgenograms one can see a band of barium joining the shadow of the pyloric end of the stomach with that of the duodenal cap. Because this connecting shadow is often so wide and so well marked, they felt that the sphincter must be open a good part of the time. Case (111) doubted this and said that even when the pylorus is closed, a narrow channel, measuring about one-eighth inch in diameter, is made visible simply by the adhesion to the mucosa of a little barium. According to Case, when the pylorus is really open, the canal is one half inch in diameter. Wilson, Dickson and Singleton (457) concluded that waves of any strength always push something out when the meal is in contact with the pylorus. After reviewing much of the literature, they concluded that food does not leave the stomach except when a wave is approaching the pylorus. They observed some material going out with almost every wave. However, many a roentgenologist cannot accept this idea since with a powerfully contracted pylorus which will not permit the cap to fill even when strong manual pressure is brought to bear on the full stomach.

The pylorus with such complicated mechanism makes one hardly believe that when the pyloric ring is removed surgically the stomach continues to empty much as it did before without causing great disturbances in function. Actually the surgeon cuts out a section or removes the whole structure without the slightest fear that the health of his patient will suffer. Tanaka (20) studied the emptying of the stomach of dogs and cats at various intervals after the performance of gastroenterostomy or resection; he took motion pictures through an abdominal window and concluded that the emptying of the stomach is controlled not by the pylorus, but by the bowel just beyond the stomach. This is the so-called holding back effect of the intestine. The fact is that the stomach continues to empty intermittently and almost normally after the operation of pylorectomy as reported by many observers (86) (234) (150) (163) (181) (125) (388) (315). Gianturco (163) confirmed Cannon's observation (269) that gastroenterostomy and pylorectomy have little effect on the rate of gastric emptying. Crider and Thomas (125) found that the stomach emptied no differently when a mechanical device is fitted into the pylorus to keep it open. Pendergrass et al (367) did not see the dumping effect as commonly claimed in gastric operated cases. They observed that the stomach has the same function as the pylorus is intact.

Using dogs and cats, McCrea and McSwiney (284) (285)

found that the hepatic branch of the vagus supplies and regulates the pyloric region. Stimulation of the peripheral end of the vagus, total contraction of the pyloric region was most frequently obtained. Movements of the isolated pyloric region are similar to those observed in the pars pylorica of the intact stomach. Stimulation of the peripheral end of the splanchnic nerve is dependent on the existing tonus, and may be inhibitor or augmentor. Carlson and Litt (106) made the conclusion that the atonic sphincter is markedly contracted upon stimulation of the splanchnic nerve, while sometimes they observed the hypertonic to be relaxed. Thomas (416) used epinephrine and observed a slight preponderance of inhibitory over motor components in the sympathetic innervation of the pyloric sphincter in the dog and cat and marked preponderance of motor over inhibitory components in the rabbit. The excitatory effect of pilocarpin on the pyloric sphincter and the antagonism of atropine for the pilocarpine effects were also demonstrated in these three animals. According to Wiggers (450) and Babkin (38) stimulation of vagus in man or section of the splanchnic nerve tends to increase the contractions of the stomach and intestines, to relax the sphincters, and to shorten the evacuation time; whereas stimulation of the splanchnic or section of the vagus nerves tends to depress the motility of the stomach and gut and to cause spastic contraction of sphincters.

The ileocolic sphincter when competent permits the passage of the contents of the small intestine at intervals into the cecum, but hinders the return of the material into the ileum. Its ability to do this depends, according to one view, not upon any mechanical valve-like device, but upon the contraction of the circular fibers of the gut which are thickened in this region to form a sphincter guard for the ileocolic orifice. Most observers agree, however, that the competency of the ileocolic valve is actually due to a valve-like construction.

The ileocolic opening has been observed in man through a cecal fistula (449). It appears as an oval or round opening from 2 to 3 cm. in diameter situated in the center of a small papilla. When contracted the sphincter was found to offer considerable resistance to the passage of the finger. While digestion was in progress the papilla was observed to flush, its color altering from a pale pink to a vivid red. The sphincter opened rhythmically at frequent intervals and allowed a jet of fluid to escape into the cecum. Emotional excitement or the swallowing of food increased the frequency of the ejections. During fasting nothing passed through for long periods but in from ½ to 4 minutes after food was taken into the mouth, fluid appeared in gushes of about 15 c.c. every half minute or so. There is evidence in man that the sphincter muscle is more irritable than is the bowel on either side. This would help to keep it contracted and the sphincter

tightly closed.

The function of the sphincter appears to be (a), to prevent the contents of the ileum from passing into the cecum before the digestive processes are complete and (b), to act as a barrier which prevents the bacteria-laden contents of the large bowel from contaminating the small intestine.

The sphincters of ileocolic, and the internal and external anal sphincters exemplify the principle of reciprocal innervation or what Meltzer termed contrary innervation. For instance, the motor nerve to the ileocolic sphincter is the same as that which causes inhibition of the bowel wall, namely, the sympathetic. Stimulation of this nerve will in consequence produce a double effect, contraction of the sphincter and inhibition of the wall of the ileum (207). The action of the vagus in man is without any effect upon the sphincter at this region. Hinrichsen and Ivy (208) using dogs observed that the vagus nerve contains both motor and inhibitory fibers for the ileocolic sphincter. They expressed that the normal vagal control of the ileocolic, pyloric and cardiac sphincters results in relaxation followed by contraction. The splanchnic nerves contain only motor fibers in dog.

The internal anal sphincter is also innervated in a fashion contrary to that of the rest of the large bowel. The pelvic is the inhibitory nerve, while the sympathetic is motor. Stimulation of the parasympathetic nerves will therefore induce evacuation of the bowel by excitation of the bowel

bowel wall and relaxation of the sphincter. Stimulation of the sympathetic on the other hand inhibit the intestinal activity and increase the tone of the sphincter (261).

The external anal sphincter is composed of striated muscle, it is kept tonically contracted and is under voluntary control. The muscle of the external anal sphincter is peculiar in that it does not degenerate after removal of its nerve supply, but to recover its tone to a large extent after section of the perineal branch of the pudendal nerve. The physiological reactions of the muscle are also peculiar, somewhat resembling those of smooth muscle. Findings such as these had led to the belief that the external anal sphincter is practically independent of connection with the central nervous system and is probably under control of local nerve ganglia.

Pathology of sphincters:

Cardiospasm. Cannon (78), Carlson, Boyd and Pearcy (103) found that the cutting of the vagus nerves in the neck produced a temporary spasm or a failure of relaxation of the cardia, however, such spasm seen after cutting the nerves is generally transient and is soon replaced by relaxation of the sphincteric ring. Morley (325) and Rake (363) noted that, in specimens which they removed from patients who had died of cardiospasm, the esophageal dilatation terminated at a point where the lumen normally narrows, but at this point there was no sign of a hypertrophied muscular sphincter. Curiously, the finger could

easily be pushed through the contracted segment. This failure of normal relaxation is what led Hurst to give the term "achalasia" for this type of disease. It is interesting to note that the pathologist does not find any hypertrophy of the muscle around the cardia such as we would expect to see if the esophagus had fought for years against a contracted tonus ring. The same peculiarity is found in Hirschsprung's disease, where the pathologist cannot see anything grossly wrong at the point where the tremendously dilated part of the colon joins the normal part in sigmoid flexure or rectum.

Because gastro-intestinal upsets sometimes follow unilateral phrenicotomy, Ballon et al (43) investigated the condition of the cardia and stomach after this operation. The gas bubble in the stomach was sometimes enlarged when the left leaf of the diaphragm was markedly elevated, but there was no evidence to indicate that phrenicotomy produces cardiospasm or obstruction of the lower end of the esophagus.

A simple explanation for the production of cardiospasm and Hirschsprung's disease would be a loss of function in certain ganglion cells in the intestinal plexuses. Robertson and Kernohan (372) showed that not only was the myenteric plexus practically absent in the undilated segment of the colon, but it was largely gone in the dilated segments. There were no signs of an inflammatory process. Stokes (409), Rake (362), Cameron (73), Mosher and McGregor (328) and particularly Lendrum (264) all showed that by making serial sec-

tions of the cardia removed from patients who have died of cardiospasm, there is a more or less complete absence of ganglion cells between the coats of muscle.

Against this simple assumption of the causation of contraction rings is the work of Wade and Royle (436), Judd and Adson (233), Adson (3), and Telford and Stopford (413) who found that in some cases of Hirschsprung's disease much of the spasm or whatever it is that causes the obstruction can be relieved by sectioning the lumbar sympathetic nerves. According to Rives and Strug (370), in the case of a child observed by them the induction of spinal anesthesia was enough to give relief for a month. Adamson and Aird (2) published roentgenograms showing that, in cats, they were able to produce great enlargement of the colon by removing the parasympathetic nerve supply from its distal end.

Congenital pyloric stnosis. Some interesting physiologic problems are connected with congenital pyloric stenosis. As is now well known, infants with this trouble do badly on liquids and sometimes get well when fed semisolids. Solid foods seem to increase the tonus of the gastric wall more than liquids do, and this should help in getting the gastric contents into the bowel. It may be also that the waves can grip solids and push them onward in a way that they cannot do with fluids.

It is interesting also that these infants promptly get well and stay well after the Fredet-Ramstedt operation, which consists of cutting the sphincter across down to the mucous

membrane. Subsequent explorations or necropsies show that after this operation the muscular tumour disappears (116), but it does not do so after gastro-enterostomy (267). After the Ramstedt operation, the resultant scar tissue pulls the ends of the muscle together and welds them into a practically normal sphincter which never seems to give any more trouble.

Megacolon - Hirschsprung's disease. This is a relatively rare condition appearing in childhood and characterized by constipation, tremendous dilatation of the colon and more or less hypertrophy of its wall. According to Fulton (159), the condition is due to an abnormality in the innervation of the colon, an imbalance between the activities of the thoraco-lumbar and sacral outflows. Such imbalance between the two divisions is revealed in the clinical conditions of cardio-spasm, pylorospasm and megacolon, in all of which the sympathetic side dominates the picture. Fraser (156) believes that the innervation of the gut through the thoraco-lumbar outflow precedes developmentally the innervation through the balbo-sacral outflow. Thus, in the early days life, nerve impulses leading to inhibition of the colon and to contraction of the internal anal sphincter, may be the cause of Hirschsprung's disease. Ross (378) has offered the interesting suggestion that in certain individuals there may be developmentally an anatomical gap between the end of the vagus and the beginning of the sacral innervation to the large intestine, and that in this interval the sympathetic nerves provide the only extrinsic innervation.

Loss of function in certain ganglion cells has been described. Specially the degeneration of the cells of Auerbach's plexus would suggest that the cause of the condition is underactivity of the parasympathetic innervation rather than overactivity of the sympathetic. According to Hurst (222), who believes that there is a failure of relaxation rather than a spasm of sphincters and this failure of the internal anal sphincter to relax coordinately with contraction of the colonic wall is an important element in the pathogenesis of megacolon. The marked hypertrophy of the bowel wall seen in some cases supports this view. It is most likely, however, that the imbalance between the sympathetic and parasympathetic innervations is not only confined to the sphincters but affects the bowel wall as well. This conclusion is based upon the fact that the dilated and immobile colon shows strong and effective contractions after a spinal anesthesia (384). It seems to indicate that the motor mechanism is intact but under the influence of an inordinate inhibitory action exerted through the sympathetic. Generally, the most successful treatment of the condition consists in excision of the lumbar sympathetic ganglia, or section of the presacral and inferior mesentery nerves.

# THE EFFECT OF POTASSIUM ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT

Physiological considerations. The metabolism of some electrolytes in the body is intimately related to the water balance and acid-base equilibrium of the body, e.g., sodium, potassium, and chloride. These substances are concerned in at least four fundamental physiological processes: a, the maintenance of normal water balance and distribution; b, the maintenance of normal osmotic equilibrium; c, the maintenance of normal acid-base equilibrium; and d, the maintenance of normal muscle irritability (91).

Potassium is the chief cation of the muscles and of most other cells ( intracellular fluid ), whereas sodium is the chief cation of extracellular fluid of the body. Although some movement of potassium and water occurs from cells to plasma, particularly when excessive amounts of sodium chloride and water are lost from the body, and in disturbances of acid-base balance, the potassium is usually excreted promptly in the urine. Any considerable replacement of sodium by potassium in the extracellular fluids is accompanied by seriuos disturbances and is eventually fatal. Moreover, no other cation can entirely replace potassium in the intracellular fluid without interferring to a certain extent with the functional activity of the cell. In low concentrations potassium is excitatory and in higher concentrations it is inhibitory (68) (149), these effects being particularly important in relation to nerve synapses or myoneural junctions. Under normal conditions, its

effects resemble those of parasympathetic stimulation, and are usually inhibited by calcium (91), for instance, neuromuscular excitability. The K / Na ratio is also important in this connection. Potassium and calcium modify the most fundamental properties of protoplasm and cells, including the permeability of cell membranes, and thus they play a role in almost all vital processes.

The actions of the different cations upon the heart beat have benn well established. Ringer (369) observed that if the heart were perfused with 0.6 per cent sodium chloride solution a few beats were executed, but the heart then stopped in diastole. The addition of calcium restored the beat for a time but the heart again came to a standstill, this time in systole. The addition of potassium antagonized the calcium effect; the beat recommenced and was maintained. It is well known that calcium in excess, or in normal concentration, but in the absence of potassium, lengthen the systole at the expense of diastole. The heart finally stops in the fully contracted state, so-called calcium rigor. Potassium acts in a reversed manner if in excess or unbalanced by the calcium. More and more of the cardiac cycle is occupied by diastole and the heart ultimately comes to rest in the completely relaxed state and this is potassium inhibition. A solution containing calcium and potassium alone will not sustain the beat; sodium is essential. It is apparent that these three cations are absolutely necessary for the normal beat of the heart, the calcium increasing the contractility and prolonging the systole. Potassium has the reverse effect, reducing the contractility and favoring relaxation. The

presence of these substances in proper proportion ensures the rhythmicity of the contractions. The underlying physical and chemical changes through which these elements influence the heart beat is not definitely known. One assumption that calcium decreases and potassium increases the permeability of the cell membrane. The excitability and contractility of the muscle fiber is dependent upon the relative concentrations of H ions on the two sides of the cell membrane. The calcium and potassium ions through altering the cell permeability may in this way affect the diffusion of H ions across the membrane and so vary their relative concentrations on the two sides.

The potassium ions also play an important role in the synaptic transmission of the nerve. The injection of small amount of potassium chloride into the fluid perfusing the superior cervical ganglion stimulates the nerve cells (147). When the concentration of the potassium chloride is raised to four times the normal, acetylcholine appears in the venous outflow from the ganglion (68). It had been reported previously by Beznak (55) that potassium chloride causes the liberation of acetylcholine in the frog's heart. After section of the cervical sympathetic and degeneration of the preganglionic fibers the addition of potassium chloride to the fluid perfusing the superior cervical ganglion, though still causing excitation of the cells, results in the liberation of an insignificant amount of acetylcholine. This fact indicates that the potassium ions itself have a stimulant action upon the ganglion cells. Brown and Feldberg (68) found, for instance, that curare, which blocks transmission at synaptic junctions, does so

by preventing acetylcholine from acting on the ganglion cell; but it actually enhances the response to potassium chloride. The output of acetylcholine from the preganglionic endings was not affected by the poison. Brown and Feldberg proposed that the liberation of acetylcholine under normal circumstances is dependent upon the movement of potassium ions accompanying the preganglionic impulse and that the appearance of potassium ions at the synapse also contions the action of acetylcholine upon the ganglion cell.

The calcium also plays an important role in the excitation mechanism as shown by Bronk (66) who found that the absence of calcium ions caused a long continued spontaneous discharge from sympathetic ganglion cells. Bronk has also reported that doubling the calcium concentration greatly reduces the frequency of the impulses discharged by nerve cells stimulated by acetylcholine. Lowering the concentration of potassium had a similar effect. Either lower the concentration of calcium or increasing that of potassium increased the frequency of the impulses. Harvey and McIntosh (188) found that absence of calcium from the fluid perfusing the ganglion results in failure of synaptic transmission and of acetylcholine liberation from the preganglionic terminals. The absence of calcium was not followed by spontaneous activity of the ganglion cells unless potassium was present. It did not result, therefore, when the ganglion was perfused with a 0.9 per cent sodium chloride solution. These observers conclude from their experiments that calcium is necessary in order that potassium can act to liberate acetylcholine from the nerve endings. Impairment of transmission at the myoneural junction has been observed

by Brown and Harvey in young animals kept on a diet deficient in calcium.

The potassium concentration of normal blood serum in man, is 16-22 mg per 100 c.c., average 19.5 mg; these values correspond to a concentration of 5 m.eq. per liter. While there is little or no sodium in the erythrocytes, the average concentration of potassium in these cells is about 420 mg per 100 c.c. (56) (91).

Under conditions of normal gastro-intestinal function, potassium is practically completely absorbed from the gastro-intestinal tract. Normally, about 90 per cent of the excreted potassium is eliminated in the urine; less than 10 per cent of the potassium ingested is eliminated in the feces. Large quantities are eliminated in the feces in patients with diarrhea, but this excess may be due in large part to failure of reabsorption of digestive fluids rather than entirely to failure of absorption.

As stated above potassium is the predominant base in the cells, and sodium predominates in the blood plasma and other extracellular fluids of the body. The exact significance of this inequality of distribution and the mechanism whereby it is preserved are not clearly understood. It is clear, however, as stated by Peters and Van Slyke (344) that potassium is prevented from diffusing out of the cells by a membrane or some other restraining factors present in the cellular and extracellular media. It also appears that the same or similar factors tend to prevent the undue passage of sodium into the

cells under physiological conditions. There is plenty of evidence, however, that this impermeability of cells, at least to potassium, and perhaps also to sodium, is by no means complete, and it is certainly not so in a variety of abnormal conditions.

The distribution of potassium, sodium and chloride, as well as water, between intracellular and extracellular fluids of the body is influenced profoundly by the disturbances of the adrenal cortical hormone. Numerous investigations have clearly established the fact that removal of the adrenal cortex leads eventually to low sodium and high potassium concentrations in the serum due to excessive excretion of sodium and chloride and defective excretion of potassium. In many respects the symptoms of adrenal insufficiency resemble those of toxic doses of potassium. Potassium is abnormally toxic after adrenalectomy and a low potassium diet as also a high sodium diet is favorable to survival. Injection of cortin lowers serum potassium by decreasing the excretion of sodium and increasing the excretion of potassium.

From the point of view of physiology of the potassium it is of prime importance to determine whether the changes in the concentration of this ion which have been described for adrenalectomized animals are directly determined by the presence or absence of cortin or whether cortin acts only on the excretion of sodium and chloride, all the other changes being secondary to resulting decrease of blood volume. A good account can be made out for the latter view for a loss of sodium and chloride leads to a loss of water thus simula-

ting the conditions of hemorrhage and shock. Other observations indicate, however, that some definite effect of cortin upon potassium both in the kidney and in the tissues has to be postulated in addition. Thus even after removal of the kidneys from adrenalectomized rats the administration of cortin caused the usual fall in the concentration of potassium in the serum as reported by Ingle (226). Direct analysis of tissues of adrenalectomized animals for potassium has provided further evidence. Still further evidence that the adrenal cortex has some specific potassium effect was provided more recently by experiments with desoxycorticosterone (274). After daily administration to dogs for 10 to 20 days the serum potassium fell to about half the normal value and symptoms resembling those of familial periodic paralysis developed. Administration of cortical hormone to normal subjects causes retention of sodium, chloride and water and potassium diuresis (426) (427) (428) (429). The exact mechanism of action of this adrenal cortical hormone in this connection is not known. There are observations which, suggest that the regulation of potassium rather than sodium metabolism is the most important fundamental action of this hormone and that the alteration in potassium metabolism mentioned above constitutes the most important and most characteristic feature of adrenal insufficiency.

Completely adrenalectomized animals can be maintained in good health without adrenal cortical hormone if placed upon a diet low in potassium but high in sodium chloride (226),

and in order to prevent acidosis which otherwise develops containing sodium citrate. The tendency to hypoglycemia is controlled by a high carbohydrate diet. These measures, however, do not completely restore an animal to a physiological state, for they are unable to withstand stress or to perform work with full efficiency unless adrenal cortical hormone is added. It is claimed that cortin, not desoxycorticosterone, postpones muscular fatigue, a normal animal being capable of greater work under its influence (226).

Significant abnormalities in the concentrations of sodium, chloride and potassium in the serum in adrenal cortical insuffiency occur only during impending or actual crisis. Studies of the concentrations of these elements in the blood are no wonder of little or no practical value in states of mild or moderate impairment of adrenocortical function. The earliest metabolic abnormalities are reflected in excessive excretion of sodium, chloride and water in the urine, these phenomena constituting the basis for a diagnostic procedure that has been proven to be of value in the early diagnosis of adrenocortical inadequacy. Another procedure has been proposed also for the diagnosis of adrenal cortical insufficiency, which based upon the findings that patient and animals with adrenal insufficiency exhibit a diminished tolerance to ingested potassium (464) (465). In normal subjects, the ingestion of 10 mg of potassium per pound of body weight is followed by no significant alteration in serum potassium concentration. Subjects with adrenocortical insufficiency exhibit a sharp increase in

serum potassium concentration ( 100-200 per cent ), usually within 30 minutes after ingestion, with a subsequent fall of serum potassium to within normal limits at about one and one half hours.

Addison's disease and desoxycorticosterone. Addison's disease is relatively rare. The rate of admission to the Mayo Clinic is about 16 per 100,000. Guttman (181) collected 566 cases from the literature over the period 1900 to 1930. The essential lesion is a progressive necrosis with collapse of the stroma of the cortex. Guttman found bilateral tuberculosis reported in 69.7 per cent of the cases he reviewed. Though the essential lesion is in the cortex, actually a given lesion may involve the whole gland and symptoms may be due to dysfunction of both cortex and medulla. These are chiefly asthenia, loss of weight, hypotension and hypoglycemia.

Biochemical study has been outstandingly successful in contributing to an understanding of the mechanism and pathology of Addison's disease. In 1932, Loeb (273) reported the chemical changes in Addison's disease and the figures are quoted in the next page.

Some twenty crystalline steroids or compounds have been isolated from the adrenal cortex which exhibit in greater or less degree the physiological properties of crude cortical extracts. Desoxycorticosterone was synthesized by Steiger and Reichstein from stigmasterol. This synthetic compound, which exerts its action predominantly upon water and salt ( sodium and potassium ) metabolism, is administered in the

Table 3

The blood chemistry in Addison's disease.
( based on Loeb's series of 23 cases ).

| | |
|---|---|
| Non-protein nitrogen<br>normal - 33 mg N<br>per 100 c.c. | 1. Increased in 41.7 % of observations.<br>2. Increased in 6.4 % of observations when Na was normal. |
| Potassium (serum)<br>normal - 5 m. eq.<br>or 315 mg per<br>100 c.c. | 1. Increased in 43.7 % of observations.<br>2. Increased in 3.8 % of observations in which Na was normal.<br>3. Remained in normal in 32.1 % of observations when Na was decreased. |
| Sodium (serum)<br>normal 137 m. eq.<br>or 315 mg per 100 c.c. | 1. Decreased in 75.7 % of observations.<br>2. Decreased in 32.1 % of observations when Na was normal.<br>3. Decreased in 44.8 % when N.P.N. normal. |
| Calcium (serum)<br>normal - 10 mg<br>per 100 c.c. | 1. 8 out of 20 patients showed at some time or other over 11 mg.<br>2. 2 out of 20 pts showed over 13 mg. |
| Phosphorus (serum)<br>upper normal limit<br>4 mg per 100 c.c. | 1. Increased in 42 % of observations.<br>2. Accompanied N retention in 29 observations.<br>3. In 39 out of 42 observations P was greater than 4 mg, there was decrease in Na. |
| Sugar<br>normal - 70-90 mg<br>per 100 c.c. | 1. 5 out of 23 patients had hypoglycemic ep episodes with blood sugar below 50 mg.<br>2. 9 out of 23 patients had at one time or other blood sugar below 70 mg. |
| Chloride (serum)<br>normal average -<br>102 m. eq. or<br>362 mg per 100 c.c. | Decreased. |
| Bicarbonate (serum)<br>normal average -<br>24.5 m. eq. or<br>55 vol. per cent<br>total $CO_2$. | Decreased. |

form of the acetate either subcutaneously or intramuscularly in oil, or in the form of pellets implanted beneath the skin (288) (428). Desoxycorticosterone has little or no effect upon carbohydrate metabolism, whereas corticosterone which shows this effect to a marked degree exerts a minor action upon the metabolism of water and salt.

The clinical application of desoxycorticosterone followed the demonstration of its effectiveness in maintaining completely adrenalectomized animals. In 1938 Levy Simpson (396) first reported its successful use in Addison's disease. More recently, Thorn et al (427) (428) (429) studied its administration in a larger series of patients. They found that about 10 mg of desoxycorticosterone acetate per day were necessary for the maintenance in a normal state of patients with Addison's disease; smaller amount could be given if sodium chloride was also administered. In addition to the clinical evidences of improvement, it was found that due to the most outstanding action of desoxycorticosterone upon salt and water metabolism, it increases the plasma volume and the concentration of sodium in the body fluids, but reduces that of potassium. These effects are due largely but not entirely to an action upon the renal tubules. They are partly extrarenal for this steroid appears to influence the membrane permeability of the tissues generally; the intracellular potassium concentration is increased and the sodium concentration is reduced. As a result of its effect in causing the retention of sodium and water, desoxycorticosterone administration may be followed by edema (288) (427) (428).

In large doses it may cause more serious effects, e.g., hypertension, dilatation of the right ventricle and pulmonary congestion. Death from cardiac failure has resulted from its clinical use. The manner in which desoxycorticosterone induces these ill-effects is not altogether clear. The rapid increase in plasma volume, and, as a result of this, the extra burden thrown upon the cardiovascular system is suspected of being an important factor. Depression of the potassium concentration of the body fluids may be the lethal factor in some instances; Loeb and his associates (274) have shown that the administration of desoxycorticosterone to normal dogs may lower the potassium level to the point where muscular weakness and paralysis develop. This paralysis is associated with a partial replacement of the intracellular potassium of the skeletal muscles by the sodium. The administration of potassium salts or a reduction in the sodium intake is undoubtedly of benefit in patients receiving large doses of desoxycorticosterone.

An increase in serum potassium concentration is one of the most constant features of severe clinical and experimental adrenal cortical insufficiency, 50 mg per 100 c.c. having been reported (465), but equally high concentrations may occur in other conditions with or without similar symptoms. There is a prevalent opinion that a high growth rate of tissues is related to a high potassium content (149). In mice large rapidly growing tumors had a high potassium and low calcium content while the reverse was true in slowing growing tumors.

In general potassium falls and calcium rises with increasing age of the tumor. In the chicken sarcoma there is in general a fall of potassium and magnesium and a rise of sodium, calcium and chloride in passing from the normal through the actively growing periphery of the tumor to the necrotic interior and the same changes occur progressively as the tumor ages. In human tumors the potassium content has been found uniformly higher than in the normal corresponding tissues, and a low potassium diet has been recommended for cancerous patients. The bone marrow has also been reported high in potassium during the growth of carcinomas in the body. During pregnancy the potassium content of the uterus increases with the growth of that organ. This is probably due, however, merely to a decrease in the relative amount of non-muscular tissue. In plants also most potassium is found when growth is rapid. A high potassium content, however, is presumably the result rather than the cause of the rapid growth and there seems to be no evidence that potassium has any specific effect upon growth except that it supplies an essential component of the new protoplasm.

It is proposed by Brewer (65) that there seems to be some positive correlation between the change in metabolic activity and the plasma potassium level. It is based on his experiments that sudden changes in cellular activity induced by inhibiting or exciting stimuli frequently to be accompanied by marked permeability changes particularly with respect to the potassium ion. This is reflected in decreases or increa-

uniformly lower the plasma potassium but this decrease may be prevented or converted to an actual increase by the administration of dinitrophenol which has an exciting effect on the general cellular metabolism. Muscular activity is known to deplete the muscle of potassium (148), and to bring about an increase in plasma potassium (241). This has been taken to indicate that the potassium level in the blood follows the metabolic rate as it often does. The heart muscle like the skeletal muscle probably loses potassium during activity for low potassium contents have been found in the over-worked hearts of cardiac patients after death. The possibility of loss of potassium from smooth muscle or the central nervous system during activity has not been adequately investigated. To date, there is no evidence so far reported in the literature to clear this point. Various other conditions such as severe hemorrhage and surgical shock (386) (467) act similarly to effect an increased plasma potassium level. The rise of potassium in severe hemorrhage represents an attempt to build up the blood volume at the expense of cell fluids after extracellular fluids are exhausted.

The injection of epinephrine is quickly followed ( within one minute ) by a 50 per cent increase in serum potassium concentration, which returns to normal after a few minutes (136). This phenomenon appears to be dependent upon mobilization of potassium from the liver since a, exclusion of liver from the circulation abolishes the effect; b, blood from the hepatic vein contains more potassium than that from

the femoral artery; c, inject adrenaline into the portal vein produces much more marked effect on concentration of potassium in hepatic vein than that injected into the arm vein; d, adrenaline liberates potassium from a perfused liver. It is interesting to note in this connection that the administration of large doses of insulin, in normal subjects and in patients with diabetes, is followed by a decrease in serum potassium concentration.

In the terminal stages of renal failure, with uremia, the serum potassium concentration may be markedly increased (344) (345), however, it is within normal limits in the great majority of patients with chronic glomerulonephritis. The cause of this increase is unknown, but it may be dependent upon a combination of diminished excretion by the kidneys, including the so-called auto-intoxication and the passage of excessive amounts into the blood as a result of toxic nutritional disturbances in the tissues.

Increased values for serum potassium, as high as 60 mg per 100 c.c., have been observed in clinical and experimental acute intestinal obstruction (385). The possibility has been suggested that this increase may be due to increased absorption of potassium from the contents of the obstructed bowel; others attribute it to adrenal cortical insufficiency. The assumption made by Zwemer and his associates (466) that a high level of potassium in the blood is the cause of death in intestinal obstruction has not been substantiated by others. Keith and Binger (239), for example, raised the blood potas-

sium of a group of normal persons and observed no harmful effects, and in patients suffering from obstruction there is a tendency for the potassium concentration of the blood to decrease rather than to increase (144). In experiments with dogs, Greewood, Haist and Taylor (177) found a significant rise in potassium as a terminal event only, and concluded, therefore, that hyperpotassemia was a factor of little importance as a cause of death in intestinal obstruction.

It has been suggested by Scudder and his associates (386) that potassium derived from disintegrated cells (340) (412) of the injured tissues is the responsible toxic factor in traumatic shock. The blood potassium may rise to double or more than double the normal value in shock, specially in the later stages. However, potassium does not appear to be a primary or major factor in the development of shock state. On the other hand as pointed out by Winkler and Hoff (458), the picture of potassium poisoning is totally different from that of traumatic shock. Manery and Solandt (302) found that the fatal level of blood potassium ( 15 m.eq. per 100 c.c. ) was many times higher than that seen in animals dying of shock. Any statement as to the fundamental cause of shock following mechanical injury is not warranted at the present time. Hemorrhage is undoubtedly a contrubuting factor in many instances, in others nervous influences may play a part. Although it has been difficult to obtain direct evidence of a circulating toxic agent, the possibility if not the probability of such being responsible can not be neglected.

Attention has been directed to the occurrence of changes in the concentration of potassium in the blood serum in patients with bronchial asthma and certain other allergic states. Thus Rusk et al (379) and Zwemer (464) found that compared to average normal values of 19.5 mg, the serum potassium rose to average 24.4 mg during acute attacks of bronchial asthma. A slight reduction average 23.6 mg accompanied the asymptomatic period. Increased serum potassium was also noted in patients with acute and chronic urticaria. The relation of adrenal cortex to allergy has been discussed elsewhere (464). Certain allergic patients with urticarial and asthmatic manifestations were definitely relieved when treated with potassium chloride, alone, or in combination with other drugs. This paradoxical effect is hard to explain, though a possible, unverified explanation is that the increased potassium in the serum is the result of its loss from the tissues and that the therapeutic administration of this element makes available a source of potassium replacement for the depleted body cells.

It was noted for a long time whereas the sodium and chloride are retained during fever, e.g., pneumonia, the output of potassium is either undiminished or increased (340). This has been confirmed by Sunderman et al (412). The augmented output of potassium continues after the crisis and apparently reflects tissue destruction. The reduction in total base of the serum is at the expense of the sodium; serum potassium either remains unchanged or is increased.

Certain patients with Cushing's syndrome ( pituitary

basophilism ), exhibit changes in the serum electrolyte pattern and urinary excretion of sodium and potassium that are opposite to those in Addison's disease, with decreased serum potassium concentration, suggesting a state of adrenocortical hyperfunction (35) (291). This decrease of serum concentration is attributed to a state of increased adrenal cortical function due to excessive secretion of the adrenotropic hormone of the anterior hypophysis. These phenomena form the basis for a procedure that has been suggested for the demonstration of these metabolic abnormalities in early cases of this condition (93).

A decrease in serum potassium occurs during attacks of paralysis in the condition known as familial periodic paralysis. During spontaneous attacks of this disease the potassium in the blood regularly decreases, being usually below 14 mg per 100 c.c. and at times as low as 8 mg per 100 c.c. have been reported. The attacks may be induced by procedures tending to lower blood potassium such as injection of insulin, or of sugar, or a high carbohydrate meal. Injection of calcium chloride aggravates the attacks, whereas injection of potassium salts or muscular excercise tends to prevent them (4) (202) (351) (428). The urine potassium excretion may decrease during an attack, suggesting that the potassium is not lost from the body but perhaps undergoes redistribution between the intra- and extra-cellular fluids. The relation of this phenomenon to the attacks is not understood. However, as discussed before, even though the potassium cannot be properly regarded

as a humoral agent for neuromuscular transmission it undoubtedly plays an important role in the neuromuscular junction or synapse. Thus the injection of potassium chloride or potassium citrate (202) may serve to reestablish contractions from nerve stimulation in a muscle previously paralysed by curare. The striking effects of potassium in curing or preventing an attack of familial periodic paralysis are to be interpreted in this sense. Some favorable effects of potassium have also been observed in myasthenia gravis where the dramatic effect of prostigmine indicates clearly that the difficulty is myoneural in its location.

Potassium deficiency. Studies of potassium deficiency have been made by a number of workers with conflicting results and interpretations. The rat is the most convenient animal to be used for this purpose. Osborne and Mendel (335) reported that rats fed diets containing 0.033 per cent potassium survived and grew as well as control rats fed diets containing 0.833 per cent potassium. Miller (318) was unable to confirm these findings and reported growth retardation when the dietary potassium content was reduced below 0.10 per cent. Heppel and Schmidt (200) reported poor growth and early death in rats fed diets of low potassium content ( 0.0015 to 0.016 per cent ). Schrader et al (382) noted myocardial, renal and numerous other lesions in addition to growth failure and poor survival. It has been frequently postulated that this syndrome is dependent upon a concomitant vitamin B complex deficiency (198) (382) (424), and consequently not related to the low potassium content in the diets. The most recent investigation was

carried out by Kornberg et al (249) who used the potassium deficient diets contained from 0.01 to 0.17 per cent potassium. In their studies they found that diets containing 0.01 to 0.05 per cent potassium failed to gain weight and died with multiple lesions after approximately 22 days. Administration of potassium to potassium deficient rats resulted in immediate growth at a rate ( approximately 25 gm. per week ) equals to that of rats fed potassium adequate diets. While withdrawal of potassium from rapidly growing rats weighing approximately 100 gm. resulted in a prompt cessation of growth, multiple lesions and death in about 47 days. From the data in their experiments they marked out a dietary potassium-level of approximately 0.17 per cent to be the minimal for optional growth and for the prevention of lesions and at which the further addition of potassium failed to increase the rate of growth. They also found that when most of the vitamins were added to the potassium deficient diets in sufficient quantity did not prevent the development of the signs and symptoms of potassium deficiency. This finding is in agreement with some previous workers (200) (153) (334), but is not in agreement with the findings of others (424) (198) (382).

As mentioned before that there is no other cation can entirely replace potassium in the intracellular fluid without interferring to a certain extent with functional activity of the cell. This may be accounted for most of the pathological lesions as reported by many investigators in their animal experiments with fed rations low in potassium. The work

reported by Heppel (199) provided some evidence to show that the muscles of the rats deprived of potassium take out sodium instead of potassium. This occurs to such an extent that in some instances the muscles of the experimental animals are found to be richer in sodium than in potassium. The serum potassium drops to one-half of the normal value and the concentration of chloride is reduced by about 15 per cent. This shows the condition in which sodium must occur largely as an intracellular cation. In another report he used radioactive isotopes of sodium (198), confirmed that both the extracellular and intracellular fractions of the muscle sodium exchanged readily with the sodium in the plasma. The membranes of the muscle cells were apparently permeable to sodium (321). Loeb (274) and Orent-Kelles (334) both in 1941 made the same observation. Heppel also observed that rats raised on a low potassium diet lose as much as half the potassium of their muscles, replacing it by sodium, but the liver remained unchanged in composition. Orent-Kelles noted some appreciable decrease in potassium both in the heart and kidney beside the muscular changes.

Normally the muscular fiber seems to be impermeable to anions and to the larger cations, such as sodium, lithium and calcium. It is permeable to potassium, cecium, rubidium, ammonium and hydrogen ions. Microscopic studies were made by Follis (152) of the hearts and kidneys of the rats that had been placed on a low potassium diet to which the rubidium or cecium were added. Whereas myocardial and renal necrosis

appeared in control animals in the low potassium diet, the addition of rubidium prevented their appearance. Cecium partially protected the kidney and to even a lesser extent to the heart. Skinner (397) showed that the rats consuming low potassium rations supplemented with either boric acid or borax survived longer than pair mates which received no boron. After 21 days on the low potassium ration rats fed boron contained in their liver 47 per cent more glycogen than those receiving no additional boron. The body fat was also increased in the low potassium rations with boron compound. From above observations it is purely speculative to assume that the metabolism of potassium can be replaced by other electrolytes, since the increase in survival periods when the low potassium ration was supplemented with boron compound was probably due to the effect of boron upon maintenance of these energy-reserves in the body. However, it appears likely that boron is able to substitute in a limited way for potassium in certain roles which the latter element performs in the body, perhaps in connection with certain enzyme systems (397).

Miller and Darrow (320) (321) demonstrated that diets low in potassium made rats more resistent to the toxic effects of potassium. It was known for a long time that potassium is a metabolite which, by accumulation in extracellular fluids is considered to exert a profound toxic effect on the heart. The clearest demonstration is brought out by Hoff, Smith and Winkler (212) and Crismon et al (127) who showed that the toxic effects are accompanied by eletrocardiographic changes

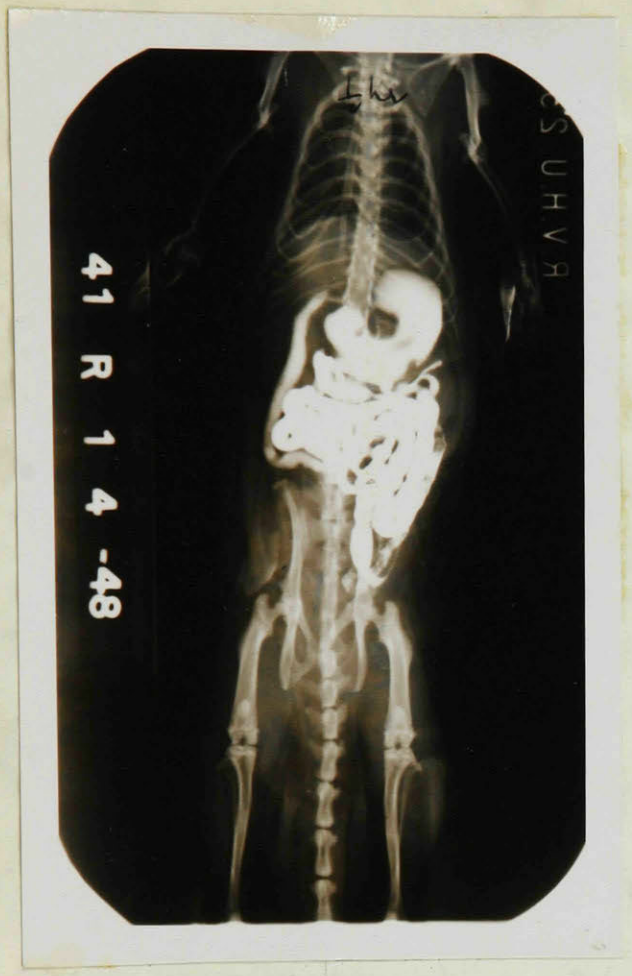
which follow the sequence as poisoning produced by the injection of potassium and each type of electrocardiographic alteration occurs at the same level of serum potassium in the two conditions. The experimental work of Durlacher et al (138) by nephrectomy and ureteral ligation in rats to produce the auto-intoxication of potassium or as Selye and Neilson showed by injections of desoxycorticosterone acetate have a similar effect. The mechanism of this protective action is, in both cases, depletion of muscle potassium which enables this cation to enter the muscle when potassium is injected and thus protect the extracellular fluids from a toxic rise in concentration.

Numerous pathological lesions in potassium-deficient rats have been reported by various investigators. A striking enlargement of the kidneys aws consistently found (139) (402) (198). Histologically, marked dilatation of the collecting tubules was observed with considerable congestion of renal blood vessels. No changes were evident in the glomeruli. Growth and body weight were arrested. The suprarenal glands showed neither congestion nor hemorrhage. Ascites and hydrothorax were occasionally noted. Some opaque areas at the apex of the heart was not uncommon. Sections through these areas showed erosions of the myocardia and replacement with scar tissue. The liver was not involved on gross examination.

The intestinal lesions remain the most controversial point among different investigators in the literature, even

the same group of workers reported different findings at different times (200) (198). This is mainly, perhaps, due to different fed rations used by different investigators. According to the positive findings, the intestinal tract was enlarged with progressive abdominal distention and the autopsy showed a very flaccid and dilated gastro-intestinal tract. Since the potassium causing a contracture of the skeletal muscle and an increase of tone in the heart and smooth muscle under proper conditions, it is not surprised to observe the rats fed low potassium in diet to be present with such atonic state in the intestinal tract. Intussusceptions and areas of annular thickening in the ileum were noted (200) (249) (382).

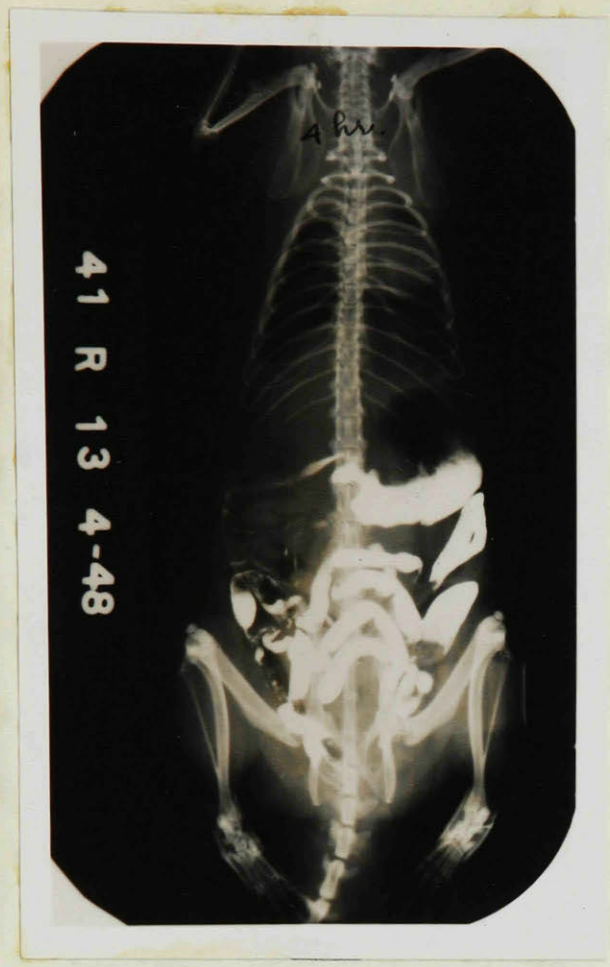
Regarding the effects of potassium deficiency on the gastro-intestinal motility, the information as reported in the literature not only remains controversial but is fairly rare and meager. For this reason experiments were carried out under the instruction of Professor H.E. Hoff. Roentgen-rays were used and rats were the choice. Before the experiments started, eight adult albino rats were examined with barium series in order to get normal x-ray control and all animals appeared normal. This is demonstrated in Fig. 3 and Fig. 6 ( see and compare with normal x-ray control Fig. 1 and Fig. 2 ). It is claimed that during the procedure of force feeding two weeks at least are required as the adaptive period before the low-potassium diet is introduced. 12 c.c. of normal potassium wet diet was given to each animal by force feeding



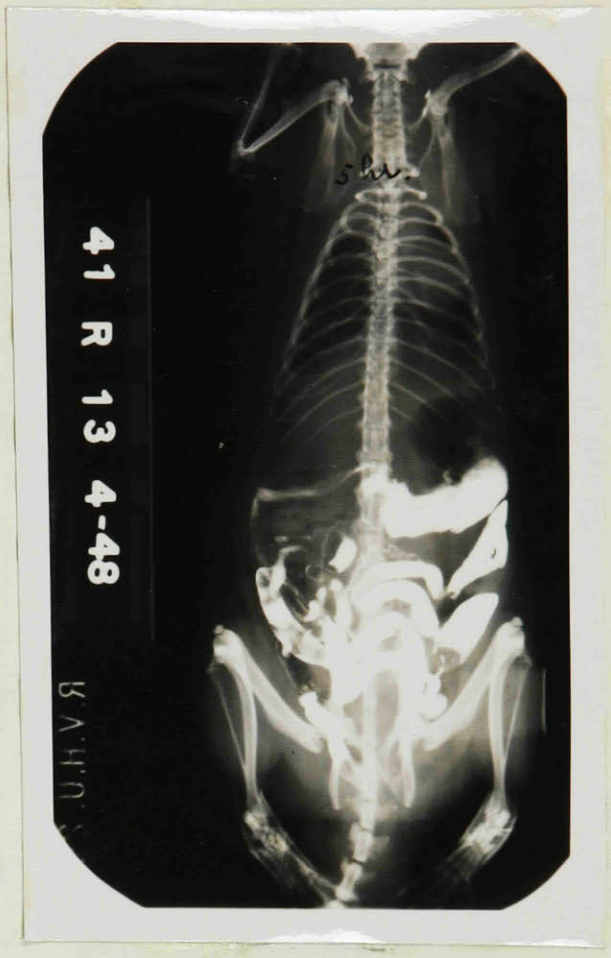

( half hr ) ( 3 hrs )

Fig. 3. Roentgenograms of rat No. 41
( normal barium series for control )

A barium series was carried out before the experiment started. Compare with Fig. 1 and Fig. 2, which are demonstrated as normal barium series, the gastro-intestinal pattern of this rat is normal throughout. The stomach and small bowel show quite active peristaltic movements. Segmenting activity of the small bowel is also active. At the end of 3 hours, stomach is practically emptied. Some trace of barium ~~is~~ still remained in the small bowel whereas the colon is seen to be accumulated with most part of the barium. It also shows that this rat started to excrete barium at the time only 3 hours after the ingestion of it.



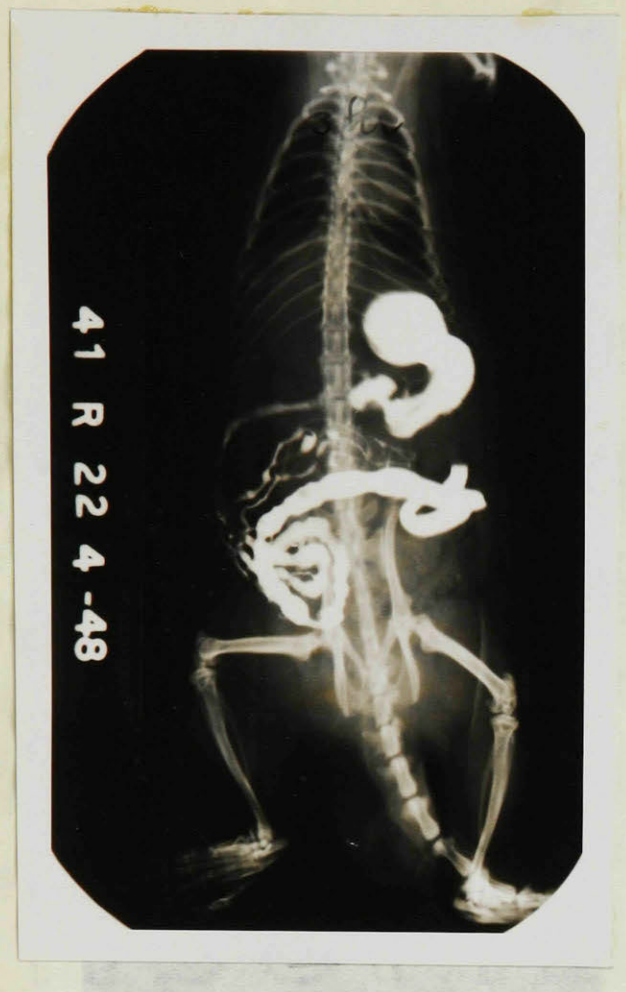

( 4 hrs )



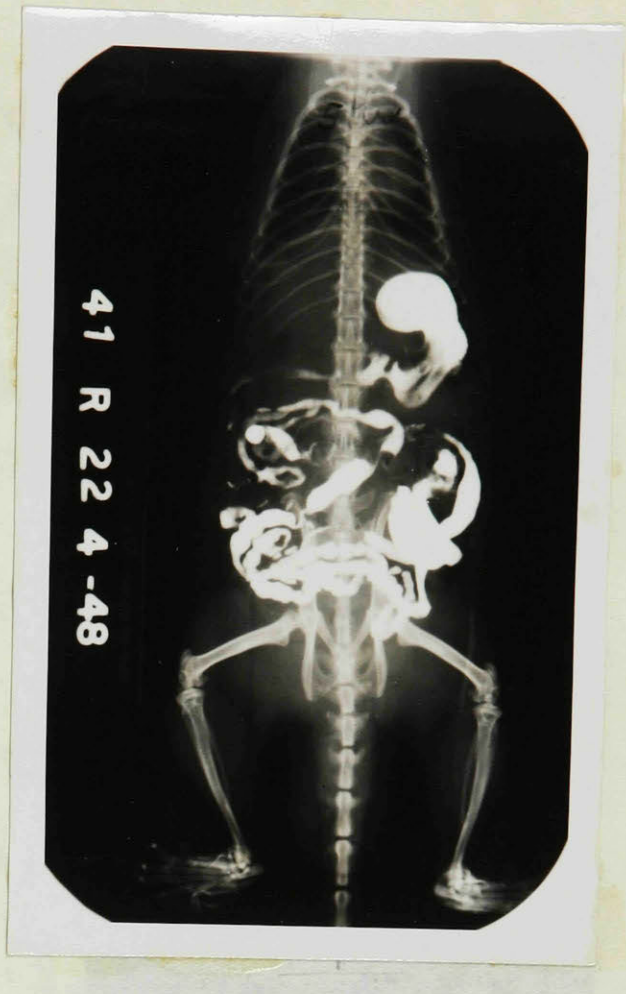

( 5 hrs )

Fig. 4. Roentgenograms of rat No. 41
( force feeding with normal potassium diet
for two weeks )

After two weeks of force feeding with normal potassium containing diet, remarkably abnormal patterns are demonstrated on these films. The stomach is gas-distended and atonic with sluggish peristalsis and shows about 30 % gastric retention at the end of 5 hours. Gas is also present in the whole small bowel. Transit period through the small bowel is greatly delayed - hypomotile. No barium reached the colon at the end of 5 hours. The caliber of both the stomach and small bowel is definitely increased and widened. The small bowel tends to become into separated loops whereas the normal control film shown in Fig. 3 is continuous and smooth throughout. Practically there are no peristaltic and segmenting movements shown on these two films except some abnormally constricted segments of the small bowel are present at the right upper quadrant.



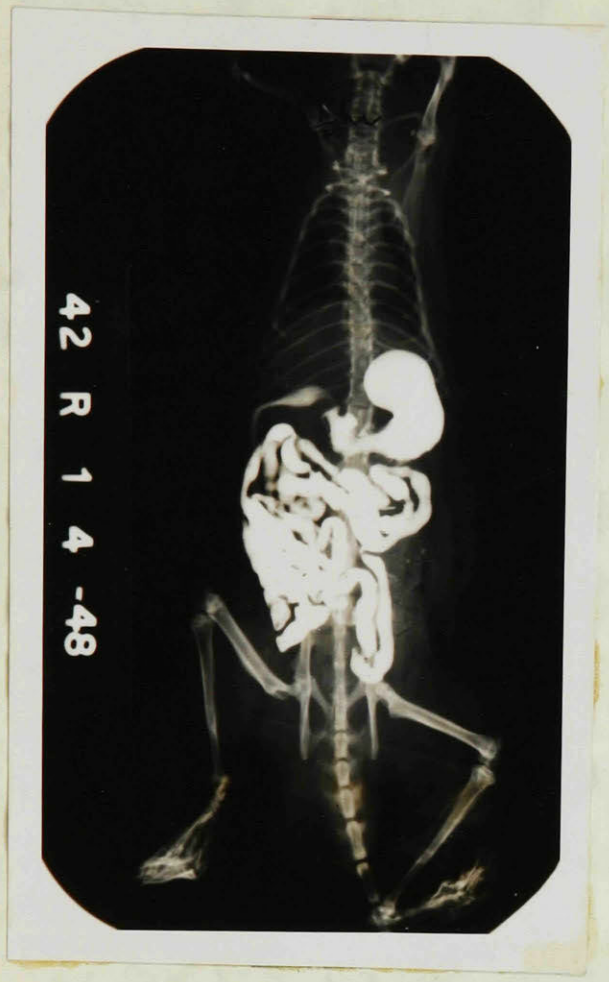

( 3 hrs )



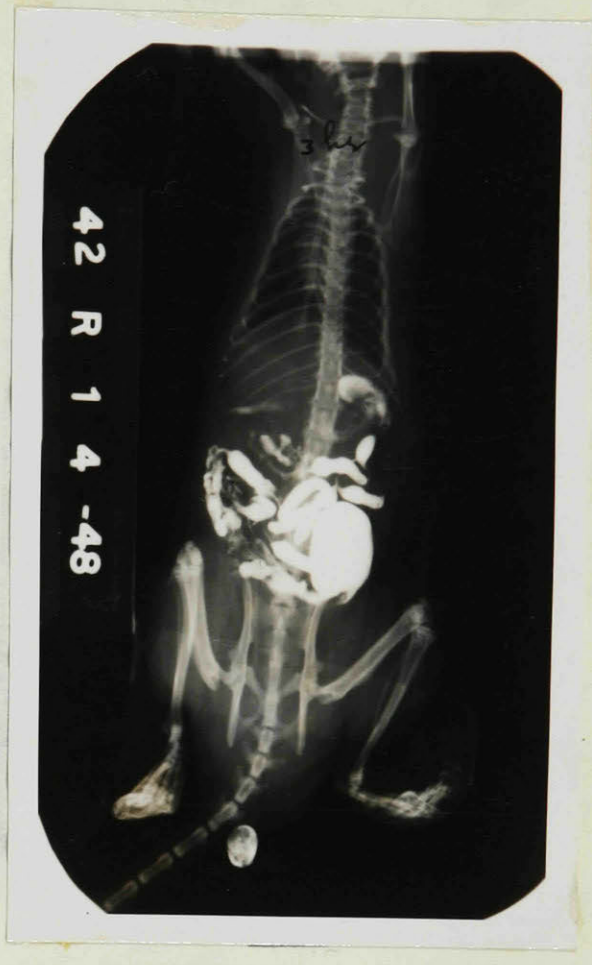

( 5 hrs )

Fig. 5. Roentgenograms of rat No 41
( 10 days after force feeding was abandoned )

After the force feeding was abandoned, this rat was fed ad. lib. with normal potassium containing Purina chow for 10 days, and a barium series was done. The stomach shows definite improvement with active peristalsis. It is not atonic any more, however, a 30 % gastric retention ~~is~~ still persisted at the end of 5 hours. Gas-distention is disappeared in the whole digestive tract. Segmenting movements of the small bowel ~~are~~ recurred, nevertheless, abnormally separated loops as well as constricted segments are still present. The caliber of the digestive tract, except the stomach, has not been returned to normal yet. Transit period is still delayed and no barium excreted at the end of 5 hours.



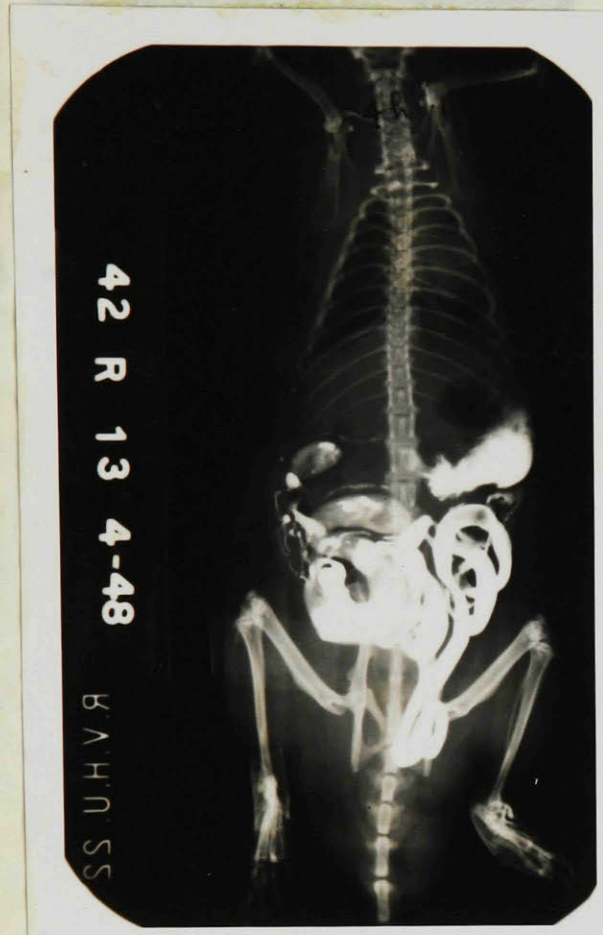

( half hr )



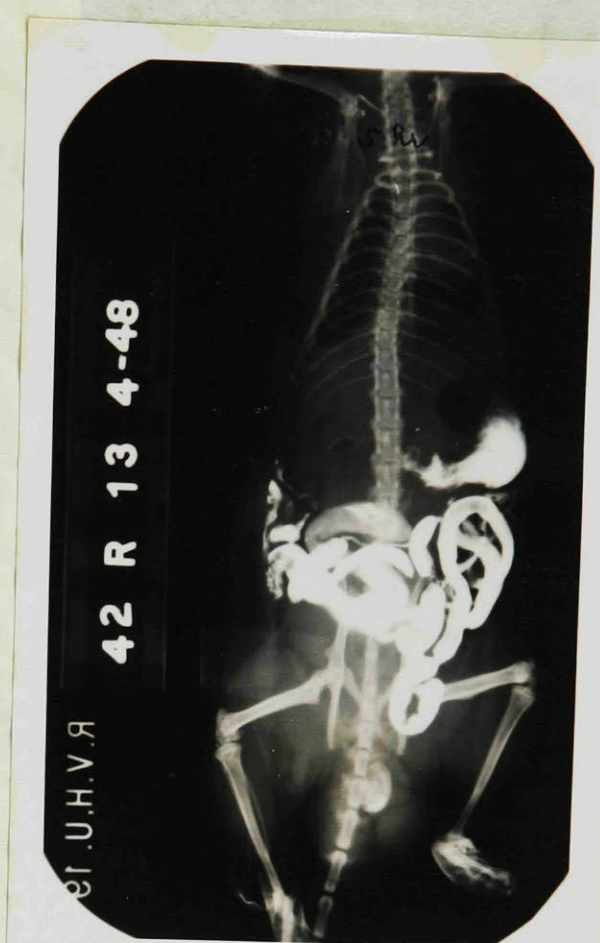

( 3 hrs )

Fig. 6. Roentgenograms of rat No. 42
( normal barium series for control )

The findings as shown on these two films are practically the same as rat No. 41. See the description in Fig. 3.



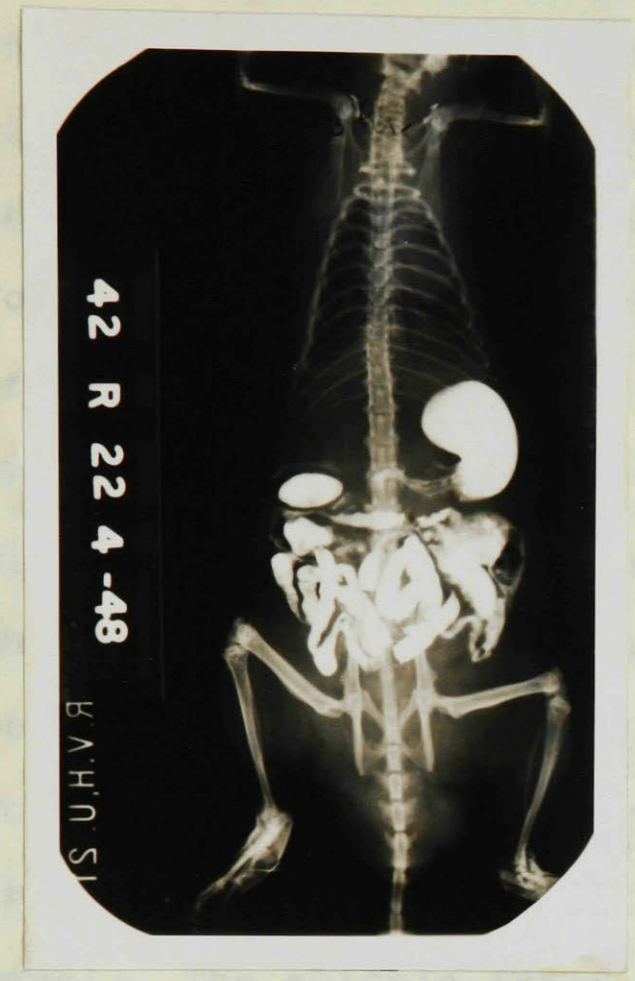

( 4 hrs )




( 5 hrs )

Fig. 7. Roentgenograms of rat No. 42
( force feeding with normal potassium diet for two weeks )

All the abnormal findings as shown on these two films are nearly identical with that of rat No. 41 as demonstrated in Fig. 4. See the description in Fig. 4.




( 3 hrs ) ( 5 hrs )

Fig. 8. Roentgenograms of rat No. 42
( 10 days after force feeding was abandoned )

After the force feeding was abandoned, this rat was fed ad. lib. with normal potassium containing Purina chow for 10 days. A barium series was done and showed definite improvement, however, some abnormal patterns of the gastro-intestinal motility are persisted to certain extent. Stomach shows 40 % retention. The barium has reached the colonic tract but no barium is excreted at the time about 5 hours after the ingestion. See the description in Fig. 5 and compare the changes.

twice daily for two weeks. The composition of the diet is tabulated in Table 3, which contains 1.2 per cent of potassium or 1.685 m. eq. potassium in 24 c.c. of diet or 65.615 mg of potassium as the daily intake. After two weeks of force feeding with this normal potassium diet, another barium series was carried out in order to make sure that the gastro-intestinal motility still remains normal before low potassium diet is introduced. It is unexpected and surprised to find that remarkable disturbances of gastro-intestinal motility occurred in all animals. The major lesions as caused by the force feeding and demonstrated by roentgen-rays are atonic state and decreased motility of both the stomach and small bowel. The colonic tract is not involved in this respect. The stomach and small bowel are both remarkably increased in caliber with gas-distention. Peristaltic and segmenting movements are greatly decreased. The small bowel tends to become into dilated separated loops. This condition is consistent with the pictures seen in non-tropical sprue, vitamin B deficiency and other nutritional disorders of the small bowel in man, and roentgenologist called this condition as segmentation of the small bowel. The transit period is also greatly delayed, apparently with 30 or 40 per cent gastric retention and no barium excreted at the end of 5 hours. All the changes as shown in Fig. 4 and 7 are quite uniform which appeared in every animal and practically to the same extent, consequently, it is safe to rule out any coincidence and the force feeding per se seems to be the

Table 3
( composition of normal potassium diet )

| | |
|---|---|
| Casein, low ash content | 396 gm. |
| Dextrin | 450 gm. |
| Sucrose | 540 gm. |
| Cellu flour | 180 gm. |
| Corn oil | 117 gm. |
| Wheat germ oil | 27 gm. |
| Cod liver oil | 27 gm. |
| Salt mixture | 37 gm. |
| Sodium chloride | 7.5gm. |
| Vitamins mixture | 0.9 gm. |
| Water | 1315 c.c. |

(a) Composition of salt mixture

| | |
|---|---|
| $MgSO_4$ | 11.20 gm. |
| $CaHPO_4$ | 11.60 gm. |
| NaI | 1.40 gm. |
| $MnSO_4$ | 9.20 gm. |
| $ZnSO_4$ | 0.45 gm. |
| $CuSO_4$ | 0.58 gm. |
| Fe citrate | 2.40 gm. |
| $KHPO_4$ | 15.00 gm. |
| Calcium lactate | 26.50 gm. |

(b) Composition of vitamins mixture

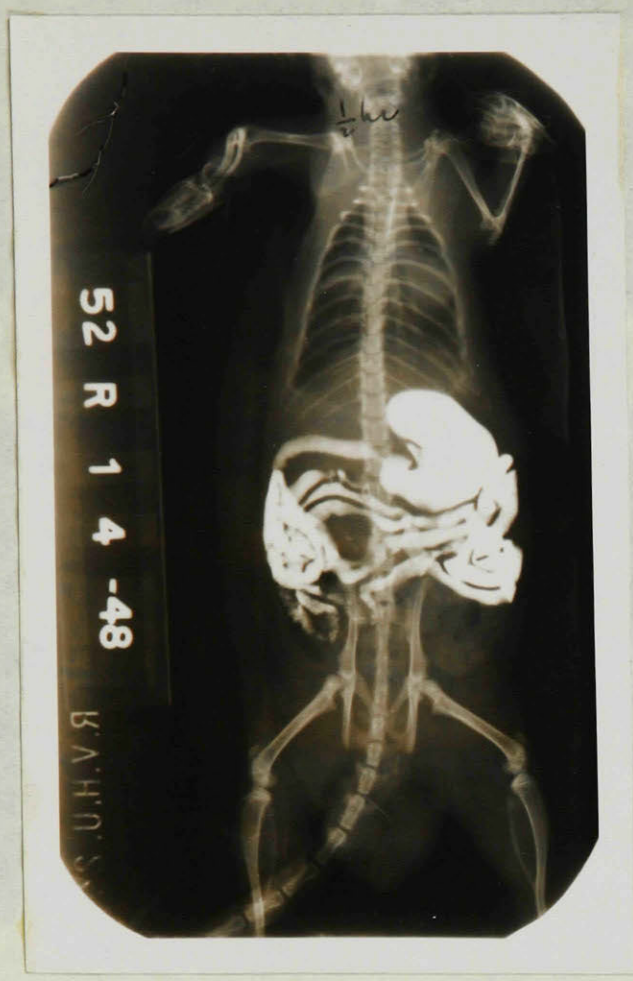
| | |
|---|---|
| Vitamin K | 240 mg. |
| Thiamine | 30 mg. |
| Riboflavin | 15 mg. |
| pyridoxine | 15 mg. |
| Pantothenic acid | 45 mg. |
| Nicotinic acid | 15 mg. |
| Choline chloride | 450 mg. |
| Vitamin C | 90 mg. |

only factor to be responsible for such disturbances.

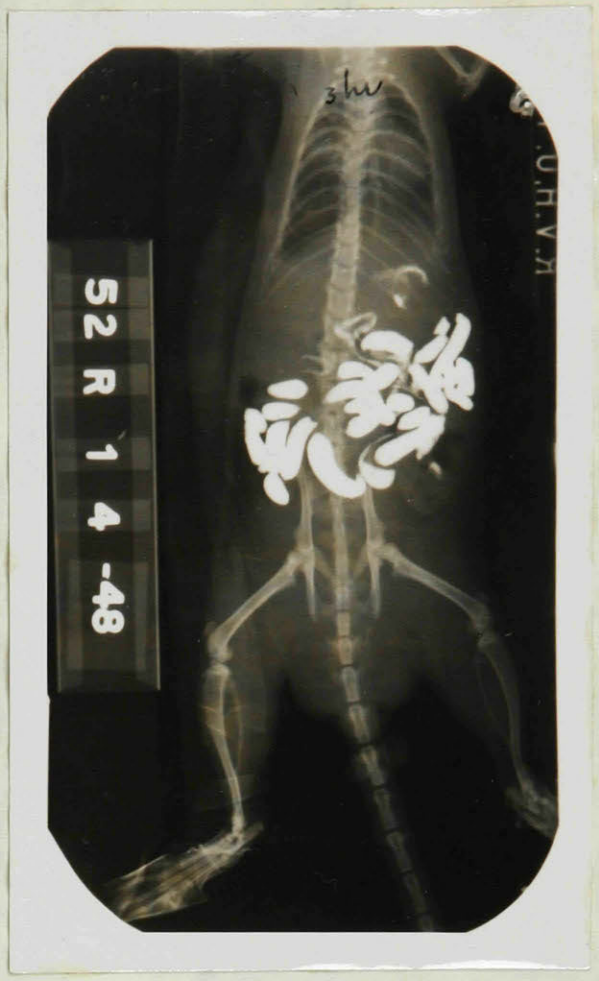
Force feeding was stopped immediately after the abnormal findings. Purina chow, which has a high potassium content, was fed ad. lib. for 10 days. Another barium series was taken

and showed that the gastro-intestinal motility is much improved, however, gastric retention and slowed transit period through the small bowel ~~are~~ still persisted. From this finding, which never reported in the literature, it is evident that as the study of the gastro-intestinal motility is concerned, the procedure of force feeding should not be used.

As soon as the effects of force feeding on the gastro-intestinal motility is elicited, another experiment was carried out without force feeding. Four young albino rats, weighing between 150 and 200 gm., were used. First, a control barium series examination was made for all the animals and all showed normal findings, see Fig 9 and 12. Low potassium diet was fed ad. lib. This diet is in dry form which contains 2.94 m.eq. of potassium per liter or 11.51 mg of potassium per cent or 0.011 per cent of potassium in the diet. The composition of this diet is tabulated in Table 4. After the four rats were fed ad. lib. with this low potassium diet for two weeks, a barium series was done. The films taken at 3 hours did not show any particular abnormality. The stomach was completely emptied at the end of 3 hours and most part of the barium was accumulated in the colon. The transit period was not appreciably delayed. In addition to the low potassium diet fed ad. lib., desoxycorticosterone acetate was injected twice daily for 6 days with daily dosage amounted to 3 mg for each animal. By the end of this time, all animals received 18 mg of desoxycorticosterone and all



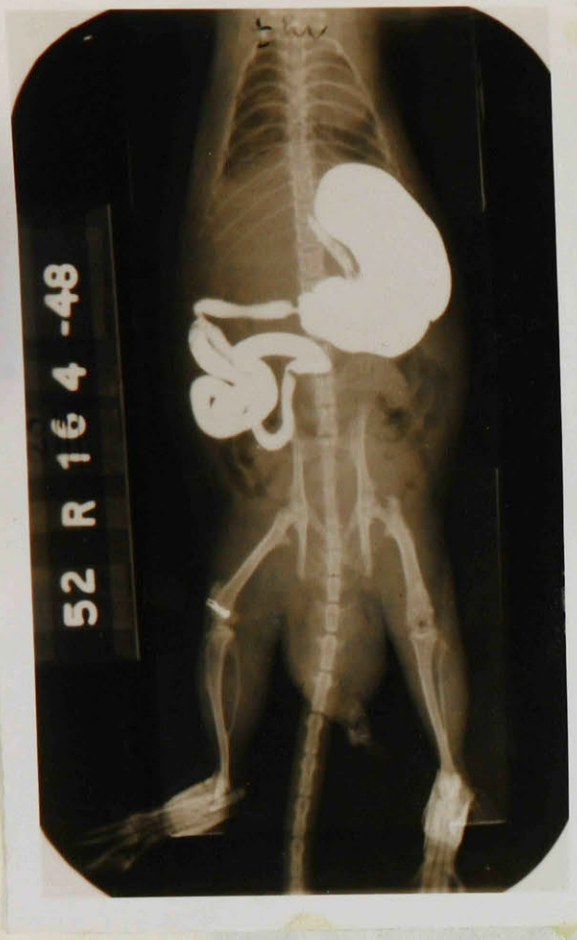

( half hr )




( 3 hrs )

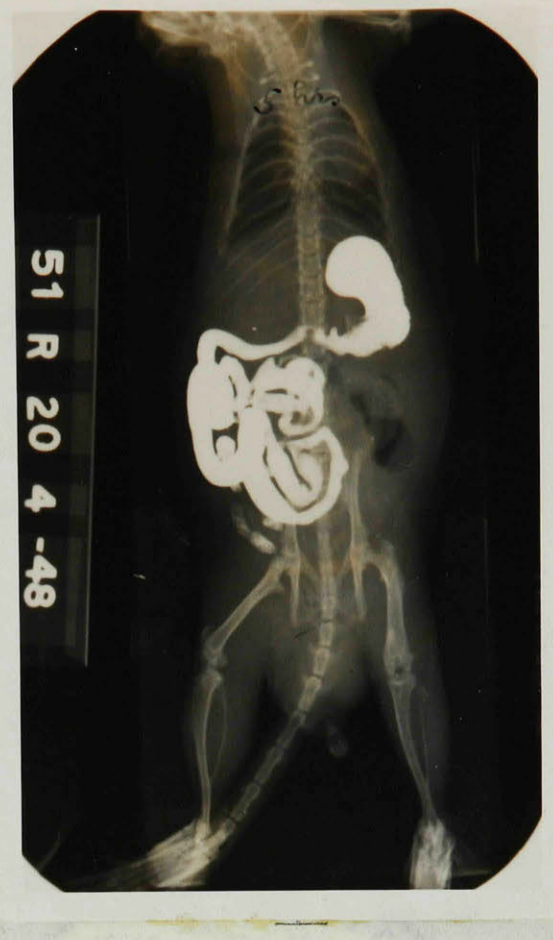
Fig. 9. Roentgenograms of rat No. 52 ( normal barium series for control )

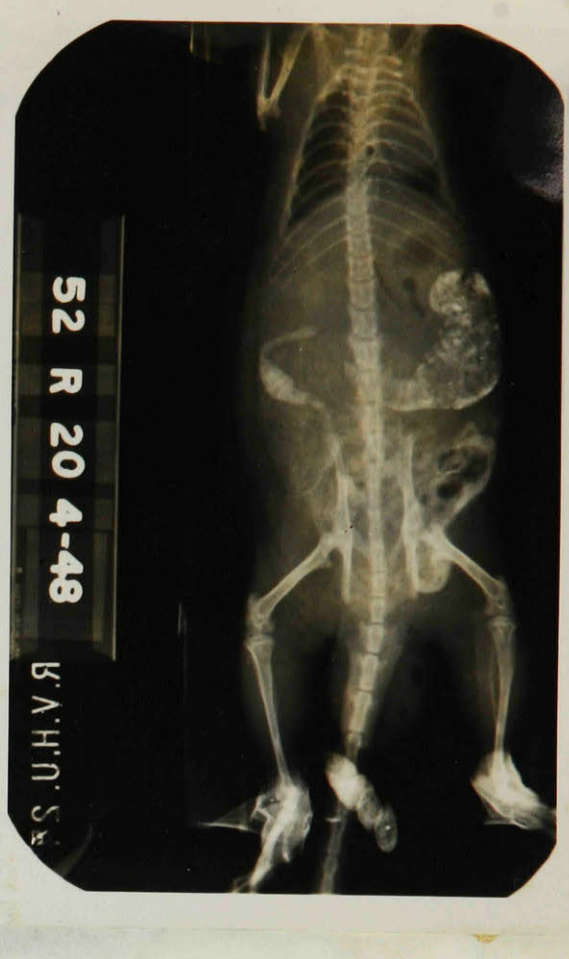
Serial films were taken at half hour and 3 hours after the ingestion of barium. Compare with Fig. 1, 2, 3, and 6, this rat shows quite normal activity in the digestive tract. This rat started to excrete the barium feces at the end of 3 hours but the barium feces was swept off when this picture was taken, so there is no shadow of the barium feces shown on this film.







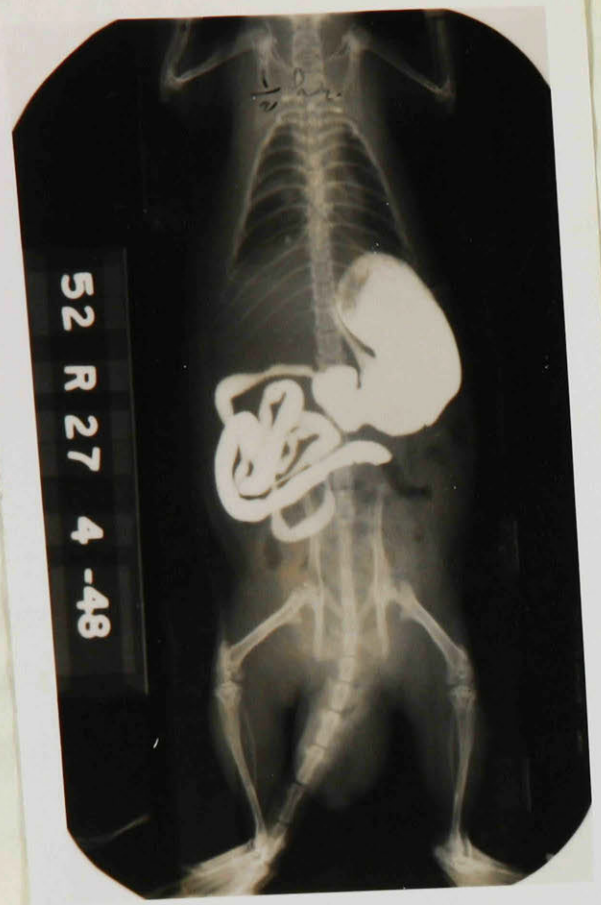


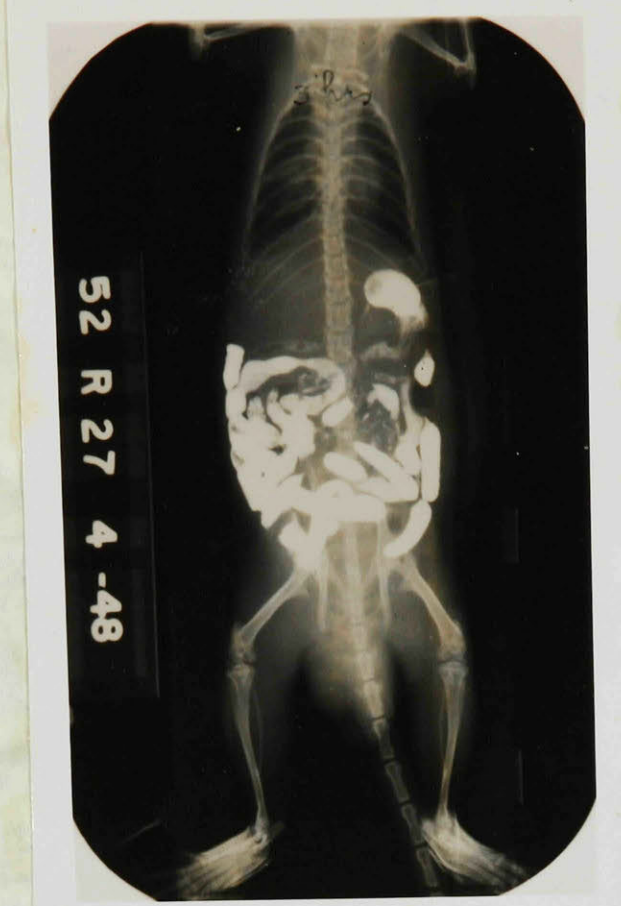

( half hr ) ( 3 hrs ) ( 5 hrs ) ( 24 hrs )

Fig. 10. Roentgenograms of rat No. 52 ( barium series after 3 weeks fed low potassium diet ad. lib., plus injections of desoxycorticosterone acetate for 6 days )

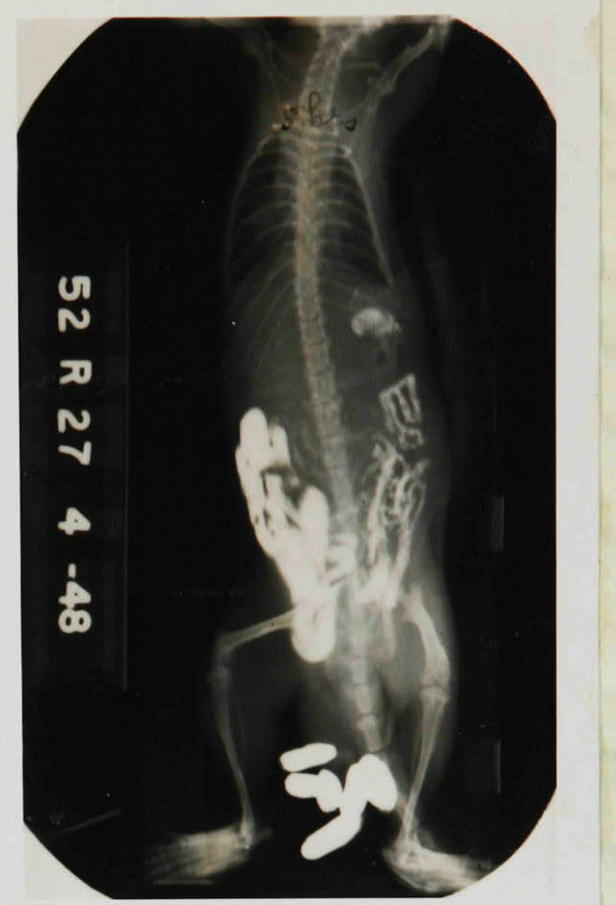
(1) Half hour film shows a atonic stomach. Only a few loops of the proximal jejunum were filled.
(2) 3 hours film shows a 50 % gastric retention. The loops of the small bowel are dilated and gas-distended.
(3) 5 hours film shows a 40 % gastric retention. The barium is still remained in the jejunum. Transit period is remarkably delayed.
(4) 24 hours film shows a 10 % gastric retention. Most of the barium has been excreted at this time.




( half hr )



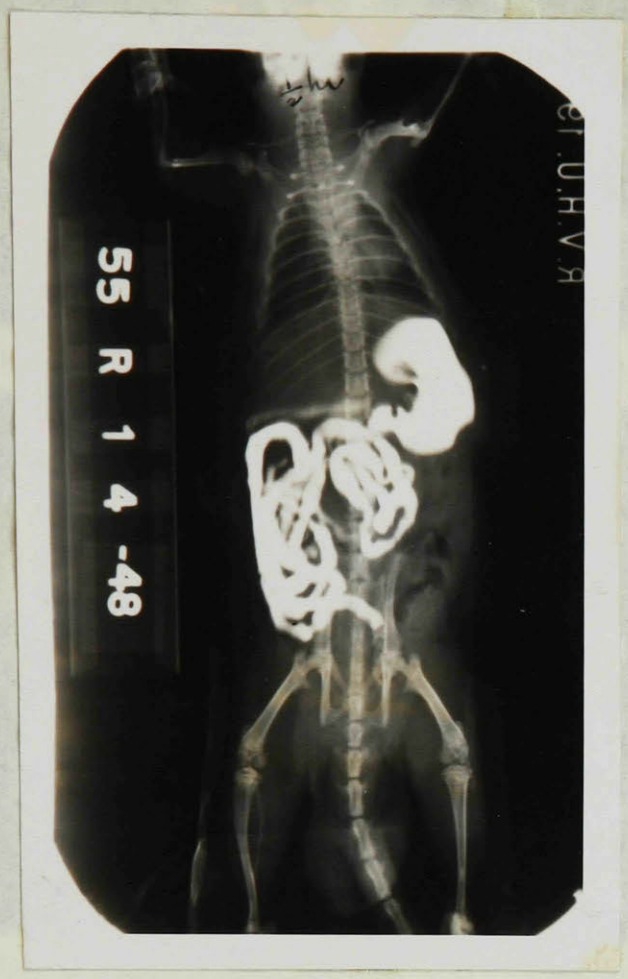

( 3 hrs )



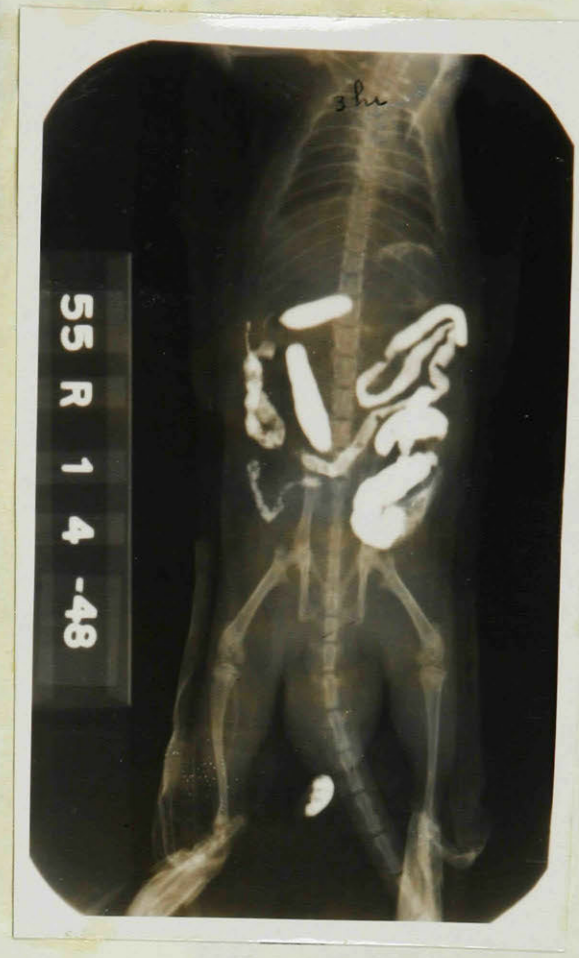

( 5 hrs )

Fig. 11. Roentgenograms of rat No. 52 ( barium series one week later after fed normal potassium diet ad. lib., and plus intake of KCl solution )

(1) Half hour film shows that the stomach is definitely improved. It becomes less atonic and active peristalsis is present. Compare with the half hour film in Fig. 10. The column of the barium has not reached the ileum yet.
(2) 3 hours film shows only a 10 % gastric retention. The barium has reached the colonic tract at this time.
(3) 5 hours film shows nearly a complete evacuation of the stomach. Most of the barium is accumulated in the colon and the animal has started to excrete the barium feces.



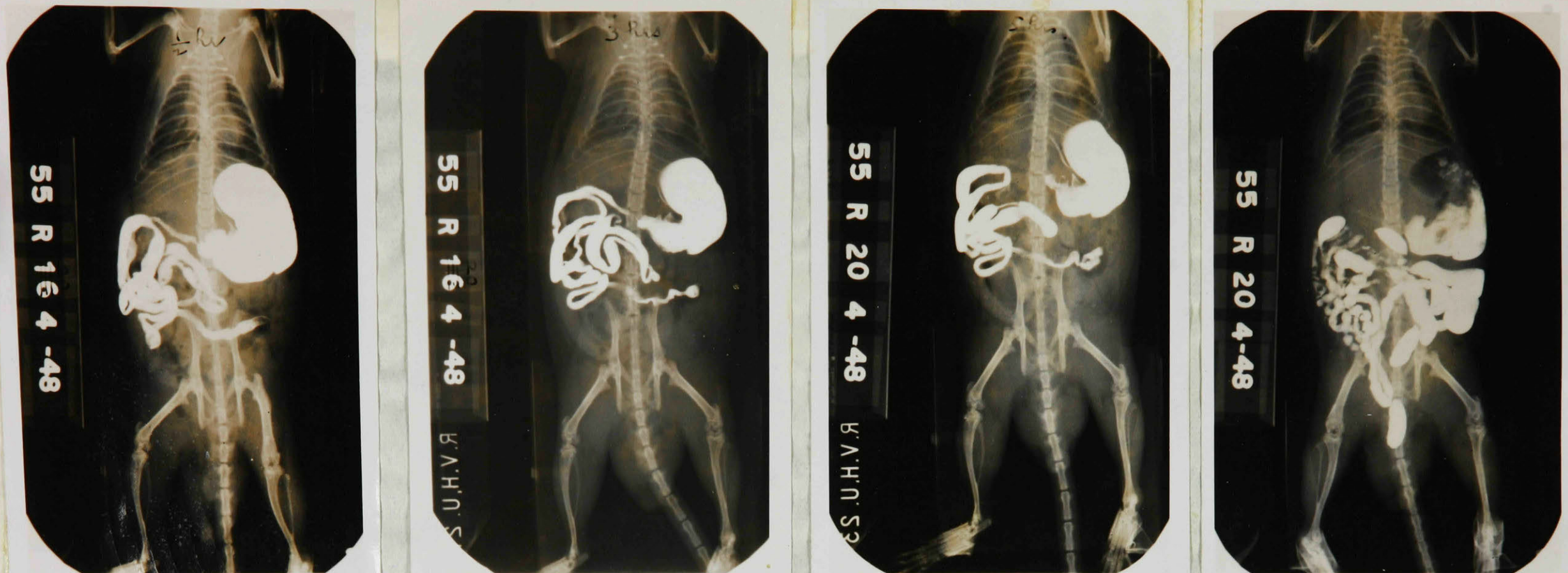

( half hr )




( 3 hrs )

Fig. 12. Roentgenograms of rat No. 55 ( normal barium series for control )

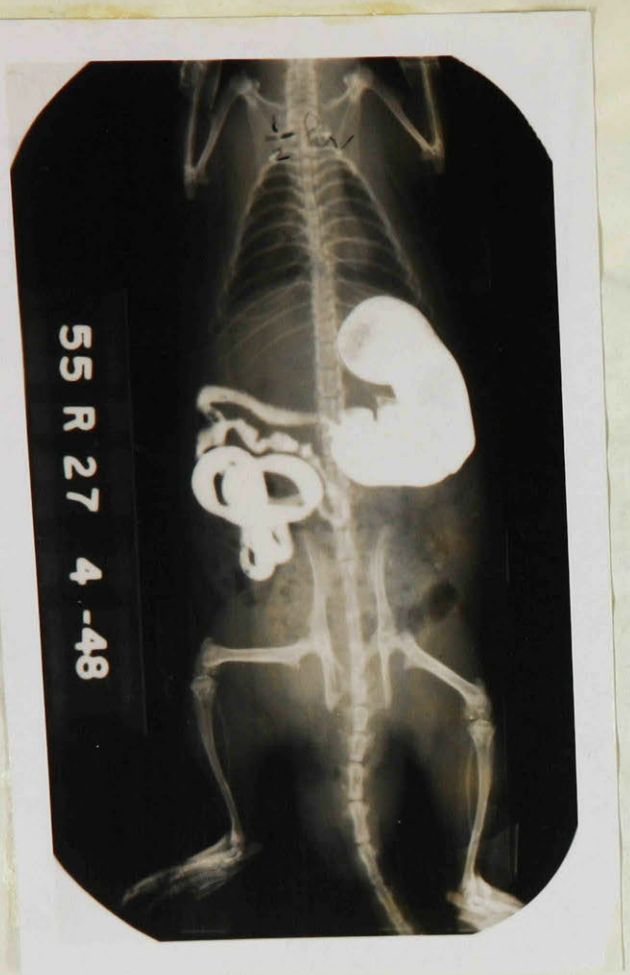
Serial films were taken at half hour and 3 hours after the ingestion of barium. Compare with Fig. 1, 2, 3, 6, and 9, this rat shows fairly n normal motility of the gastro-intestinal tract.



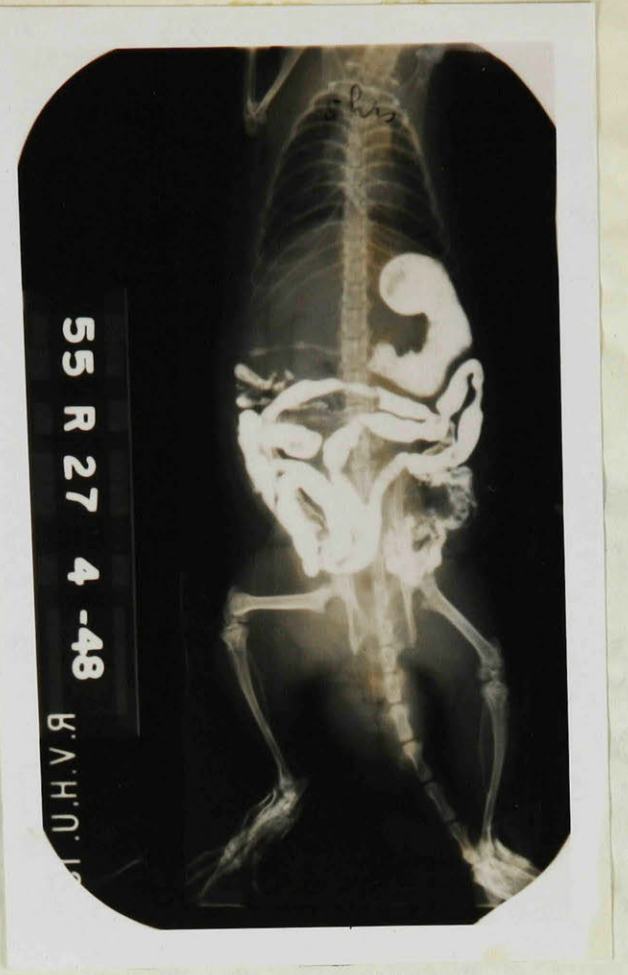

( half hr ) ( 3 hrs ) ( 5 hrs ) ( 24 hrs )

Fig. 13. Roentgenograms of rat No. 55 ( barium series after 3 weeks fed low potassium diet ad. lib., plus injections of desoxycorticosterone acetate for 6 days )

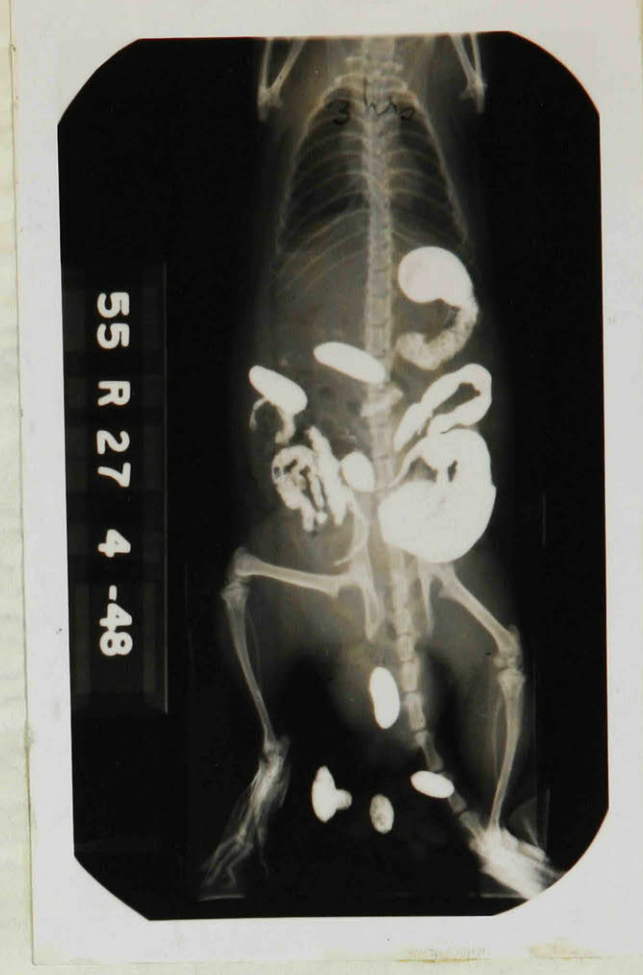
(1) Half hour film shows a atonic stomach with sluggish peristalsis. The capacity of the stomach is greatly dilated.
(2) 3 hours film shows a 80 % gastric retention. The caliber of the small bowel of this animal is not particularly dilated. Some gas bubbles are present.
(3) 5 hours film shows a 70 % gastric retention. The barium ~~is~~ still remained in the proximal jejunum. Progress of the barium is nearly in standstill at this time and, the transit period through the small bowel is tremendously delayed in this animal.
(4) 24 hours film shows a 40 % gastric retention. The small bowel is still filled with barium. The animal, however, has started to excrete barium feces.




( half hr )




( 3 hrs )




( 5 hrs )

Fig. 14. Roentgenograms of rat No. 55 ( barium series one week later after fed normal potassium diet ad. lib., and plus intake of KCl solution )

(1) Half hour film shows that the stomach is definitely improved. It is less atonic and has marked peristalsis when compared with the half hour film taken one week before.
(2) 3 hours film shoes a 30 % gastric retention. Transit period is markedly improved. Some barium has reached even descending colon.
(3) 5 hours film shows a 20 % gastric retention. About one half of the barium ingested is accumulated in the colon and the animal has started to evacuate barium feces.

Table 4
( composition of low potassium dry diet )

| | |
|---|---|
| Casein, low ash content | 396.0 gm. |
| Dextrin | 450.0 gm. |
| Sucrose | 540.0 gm. |
| Cellu flour | 180.0 gm. |
| Corn oil | 117.0 gm. |
| Wheat germ oil | 27.0 gm. |
| Cod liver oil | 27.0 gm. |
| Salt mixture | 37.0 gm. |
| Sodium chloride | 7.5 gm. |
| Vitamins mixture | 0.9 gm. |

(a) Composition of salt mixture

| | |
|---|---|
| $MgSO_4$ | 11.20 gm. |
| $CaHPO_4$ | 14.60 gm. |
| NaI | 1.40 gm. |
| $MnSO_4$ | 9.20 gm. |
| $ZnSO_4$ | 0.45 gm. |
| $CuSO_4$ | 0.58 gm. |
| Fe citrate | 2.40 gm. |

(b) Composition of vitamins mixture is the same as shown in page 193.

animals had been fed ad. lib., with low potassium diet for 3 weeks. A barium series at this time showed tremendous changes in the motor pattern of the gastro-intestinal tract. These changes are demonstrated in Fig. 10 and 13. The stomach became dilated and atonic with very sluggish peristalsis. It also showed 10 to 40 per cent gastric retention at the end of even 24 hours. Only a few proximal loops of the jejunum were filled with barium at the end of 3 hours. Practically no segmenting movements could be seen. The small bowel loops were dilated and were more or less gas-distended.

Peculiarly, there were no such separated loops of the small bowel as seen in force feeding. The most remarkable changes in the gastro-intestinal tract as introduced by potassium deficiency in this experiment were the 24 hours gastric retention and the extraordinarily delayed transit period through the small bowel. There was practically no barium reached the cecum and even not reached the lower ileum at the end of 5 hours, particularly as seen in rat No. 55.

During the time when desoxycorticosterone was injected, all the animals were watched very carefully and were checked either by fluoroscopic examination or roentgenograms as frequent as possible in order to prevent the occurrence of advanced or permanent pathology. Due to some experience as secured from a preliminary experiment, if the rats showed some advanced lesions such as swelling up of the abdomen, it would be very difficult to feed them back into normal state even with adequate quantity of potassium in the diet. As soon as the animals showed some perceptible abdominal distention, sooner or later they will die. Apparently, due to frequent check with roentgen-rays, these four rats did not get chance to go beyond the changes as shown in Fig. 10 and 13. As the rats reached this stage, low potassium diet was replaced by the normal potassium containing Purina chow. In addition, twice daily 5 c.c. of 1.7 per cent potassium chloride solution was introduced into the stomach by a catheter as used in force feeding. The daily amount 10 c.c.

of this solution contains 2 m.eq. or 78 mg of potassium. After one week, a barium series was done and showed marked improvement and this improvement is demonstrated in Fig. 11 and 14. As shown on the films, the barium reached the desconding colon at the end of 3 hours and all the rats started to excrete the barium feces at the end of 5 hours.

From what have been done in this experiment, it seems no doubt that it provides a clear cut evidence to show that the effect of potassium plays an important role on the motility of the gastro-intestinal tract. During the period of feeding back the sick animals with potassium, one point remained worth while to be investigated is that, suppose, if the potassium chloride solution was administered parenterally instead of introducing it into the stomach by the procedure of force feeding, all the rats might make a quicker or a prompt complete recovery since the force feeding per se will produce motor disturbances as proved before.

The potassium excretion in the urine following administration of potassium salts is directly correlated with the serum concentration and little affected by the particular associated anions (459). However, Bunge pointed out in 1873 (319), when a salt, such as potassium citrate gains entrance into the blood stream, a proportion of it reacts with sodium chloride, forming potassium chloride and sodium citrate. As the kidney functions in keeping composition of the blood nearly constant, the abnormal constituents, sodium citrate

and excess of potassium salts are eliminated. In this manner a high potassium intake may cause increased sodium and chloride excretion. Miller's experiments on pigs (319) found that when potassium phosphate was given, only a small proportion of potassium excreted, consequently the rate of sodium and chloride excretion is not affected. The cathartic effect of potassium phosphate is another factor in producing the delayed recovery of potassium deprived rats. Keith et al observed that the potassium nitrate produced most marked diuretic effect in man (239).

It might be possible to keep young rats on a potassium deficient diet in much beter shape and condition without introducing large amounts of potassium if any one or all of the following points are duely considered:

(a) To provide a rich source of water soluble vitamins if super-abundant amounts of all of the components of the vitamin B complex are added to the potassium deficient diet.

(b) Boron compounds are added to maintain a high energy reserves in order to lengthen the survival period.

(c) Rubidium or cesium may be supplemented to the diet if available.

(d) Enough sodium chloride should be added to the low potassium diet in order to provide in excess a cation which can exchange with potassium to some extent.

(e) Other inorganic constuents should be sufficient in the low potassium diet. Early reports mentioned,

for instance, characteristic abdominal distention occurring in rats on rachitic diet (323). Skinner (397) stated that the requirements of the animal body for a given element may be markedly influenced by the concentration of one or more additional elements in the ration.

## BIBLIOGRAPHY


1. Abbott, W.O. and Pendergrass, E.D. Intubation studies of the human small intestine. (5). The motor effects of single clinical doses of morphine sulfate in normal subjects. Am. J. Roentgenol. 1936, 35, 289-299.

2. Adamson, W.A.D. and Aird, I. Megacolon: evidence in favor of a neurogenic origin. Brit. J. Surg. 1932, 20, 220-230.

3. Adson, A.W. Hirschsprung's disease: indications for and results obtained by sympathectomy. Surgery, 1937, 1, 859.

4. Allott, E.N. Clin. Sc., 1938, 3, 229.

5. Alvarez, W.C. Differences in rhythmicity and tone in different part of the wall of the stomach. Am. J. Physiol. 1916, 40, 585-602.

6. Alvarez, W.C. Differences in latent period and form of the contraction curve in muscle strips from different parts of the mammalian stomach. Am. J. Physiol. 1917, 42, 435-449.

7. Alvarez, W.C. Differences in latent period and form of the contraction curve in muscle strips from different parts of the frog's stomach. Am. J. Physiol. 1917, 42, 422-434.

8. Alvarez, W.C. Differences in the action of drugs on different parts of the bowel. J. Pharmacol. & Exper. Therap. 1918, 12, 171-191.

9. Alvarez, W.C. The metabolic gradient underlying peristalsis. J.A.M.A. 1919, 73, 1438-1440.

10. Alvarez, W.C. The electrogastrogram and what it shows. J.A.M.A. 1922, 78, 1116-1119.

11. Alvarez, W.C. New methods of studying gastric peristalsis. J.A.M.A. 1922, 79, 1281-1284.

12. Alvarez, W.C. New light on gastric peristalsis. Am. J. Roentgenol. 1923, 10, 31-35.

13. Alvarez, W.C. Bayliss and Starling's law of the intestine or the myenteric reflex. Am. J. Physiol. 1924, 69, 229-248.

14. Alvarez, W.C. Physiological studies on the motor activities of the stomach and bowel in man. Am. J. Physiol. 1929, 88, 650-662.

15. Alvarez, W.C. Ways in which emotion can affect the digestive tract. J.A.M.A. 1929, 92, 1231-1237.

16. Alvarez, W.C. The length of the interval between the eating of a food and the appearance of distress caused thereby. Proc. Staff Meetings, Mayo Clin., 1935, 10, 103-109.

17. Alvarez, W.C. New light on intestinal peristalsis in health and disease. Proc. Staff Meet., Mayo Clin. 1937, 12, 657-661.

18. Alvarez, W.C. Anoxemia used as a means of analyzing the structure and functions of the nervous system of the bowel. Am. J. Digest. Dis. & nutrition. 1937, 4, 550-561.

19. Alvarez, W.C. The effect of nicotine on intestinal peristalsis. Am. J. Digest. Dis. & nutrition. 1937, 4, 417-425.

20. Alvarez, W.C. An introduction to gastro-enterology. Paul B. Hoeber, Inc. third edition, 1940.

21. Alvarez, W.C. and Ascanio, H. Studies on the intestinal muscle of man. Am. J. Physiol. 1929, 90, 607-610.

22. Alvarez, W.C. and Freedlander, B.L. The rate of progress of food residues through the bowel. J.A.M.A. 1924, 83, 576-580.

23. Alvarez, W.C. and Kiyoshi Hosoi. The experimental reversal of intestinal gradients. Am. J. Physiol. 1929, 89, 187-200.

24. Alvarez, W.C. and Kiyoshi Hosoi. A gradient of irritability in the small intestine. Am. J. Physiol. 1929, 89, 182-186.

25. Alvarez, W.C. and Kiyoshi Hosoi. The latent period of intestinal muscle. Am. J. Physiol. 1929, 89, 201-212.

26. Alvarez, W.C. and Mahoney, L.J. Peristaltic rush in the rabbit. Am. J. Physiol. 1924, 69, 221-225.

27. Alvarez, W.C. and Mahoney, L.J. Peristaltic rush as depicted in the electroenterogram. Am. J. Physiol. 1924, 69, 226-228.

28. Alvarez, W.C. and Mahoney, L.J. The myogenic nature of the rhythmic contractions of the intestine. Am. J. Physiol. 1922, 59, 421-430.

29. Alvarez, W.C. and Starkweather, E. The metabolic gradient underlying colonic peristalsis. Am. J. Physiol. 1918, 47, 293-301.

30. Alvarez, W.C. and Starkweather, E. The motor functions of the cecum. Am. J. Physiol. 1918, 46, 563-569.

31. Alvarez, W.C. and Starkweather, E. The metabolic gradient underlying intestinal peristalsis. Am. J. Physiol. 1918, 46, 186-208.

32. Alvarez, W.C. and Zimmermann, A. Gastric wavelets. Am. J. Physiol. 1926, 78, 405-410.

33. Alvarez, W.C. and Zimmermann, A. The absence of inhibition ahead of peristaltic rush. Am. J. Physiol. 1927, 83, 52-59.

34. Alvarez, W.C. and Zimmermann, A. Movements of the stomach. Am. J. Physiol. 1928, 84, 261-270.

35. Anderson, E., Haymaker, W. and Joseph, M. Hormone and electrolyte studies of patients with hyperadrenocortical syndrome (Cushing's syndrome). Endocrinol. 1938, 23, 398-402.

36. Apperly, F.L. The use of hydrochoric acid and sodium bicarbonate in the treatment of certain common diseases. M. J. Australia, 1926, 1, 354-358.

37. Babkin, B.P. The digestive work of the stomach. Physiol. Rev. 1928, 8, 365-392.

38. Babkin, B.P. Lectures of med. diploma course, Apr. 1947.

39. Babkin, B.P., Hebb, C.O. and Serfeyeva, M.A. The parasympathetic-like effect of splanchnic nerve stimulation on pancreatic secretion. Quart. J. Exper. Physiol. 1939, 29, 217-237.

40. Bailey, E. Textbook of histology. 11th edition, 1944.

41. Bailey, P. and Sweet, W.H. Effects on respiration, blood pressure and gastric motility of stimulation of orbital surface of frontal lobe. J. Neurophysiol. 1940, 3, 276-281.

42. Baird, M.M., Campbell, J.M.H. and Hern, J.R.B. The importance of estimating chlorides in the fractional test meal samples and some experiments with the duodenal tube. Guy's Hosp. Rep. 1924, 74, 25-54.

43. Ballon, H.C., Wilson, H.M., Singer, J.J. and Graham, E.A. Esophagus, stomach and heart following unilateral phrenicotomy. Arch. Surg. 1930, 21, 1291-1314.

44. Barclay, A.E. Note on the movements of the large intestine. Arch. roent. ray. 1912, 16, 422-424.

45. Barclay, A.E. Normal mechanism of swallowing. Brit. J. Radiol. 1930, 3, 534-546.

46. Barclay, A.E. The digestive tract - a radiological study of its anatomy, physiology and pathology. Second edition, 1936.

47. Barcroft, J. and Robinson, C.S. A study of some factors influencing intestinal movements. J. Physiol. 1929, 67, 211-220

48. Barden, R.P., Thompson, W.D., Ravdin, I.S. and Frank, I.L. The influence of serum protein on the motility of the small intestine. Surg. Gynec. & Obst. 1938, 66, 819-821.

49. Bayliss, W.M. and Starling, E.H. The movements and innervation of the small intestine. J. Physiol. 1899, 24, 99-143.

50. Bayliss, W.M. and Starling, E.H. The movements and innervation of the large intestine. J. Physiol. 1900, 26, 107-118.

51. Bayliss, W.M. and Starling, E.H. The movements and innervation of the small intestine. J. Physiol. 1901, 26, 125-138.

52. Beattie, J. and Sheehan, D. The effects of hypothalamic stimulation on the gastric motility. J. Physiol. 1934, 81, 218-227.

53. Berkson, J. Electromyographic studies of the gastrointestinal tract. (3) Observations on excised intestine. Am. J. Physiol. 1933, 104, 62-66.

54. Bernheim, F. and Bernheim, M.L.C. Action of drugs on the choline esterase of the brain. J. Pharmacol. & Exper. Therap. 1936, 57, 427-436.

55. Beznak, A.B.L. On the mechanism of the autocoid function of parasympathetic nerves. J. Physiol. 1934, 82, 129-153.

56. Bodansky, M. and Bodansky, O. Biochemistry of disease. 1946.

57. Boeke, J. Nerve endings motor and sensory, cytology and cellular pathology of the nervous system. 1932.

58. Bolton, B.D., Williams, J. and Carmichael, E.A. Sympathetic ganglionic responses in man. Brain, 1937, 60, 39.

59. Boring, E.G. The sensations of the alimentary canal. Am. J. Psychol. 1915, 26, 1-57.

60. Bozler, E. Physiological evidence for the syncytial character of smooth muscle. Science, 1937, 86, 478.

61. Bozler, E. Electric stimulation and conduction of excitation in smooth muscle. Am. J. Physiol. 1938, 122, 614-623.

62. Bozler, E. The action potentials of visceral smooth muscle. Am. J. Physiol. 1938, 124, 502-510.

63. Bozler, E. Electrophysiological studies on the motility of the gastro-intestinal tract. Am. J. Physiol. 1939, 127, 301-307.

64, Bremer, J.L. and Weatherford, H.L. Textbook of histology. 6th edition, 1944.

65. Brewer, G. The relation of plasma potassium level to metabolic activity. Am. J. Physiol. 1940, 129, 245-251.

66. Bronk, D.W. Synaptic mechanism in sympathetic ganglion. J. Neurophysiol. 1939, 2, 380-401.

67. Bronk, D.W. et al. The influence of altered chemical environment on the activity of ganglion cells. Am. J. Physiol. 1938, 123, 24-25.

68. Brown, G.L. and Feldberg, W. Effect of KCl on a sympathetic ganglion. J. Physiol. 1935, 84, 12P.
Differential paralysis of the superior cervical ganglion. Ibid, 1936, 86, 10P-11P.
The action of potassium on the superior cervical ganglion of the cat. Ibid, 1936, 86, 290-305.

69. Brunemeier, E.H. and Carlson, A.J. Contributions to the physiology of the stomach. (19) Reflexes from the intestinal mucosa to the stomach. Am. J. Physiol. 1915, 36, 191-195.

70. Burnett, F.L. Fecal units and intestinal rate, a basis for the study of health and intestinal indigestion. Boston M. & S. J. 1921, 184, 371-376; 415-422.

71. Burnett, F.L. The intestinal rate and the form of the feces. Am. J. Roentgenol. 1923, 10, 599-604.

72. Burnham, M.F. Indirect roentgen findings in chronic infections of the biliary ducts and gallbladder. Am. J. Roentgenol. 1923, 10, 105-112.

73. Cameron, J.A.M. Esophagectasia in a child. Arch. Dis. Childhood, 1927, 2, 358-360.

74. Cammidge, P.J. The feces of children and adults. Bristol, John Wright & Sons, Ltd. 1914.

75. Cannon, W.B. The movements of the stomach studied by means of roentgen ray. Am. J. Physiol. 1898, 1, 359-382.

76. Cannon, W.B. Movements of the intestines studied by means of the roentgen-rays. Am. J. Physiol. 1901-02, 6, 251-277.

77. Cannon, W.B. The passage of different foodstuffs from the stomach and through the small intestine. Am. J. Physiol. 1904, 12, 387-418.

78. Cannon, W.B. The motor activities of the stomach and small intestine after splanchnic and vagus section. Am. J. Physiol. 1906, 17, 429-442.

79. Cannon, W.B. Am. J. Physiol. 1907, 19, 436

80. Cannon, W.B. The acid control of pylorus. Am. J. Physiol. 1907, 20, 283-322.

81. Cannon, W. B. Further observations on the myenteric reflex. Am. J. Physiol. 1908, 23, 26-27.

82. Cannon, W.B. The nature of gastric peristalsis. Am. J. Physiol. 1911, 29, 250-266.

83. Cannon, W.B. The mechanical factors of digestion. New York, E. Arnold, 1911.

84. Cannon, W.B. The importance of tonus for the movements of the alimentary tract. Arch. Int. Med. 1911, 8, 417-426.

85. Cannon, W.B. Peristalsis, segmentation, and the myenteric reflex. Am. J. Physiol. 1912, 30, 114-128.

86. Cannon, W.B. and Blake, J.B. Gastro-enterostomy and pyloroplasty. Ann. Surg. 1905, 41, 686-711.

87. Cannon, W.B. and Burket, I.K. The endurance of anemia by nerve cells in the myenteric plexus. Am. J. Physiol. 1913, 32, 347-357.

88. Cannon, W.B. and Lieb, C.W. The receptive relaxation of the stomach. Am. J. Physiol. 1911, 27, 13.

89. Cannon, W.B. and Moser, A. The movements of food in the esophagus. Am. J. Physiol. 1898, 1, 435-444.

90. Cannon, W.B. and Washburn, A.L. An explanation of hunger. Am. J. Physiol. 1912, 29, 441-452.

91. Cantarow, A. Clinical biochemistry. 1946.

92. Cantarow, A. Review of phosphatase activity and calcium and electrolyte metabolism. The adrenal cortex and electrolyte metabolism. Internat. Clin. 1936, 1, 263-265.

93. Cantarow, A. Urine chloride concentration in patients with Cushing's syndrome. Science, 1939, 90, 375-385.

94. Cantarow, A. and Rakoff, A.L. Endocrinol. 1940, 27, 652.

95. Carey, E.J. Studies in the dynamics of histogenesis. (1) Tension of differential growth as a stimulus to myogenesis. J. Gen. Physiol. 1920, 2, 357-372.

96. Carey, E.J. Studies in the dynamics of histogenesis. (2) Tension of differential growth as a stimulus to myogenesis in the esophagus. J. Gen. Physiol. 1920, 3, 61-83.

97. Carey, E.J. Studies in the dynamics of histogenesis; growth motive force as a dynamic stimulus to the genesis of muscular and skeletal tissues. Anat. Rec. 1920, 19, 199-235.

98. Carey, E.J. Studies on the anatomy and muscular action of the small intestine. Internat. J. Gastro-entero. 1921, 1, 1-10.

99. Carlson, A.J. Am. J. Physiol. 1912, 33, 309.

100. Carlson, A.J. The control of hunger in health and disease. The Uni. of Chicago Press, 1916.

101. Carlson, A.J. Antiperistalsis in the upper third of the esophagus in man. Proc. Soc. Exper. Biol. & Med. 1926, 23, 771-773.

102. Carlson, A.J. and Braafladt, L.H. Contributions to the physiology of the stomach. (18) On the sensibility of the gastric mucosa. Am. J. Physiol. 1915, 36, 153-170.

103. Carlson, A.J., Boyd, T.E. and Pearcy, J.F. Studies on the visceral sensory nervous system. (13) The innervation of the cardia and the lower end of the esophagus in Mammals. Am. J. Physiol. 1922, 61, 14-41.

104. Carlson, A.J. and Bulatao, E. Contributions to the physiology of the stomach. Influence of experimental changes in blood sugar level on gastric hunger contractions. Am. J. Physiol. 1924, 69, 107.

105. Carlson, A.J. and Litt, S. Am. J. Physiol. 1923, 65, 534.

106. Carlson, A.J. and Litt, S. Studies on the visceral nervous system. On the reflex control of the pylorus. Arch. Int. Med. 1924, 33, 281-291.

107. Carlson, A.J., Smith and Gibbins. Am. J. Physiol. 1927, 81, 431.

108. Carman, R.D. The roentgen diagnosis of diseases of the alimentary canal. Philadelphia, second edition, W.B. Saunders. 1920.

109. Carter, H.S., Howe, P.E. and Mason, H.H. Nutrition and Clinical dietetics. Lea & Febiger, Philadelphia, 1921.

110. Case, J.T. The x-ray investigation of the colon. Arch. Roent. Ray, 1915, 19, 375-387.

111. Case, J.T. Roentgen observations on the duodenum with special reference to lesions beyond the first portion. Am. J. Roentgenol. 1916, 3, 314-326.

112. Castleton, K.B. An experimental study of the movements of the small intestine. Am. J. Physiol. 1934, 107, 641-646.

113. Cerqua, S. The part played by splanchnic innervation in emptying time of the stomach. J. Physiol. 1935, 84, 232-249.

114. Chase, M.R. and Ranson, S.W. The structure of the roots, trunk, and branches of the vagus nerve. J. Comp. Neurol. 1914, 24, 31.

115. Childrey, J.H., Alvarez, W.C. and Mann, F.C. Digestion. Efficiency with various foods and under various conditions. Arch. Int. Med. 1930, 46, 361-374.

116. Clopton, M.B. and Mills, R.W. Gastric motility after pyloric obstruction in infancy. Am. J. Dis. Child. 1922, 24, 404-412.

117. Cole, L.G. A radiographic studies of the pylorus and duodenum with and without artificial dilatation of the duodenum. Arch. Roent. Ray, 1912, 16, 425-428.

118. Cole, L.G. The value of serial radiography in gastro-intestinal diagnosis. J.A.M.A. 1912, 59, 1947-1949.

119. Cole, L.G. Physiology of the pylorus, pileus ventriculi and duodenum as observed roentgenologically. J.A.M.A. 1913, 61, 762-766.

120. Cole, L.G. Motor phenomenon of the stomach, pylorus and cap observed roentgenologically. Am. J. Physiol. 1916-17, 42, 618-619.

121. Cole, L.G. Motor phenomenon of the pylorus. Am. J. Physiol. 1927, 81, 470.

122. Connell, F.G. Fundusectomy. Experimental. Surg, Gynec. Obst. 1931, 53, 750-752.

123. Cooke, R.A. Protein derivatives as factors in allergy. Ann. Int. Med. 1942, 16, 71-80.

124. Cowie, C.M., Parsons, J.P. and Lashmet, F.H. (1) Studies on the function of the intestinal musculature. Am. J. Physiol. 1929, 88, 363-368.
(2) Studies on the function of the intestinal musculature. Am. J. Physiol. 1929, 88, 369-385.

125. Crider, J.O. and Thomas, J.E. A study of gastric emptying with the pylorus open. Am. J. Digest. Dis. & Nutrition. 1937, 4, 295-300.

126. Crider, J.O. and Thomas, J.E. A further study of the inhibitory effect on gastric peristalsis of the products of protein digestion. Am. J. Physiol. 1938, 123, 44-45.

127. Crismon, J.M., Crismon, C.S. and Darrow, D.C. Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning. Am. J. Physiol. 1942-43, 139, 667-674.

128. Cunningham. Textbook of anatomy. 7th edition, 1937.

129. Cushing,H. Peptic ulcers and the interbrain. Surg. Gynec. Obst. 1932, 55, 1-34. (Balfour lecture).

130. Davis, J.E. Morphography of two hundred and eighty-five colons. Am. J. Obst. and Gynec. 1916, 73, 474-484.

131. Denny-Brown, D. and Robertson, E.G. An investigation of the nervous control of defecation. Brain, 1935, 58, 256-310.

132. Dickson, W.H. and Wilson, M.J. Further observations on the motility of the human stomach. J. Pharmacol. & Exper. Therap. 1928, 34, 65-72.

133. Douglas, D.M. and Mann, F.C. An experimental study of the rhythmic contractions in the small intestine of the dog. Am. J. Digest. Dis. 1939, 6, 318.

134. Donaldson, A.N. Relation of constipation to intestinal intoxication. J.A.M.A. 1922, 78, 884-888.

135. Dragstedt, L.R. The physiology of the parathyroid glands. Physiol. Rev. 1927, 7, 499-530.

136. D'Silva, J. The action of adrenalin on serum potassium. J. Physiol. 1936, 86, 219-228.

137. Durant, R.R. The comparative effects of adrenalin infusions on blood pressure and gastro-intestinal motility. Am. J. Physiol. 1925, 72, 314-319.

138. Durlacher, S.H. and Darrow, D.C. The effect of depletion of body potassium on the time of survival after nephrectomy and ureteral ligation. Am. J. Physiol. 1942. 136, 577-583.

139. Durlacher, S.H., Darrow, D.C. and Winternitz, M.C. The effect of low potassium diet and of desoxycorticosterone acetate upon renal size. Am. J. Physiol. 1942, 136, 346-349.

140. Eggleston, C. and Hatcher, R.A. The seat of the emetic action of apomorphine. J. Pharmacol. & Exper. Therap. 1912, 3, 551-580.

141. Elliott, T.R. and Barclay-Smith, E. Antiperistalsis and other muscular activities of the colon. J. Physiol. 1904, 31, 272-304.

142. Ellis, C.G. Differential survival in isolated strips of frog intestine. Proc. Soc. Exper. Biol. & Med. 1937, 37, 68-71.

143. Evans, C.L. The physiology of plain muscle. Physiol. Rev. 1926, 6, 358-398.

144. Falconer et al. Proc. Staff Meet., Mayo Clin. 1939, 14, 22.

145. Farah, A. and Pinkston, J.C. Responses of intestinal smooth muscle of the dog to benzedrine sulfate. J. Pharmacol. & Exper. Thera. 1940, 68, 14-21.

146. Farrell, J.I. and Ivy, A.C. Studies on the motility of the transplanted gastric pouch. Am. J. Physiol. 1926, 76, 227.

147. Feldberg, W. and Vartiainen, A. Further observations on the physiology and pharmacology of a sympathetic ganglion. J. Physiol. 1935, 83, 103-128.

148. Fenn, W.O. Loss of potassium in voluntary contractions. Am. J. Physiol. 1937, 120, 675-680.

149. Fenn, W.O. The role of potassium in physiological processes. Physiol. Rev. 1940, 20, 377-415.

150. Finney, J.M.T. and Friedenwald, J. Thirteen years' experience with pyloroplasty. Surg. Gynec. Obst. 1914, 18, 273-284.

151. Flexner, L.B. The chemistry and nature of the cerebrospinal fluid. Physiol. Rev. 1934, 14, 161-187.

152. Follis, R.H. Histological effects in rats resulting from adding rubidium or cecium to a diet deficient in potassium. Am. J. Physiol. 1942-43, 138, 246-252.

153. Follis, R.H. et al. The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. Am. J. Path. 1942, 18, 29-40.

154. Forster, A.C. and Hertzman, A.B. Studies on the activity of circular and longitudinal muscle of extra-peritonealized ileum in a human subject. Am. J. Physiol. 1938, 123, 68-69.

155. Franklin, K.J. and McLachliss, A.D. Vomiting produced in the cat by ligation of the mesenteric vein. J. Physiol. 1937, 90, 254-256.

156. Frazer, J. Brit. Med. J. 1926, 1, 359.

157. Fulton, J.F. Physiology of the nervous system. Oxford Uni. Press, 1943, second edition, pp 189-222.

158. Fulton, J.F. Physiology of the nervous system. Oxford Uni. Press, 1943, second edition, pp 223-251.

159. Fulton, J.F. Physiology of the nervous system. Oxford Uni. Press, 1943, second edition, pp 429-440.

160. Galapeaux, E.A., Templeton, R.D. and Borkon, E.L. The influence of bile on the motility of the dog's colon. Am. J. Physiol. 1937, 121, 130-136.

161. Garry, R.C. The movements of large intestine. Physiol. Rev. 1934, 14, 103-132.

162. Gasser, H.S. Plexus-free preparations of the small intestine; a study of their rhythmicity and of their response to drugs. J. Pharmacol. & Exper. Therap. 1926, 27, 395-410.

163. Gianturco, C. Some mechanical factors of gastric physiology. (2) The pyloric mechanism. The effect of various foods on the emptying of the stomach. Am. J. Roentgenol. 1934, 31. 745-750.

164. Gianturco, C. Does the really empty stomach contract peristaltically? Do fluids follow the lesser curvature in the simple type of stomach of carnivora? Proc. Staff Meet., Mayo Clin., 1934, 9, 83-84.

165. Gianturco, C. Some mechanical gactors of gastric physiology. (1) The empty stomach and its various ways of filling. The pressure exerted by the gastric walls on the gastric content. The physical changes occurring to the foodstuff during digestion. Am. J. Roentgenol. 1934, 31, 735-744.

166. Gilmer, X. Effects of good or bad taste of the contrast meal. Zentralbl. f. Rontgenstrablen, 1911, 2, 235.

167. Ginsburg, H. and Tumpowsky, I. Contributions to the physiology of the stomach. (50) Studies on the control of hunger by drugs. Arch. Int. Med. 1918, 22, 553-570.

168. Gold, H. and Hatcher, R.A. Studies on vomiting. J. Pharmacol. & Exper Therap. 1926, 28, 209-218.

169. Goldon, Ross. Radiologic examination of the small intestine. Lippincott Co., 1945.

170. Goodall, J.S. The contraction of the isolated esophagus of the cat. J. Physiol. 1905, 33, 1-2.

171. Goodman, L. and Gilman, A. The pharmacologic basis of therapeutics. A textbook of pharmacology, toxicology and therapeutics for physicians and medical students. MacMillan Co., 1941.

172. Gordon, S. and Singleton, A.C. Surgery, 1939, 6, 697.

173. Gordon-taylor, G., Hudson, R.V., Dodds, E.C., Warner, J. L. and Whitby, L.E.H. The remote results of gastrectomy. Brit. J. Surg. 1929, 16, 641-667.

174. Gray, J.S., Bradley, W.B. and Ivy, A.C. On the preparation and biological assay of enterogastrone. Am. J. Physiol. 1937, 118, 463-476.

175. Gray, J.S., Wieczorowski, E. and Ivy, A.C. Inhibition of gastric secretion by extracts of normal male urine. Science, 1939, 89, 489-490.

176. Gray, I., Harten, M. and Walzer, M. Studies in mucous membrane hypersensitiveness. (4) The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. Ann. Int. Med. 1940, 13, 2050-2056.

177. Greenwood, W.F. Surgery, 1940, 7, 280.

178. Grey, E.G. Observations on the postural activity of the stomach. Am. J. Physiol. 1917-18, 45, 272-285.

179. Grove, E.W., Olmsted, W.H. and Koenig, K. The effect of diet and catharsis on the lower volatile fatty acids in the stools of normal men. J. Biol. Chem. 1929, 85, 127-136.

180. Gunn, J.A. and Underhill, S.W.F. Experiments on the surviving mammalian intestine. Quart. J. Physiol. 1914, 8, 275-296.

181. Guttman, P.H. Addison's disease. A statistical analysis of 566 cases and a study of the pathology. Arch. Path. 1930, 10, 742; 895.

182. Hanzlik, P.J. and Butt, E.M. Reactions of the crop (esophageal) muscles under tension, with considerations of anatomical arrangement, innervation and other factors. Am. J. Physiol. 1928, 85, 271-289.

183. Hare, W.K. Activity in isolated sympathetic ganglia. Am. J. Physiol. 1941, 134, 251-257.

184. Harley, V. and Goodbody, F.W. The chemical investigation of gastric and intestinal diseases by the aid of test meals. London, Edward Arnold, 1906.

185. Harrison, H. E. J. Clin. Invest. 1938, 17, 77.

186. Harrop, G.A. Studies on the suprarenal cortex. (3) Plasma electrolytes and electrolyte excretion during suprarenal insufficiency in the dog. J. Exper. Med. 1933, 58, 1-17.

187. Harrop, G.A. Bull. Johns Hopkins Hosp. 1936, 59, 11.

188. Harvey, A.M. and McIntosh, F.C. Calcium and synaptic transmission in a sympathetic ganglion. J. Physiol. 1938, 97, 408-416.

189. Hatcher, R.A. The mechanism of vomiting. Physiol. Rev. 1924, 4, 479-504.

190. Hatcher, R.A. and Weiss, S. Studies on vomiting. J. Pharmacol. & Exper. Therap. 1923, 22, 139-198.

191. Hawk, P.B. Rehfuss, M.E. and Bergeim, A. The response of the normal human stomach to the various standard foods and a summary. Am. J. M. Sc. 1926, 171, 359-369.

192. Hedblom, C... and Cannon, W.B. Some conditions affecting the discharge of food from the stomach. Am. J. M. Sc. 1909, 108, 504-521.

193. Hellebrandt, F.A. and Miles, M.M. The influence of exercise on the rate of passage of inert material through the digestive tract. Research Quart. 1934, 5, 73-82.

194. Helm, J.D., Kramer, P., MacDonald, R.M. and Ingelfinger, F.J. Changes in motility of the human small intestine during sleep. Gastro-entero. 1948, 10, 135-137.

195. Henderson, V.E. The mechanism of intestinal peristalsis. Am. J. Physiol. 1928, 86, 82-98.

196. Henderson, V.E. and Crane, J.W. The sensitivity of the small intestine at different levels to internal pressure. Am. J. Physiol. 1924, 70, 22-25.

197. Henderson, V.E. and Currie, G.C. A study of the movements of the large intestine in the guinea pig. Am. J. Physiol. 1926, 78, 287-298.

198. Heppel, L.A. The diffusion of radioactive sodium into the muscles of potassium deprived rats. Am. J. Physiol. 1939-40, 128, 449-454.

199. Heppel, L.A. The electrolytes of muscle and liver in potassium depleted rats. Am. J. Physiol. 1939, 127, 385-392.

200. Heppel, L.A. and Schmist, C.L. Uni. of Calif. Publ. in Physiol. 1938, 14, 189.

201. Herrin, R.C. The effect of atropine and pilocarpine upon the emptying time of the human stomach. Am. J. Physiol. 1936, 115, 104-112.

202. Herrington, M.S. Successful treatment of two cases of familial periodic paralysis with potassium citrate. J.A.M.A. 1937, 108, 1339.

203. Hesser, F.H., Lanworthy, O.R. and Kolb, L.C. Experimental study of gastric activity released from cortical control. J. Neurophysiol. 1941, 4, 274-283.

204. Heublein, G.W., Thompson, W.D. and Scully J.P. The effect of a vitamin B complex deficiency on gastric emptying and small intestine motility. Am. J. Roentgenol. 1941, 46, 866-875.

205. Hines, L.E., Lueth, H.C. and Ivy, A.C. Motility of the rectum in normal and in constipated subjects. Arch. Int. Med. 1929, 44, 147-152.

206. Hines, L.E. and Mead, H.C.A. Peristalsis in a loop of small intestine, a direct study. Arch. Int. Med. 1926, 38, 536-543.

207. Hinrichsen, J. The physiology of the ileocolic sphincter. Am. J. Physiol. 1930, 93, 658.

208. Hinrichsen, J. and Ivy, A.C. Studies on the ileocolic sphincter of the dog. Am. J. Physiol. 1931, 98, 494-507.

209. Hockett, A.J. Reciprocal activity of the muscle coats of guinea pig intestine. Proc. Soc. Exper. Biol. & Med. 1929, 26, 813-814.

210. Hockett, A.J. and Thienes, C.H. The reciprocal activity of the muscle coats of guinea pig intestine. Am. J. Physiol. 1929, 90, 392.

211. Hoff, E.C. and Sheehan, D. Experimental gastric erosions following hypothalamic lesions in monkeys. Am. J. Path. 1935, 11, 789-802.

212. Hoff, E.C., Smith, E.R. and Winkler, A. J. Clin. Invest. 1941, 20, 607.

213. Horton, B.T. Lymphatics of the stomach with special reference to pyloric block. Proc. Staff Meet., Mayo Clin. 1927, 2, 312-315.

214. Horton, B.T. Pyloric musculature with special reference to pyloric block. Am. J. Anat. 1928, 41, 197-226.

215. Horton, B.T. Pyloric block, with special reference to the musculature, myenteric plexus and lymphatic vessels. Arch. Surg. 1931, 22, 438-462.

216. Hosoi, K. and Alvarez, W.C. and Mann, F.C. Intestinal absorption; a search for a low residue diet. Arch. Int. Med. 1928, 41, 113-126.

217. Hurwe, H.V., Denis, W, Silverman, D.N. and Irwin, E.L. Hydrogen ion concentration in the human duodenum. J. Biol. Chem. 1924, 60, 633-645.

218. Hunter, G.W. The section of sympathetic nerves for the relief of muscle spasm. J...M.A. 1924, 83, 793.

219. Hurst, A.F. Constipation and allied intestinal disorders. London, H. Frowde, 1909.

220. Hurst, A.F. The sensibility of the alimentary canal. London, 1911.

221. Hurst, A.F. Common fallacies in the x-ray diagnosis of disorders of the alimentary canal. Arch. Roent. Ray. 1912, 17, 210-219.

222. Hurst, A.F. Essays and Addresses on digestive and nervous diseases and on Addison's anemia and asthma. London, W. Heinemann, 1924.

223. Hurst, A.E. and Briggs, P.J. The sphincters of the alimentary canal and their clinical significance. Brit. M. J. 1925, 1, 145-151.

224. Hurst, A.F., Cook, F. and Schlesinger, E.G. The sensibility of the stomach and intestines in man. J. Physiol. 1908, 37, 481-490.

225. Hurst, A.F. and Newton, A. The normal movements of the colon in man. J. Physiol. 1913, 47, 57-65.

226. Ingle, D.J. The work performance of adrenalectomized rats maintained on a high sodium chloride, low potassium diet. Am. J. Physiol. 1940, 129, 278-282.

227. Ivy, A.C. A brief review of the physiology of the duodenum. Radiol. 1927, 9, 47-59.

228. Ivy, A.C. The role of hormones in digestion. Physiol. Rev. 1930, 10, 282-335.

229. Ivy, A.C., Farrell, J.I. and Lueth, E. Am. J. Physiol. 1927, 82, 27.

230. Ivy, A.C. and McIlvain, G.B. The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa. Am. J. Physiol. 1923, 67, 124-140.

231. Jacobson, E. Voluntary relaxation of the esophagus. Am. J. Physiol. 1925, 72, 387-394.

232. Jones, C.M. and Eaton, F.B. Postoperative nutritional edema. Arch. Surg. 1933, 27, 159-177.

233. Judd, E.S. and Adson, A.W. Lumbar sympathetic ganglionectomy and ramisectomy for congenital idiopathic dilatation of the colon. Ann, Surg. 1928, 88, 479-490.

234. Judd, E.S. and Nagel, G.W. Duodenitis. Ann. Surg. 1927, 85, 380-390.

235. Jurica, E.J. Studies on the motility of the denervated mammalian esophagus. Am. J. Physiol. 1926, 77, 371-384.

236. Kantor, J. A study of atmospheric air in the upper digestive tract. Am. J. M. Sc. 1918, 155, 829-857.

237. Karr, W.G. and Abbott, W.O. Intubation studies of the human small intestine. (4) Chemical characteristics of the intestinal contents in the fasting state and as influenced by the administration of acids, of alkalies and of water. J. Clin. Invest. 1935, 14, 893-900.

238. Kasabach, H.H. Effect of indigestion of water and of dextrose solution on emptying time of normal stomach. Arch, Int. Med. 1931, 48, 1237-1240.

239. Keith, N.M. and Binger, M.W. Diuretic action of potassium salts. J.A.M.A. 1935, 105, 1584-1591.

240. Kerr, S.E. Studies on the inorganic composition of blood. (1) The effect of hemorrhage on the inorganic composition of serum and corpuscles. J. Biol. Chem. 1926, 67, 689-720.

241. Keys, A. Exchanges between blood plasma and tissue fluid in man. Science, 1937, 85, 317-318.

242. Keller, A.D. Ulceration in the digestive tract of the dog following intracranial procedures. Arch. Path. 1936, 21, 127-164.

243. Keller, A.D. Protection by peripheral nerve section of the gastro-intestinal tract from ulceration following hypothalamic lesions with preliminary observations on ulceration in the gastro-intestinal tract of the dog following vagotomy. Arch. Path. 1936, 21, 165-184.

244. Keller, A.D. and D'Amour, M.C. Ulceration in the digestive tract of the dog following hypophysectomy. Arch. Path. 1936, 21, 185-201.

245. Kennard, M.A. and Willner, D. Findings at autopsies of seventy anthropoid apes. Endocrinol. 1941, 28, 967-976.

246. King, C.E. and Arnold, L. The activities of the intestinal mucosal motor mechanism. Am. J. Physiol. 1922, 59, 97-121.

247. Klein, E. Gastric motility. (1) The origin and character of gastric peristalsis. Arch. Surg. 1926, 12, 571-582.
(2) The conduction of the gastric peristaltic wave. Ibid, pp, 583-590.
(3) The mechanism of the pylorus. Ibid, pp, 1224-1254.

248. Knight, G.C. The innervation of the sophagus and cardiac sphincter. J. Physiol. 1934, 81, 6P-7P.

249. Kornberg, A. Potassium deficiency in the rat. Am. J. Physiol. 1945-46, 145, 291-298.

250. Kosaka, T. and Lim, R.K.S. Demonstration of the humoral agent in the inhibition of gastric secretion. Proc. Soc. Exper. Biol. & Med. 1930, 27, 890-891.

251. Kosaka, T. and Lim, R.K.S. On the mechanism of the inhibition of gastric secretion by fat. The role of bile and cystokinin. Chinese J. Physiol. 1930, 4, 213-220.

252. Kosaka, T., Lim, R.K.S., Ling, S.M. and Liu, A.C. On the mechanism of the inhibition of gastric secretion by fat. A gastric inhibitory agent obtained from the intestinal mucosa. Chinese J. Physiol. 1932, 6, 107-127.

253. Krueger, H. The action of morphine on the digestive tract. Physiol. Rev. 1937, 17, 618-645.

254. Kuntz, A. On the innervation of the digestive tube. J. Comp. Neurol. 1913, 23, 173-192.

255. Kuntz, A. The structural organization of the inferior mesenteric ganglia. J. Comp. Neurol. 1940, 72, 371-382.

256. Kure, K., Ichiko, K. and Ishikawa, K. On the spinal parasympathetic. Physiologic significance of the spinal parasympathetic system in relation to the digestive tract. Quart. J. Exper. Physiol. 1931, 21, 1-19.

257. Langley, J.N. The origin from the spinal cord of the cervical and upper thoracic sympathetic fibers, with some observations on white and gray rami communicantes. Phil. Trans. Roy. Soc., London, 1892, 183, 114.

258. Langley, J.N. The sympathetic and other related systems of nerves, Schafer's textbook of physiology. 1900, vol. 2.

259. Langley, J.N. The autonomic nervous system. Brain, 1903, 26, 1.

260. Larimore, J.W. the human large intestine in the new-born and in the adult. Ann. Clin. Med. 1926, 5, 439-463.

274. Loeb, R.F. Certain effects of desoxycorticosterone. The development of diabetes insipidus and the replacement of muscle potassium by sodium in normal dogs. Am. J. Physiol. 1941-42, 135, 230-237.

275. Loeb, R.F. et al. Electrolyte balance studies in adrenalectomized dogs with particular reference to the excretion of sodium. J. Exper. Med. 1933, 57, 775-792.

276. Loew, E.R. and Patterson, T.L. The reflex influence of the lower portion of the large gut on the tonus and movements of the empty stomach in dogs. Am. J. Physiol. 1935, 113, 89-90.

277. Luckhardt, A.B., Phillips, H.T. and Carlson, A.J. Contributions to the physiology of the stomach. (2) The control of the pylorus. Am.J. Physiol. 1919, 50, 57-66.

278. McClendon, J.F. Acidity curves in the stomachs and duodenums of adults and infants, plotted with the aid of improved methods of measuring the hydrogen ion concentration. Am.J. Physiol. 1915, 38, 191-199.

279. McClendon, J.F., Bissel, F.S., Lowe, E.R. and Meyer, P.F. Hydrogen ion concentration of the contents of the small intestine. J.A.M.A. 1920, 75, 1638-1641.

280. McClendon, J.F., Meyers, F.J., Culligan, L.C. and Gydesen, C.S. Factors influencing the hydrogen ion concentration of the ileum. J. Biol. Chem. 1919, 38, 535-538.

281. McCann, J.C. Studies on the emptying of the stomach. Am. J. Physiol. 1929, 89, 497-507.

282. McClure, C.W., Reynolds, L. and Schwartz, C.O. On the behavior of the pyloric sphincter in normal man. Arch. Int. Med. 1920, 26, 410-423.

283. McClure, C.W., Wetmore, A.S. and Reynolds, L. New methods for estimating enzymatic activities of duodenal contents of normal man. Arch. Int. Med. 1921, 27, 706-715.

284. McCrea, E.D. and McSwiney, B.A. The effects of stimulation of the vagi on the pyloric region of the stomach. J. Physiol. 1926, 61, 28-34.

285. McCrea, E.D. and McSwiney, B.A. The effect on the stomach of stimulation of the peripheral end of the splanchnic nerve. Quart. J. Exper. Physiol. 1927-28, 18, 301-313.

286. McCrea, E.D., McSwiney, B.A., Morison, J.W. and Stopford J.S.B. The normal movements of the stomach. Quart. J. Exper. Physiol. 1924, 14, 379-397.

287. McCrea, E.D., McSwiney, B.A. and Stopford, J.S.B. Effects of section of the vagi nerves on the motor activity of the stomach. J. Physiol. 1925, 60, Proc. 29.

288. McCullagh, E.P. The use of desoxycorticosterone acetate in Addison's disease. J.A.M.A. 1940, 114, 2530-2537.

289. McGill, C. The structure of smooth muscle in the resting and in the contracted condition. Am. J. Anat. 1909, 9, 493-545.

290. McLanahan, S. Pyloric occlusion following the ingestion of corrosive liquids. J.A.M.A. 1934, 102, 735-739.

291. McQuarre, J. Plasma electrolyte disturbance in patient with hypercorticoadrenal syndrome contrasted with that found in Addison's disease. Endocrinol. 1937, 21, 762-772.

292. McSwiney, B.A. The structure and movements of the cardia. Quart. J. Exper. Physiol. 1929, 19, 237-241.

293. McSwiney, B.A. Innervation of the stomach. Physiol. Rev. 1931, 11, 478-514.

294. McSwiney, B.A. and Robson, J.M. The sympathetic innervation of the stomach. (3) The interaction of the vagus and sympathetic nerves. J. Physiol. 1931, 73, 141-150.

295. McSwiney, B.A. and Spurrell, W.R. Influence of osmotic pressure upon the emptying time of the stomach. J. Physiol. 1933, 79, 437-442.

296. McSwiney, B.A. and Spurrell, W.R. The outline method for investigating gastric motility. J. Physiol. 1933, 79, 423-436.

297. McSwiney, B.A. and Spurrell, W.R. The effect of fat on gastric motility. J. Physiol. 1935, 84, 41-49.

298. McWhorter, G.L. Some clinical and experimental observations on gastric acidity. Use of the gas chain method. Am. J. M. Sc. 1918, 155, 672-685.

299. Maile, W.C.D. and Scott, K.L.J. Digestibility of common foodstuffs as determined by radiography. Lancet, 1935, 228, 21-23.

300. Mall, F.P. A study of the intestinal contractions. Johns Hopkins Hosp. Rep. 1896, 1, 37-75.

301. Mall, F.P. Reversal of the intestine. Johns Hopkins Hosp. Rep. 1, 93-110, 1896.

302. Manery, J.F. and Solandt D.Y. Electrolyte changes in traumatic shock. Am. J. Physiol. 1941, 133, 376.

303. Mann, F.C. and Bollman, J.L. The reaction of the content of the gastro-intestinal tract. J.A.M.A. 1930, 95, 1722-1724.

304. Martin, C.L. and Rogers, F.T. Hunger pain. Am. J. Roentgenol. 1927, 17, 222-227.

305. Masserman, J.H. and Haertig, E.W. The influence of hypothalamic stimulation on intestinal activity. J. Neurophysiol. 1938, 1, 350-356.

306. Masten, M.G. and Bunts, R.C. Neurogenic erosions and perforations of the stomach and esophagus in cerebral lesions. Arch. Int. Med. 1934, 54, 916-930.

307. May, W.P. The innervation of the sphincters and musculature of the stomach. J. Physiol. 1904, 31, 260-271.

308. May, C.D. and McCreary, J.F. The glucose tolerance test in celiac disease, significance of low blood sugar curves. J. Pediat. 1940, 17, 143-154.

309. May, C.D., McCreary, J.F. and Blackfan, K.D. Notes concerning the cause and treatment of celiac disease. J. Pediat. 1942, 21, 289-305.

310. Meltzer, S.J. A further experimental contribution to the knowledge of the mechanism of deglutition. J. Exper. Med. 1897, 2, 453-464.

311. Meltzer, S.J. On the causes of the orderly progress of the peristaltic movements in the esophagus. Am. J. Physiol. 1899, 2, 266-272.

312. Meltzer, S.J. Secondary peristalsis of the esophagus - a demonstration on a dog with a permanent fistula. Proc. Soc. Exper. Biol. and Med. 1907, 4, 35-37.

313. Menville, L.J., Ane, J.N. and Blackberg, S.N. A comparative x-ray study of passage of foodstuffs through gastrointestinal tract of rats. Proc. Soc. Exper. Biol. and Med. 1930, 27, 641-644.

314. Menville, L.J. and Ane, J.N. X-ray study of the passage of different foodstuffs through the small intestine of man. Radiol. 1932, 18, 783-786.

315. Meschan, I. and Quigley, J.P. Spontaneous motility of the pyloric sphincter and adjacent regions of the gut in the unanesthetized dogs. Am. J. Physiol. 1938, 121, 350-357.

316. Mettler, F.A., Spinder, J., Mettler, C., and Combs, J.D. Disturbances of gastro-intestinal functions after localized ablation of cerebral cortex. Arch. Surg. 1936, 32, 618-623.

317. Miller, F.R. On gastric sensation. J. Physiol. 1910, 40, 409-415.

318. Miller, H.G. Potassium in animal nutrition. (2) Potassium in its relation to the growth of young rats. J. Biol. Chem. 1923, 55, 61-78.

319. Miller, H.G. Potassium in animal nutrition. (1) Influence of potassium on urinary sodium and chloride excretion. J. Biol. Chem. 1922, 55, 45-59.

320. Miller, H.G. and Darrow, D.C. Relation of muscle electrolyte to alterations in serum potassium and to the toxic effects of injected potassium chloride. Am. J. Physiol. 1940, 130, 747-758.

321. Miller, H.G. and Darrow, D.C. Relation of serum and muscle electrolyte, particularly potassium, to voluntary exercise. Am. J. Physiol. 1941, 132, 801-809.

322. Miller, T.G. and Abbott, W.O. Small intestinal intubation; experiences with a double lumened tube. Ann. Int. Med. 1934, 8, 85-92.

323. Mitchell, C. Ultraviolet radiations in conditions of extreme calcium and phosphorus deficiency. Am. J. Physiol. 1925, 72, 143-150.

324. Mogan, C.J. and Thomas, J.E. The effect of the pyloric sphincter of acid in the stomach and in the duodenum. Am. J. Physiol. 1931, 97, 546-547.

325. Morley, J. Cardiospasm. Lancet, 1927, 212, 431-433.

326. Morse, W.E. The effects of various neutral solutions on gastric discharge, gastric secretion, and duodenal regurgitation. Arch. Int. Med. 1918, 21, 48-58.

327. Mosher, H.P. X-ray study of movements of the tongue, epiglottis and hyoid bone in swallowing, followed by a discussion of difficulty in swallowing caused by retropharyngeal diverticulum, postcricoid webs and exostoses of cervical vertebrae. Laryngoscope, 1927, 37, 235-362

328. Mosher, H.P. and McGregor, G.W. A study of the lower end of the esophagus. Ann. Otol. Rhin. & Laryng. 1928, 37, 12-70.

329. Mulinos, M.G. The value of selective drugs in the treatment of constipation. Rev. Gastroenterol. 1935, 2, 292-301.

330. Myerson, A. and Ritvo, M. Benzedrine sulfate and its value in spasm of the gastro-intestinal tract. J.A.M.A. 1936, 107, 24-26.

331. Neilson, C.H. and Lipsitz, S.T. The effect of various procedures on the passage of liquids from the stomach. J.A.M.A. 1915, 64, 1052-1053.

332. Olmsted, W.H., Curtis, G. and Timm, O.K. Stool volatile fatty acids. (4) The influence of feeding bran pentosan and fiber to man. J. Biol. Chem. 1935, 108, 645-652.

333. Olmsted, W.H., Duden, C.W., Whitaker, W.M. and Parker, R.F. A method for the rapid distillation of the lower volatile fatty acids from stools. J. Biol. Chem. 1929, 85, 115-126.

334. Crent-Kelles, E. Potassium in animal nutrition. J. Biol. Chem. 1941, 140, 337-352.

335. Osborne, T.B. and Mendel, L.B. The inorganic elements in nutrition. J. Biol. Chem. 1918, 34, 131.

336. Ott, I. and Scott, J.C. The action of bile and some of its constituents upon intestinal peristalsis and the circulation. Proc. Soc. Exper. Biol. & Med. 1908-09, 6, 13.

337. Paget, S. On cases of voracious hunger and thirst from injury or disease of the brain. Trans. Clin. Soc., London, 1897, 30, 113-119.

338. Pancoast, H.K. and Hopkins, A.H. Effect of moderate doses of some opium derivatives on gastro-intestinal tract of man. Preliminary report on roentgen studies. J.A.M.A. 1915, 65, 2220-2224.

339. Pavlov, I.P. Conditioned reflexes. An investigation of the physiological activity of the cerebral cortex. Trans. by G.V. Anrep, London, Oxford Uni. Press, 1927.

340. Peabody, F.W. Studies of the inorganic metabolism in pneumonia with special reference to calcium and magnesium. J. Exper. Med. 1913, 13, 71-78.

341. Pearcy, J.F. and Allen, T.D. Studies on the visceral nervous system. Reflexes from the gastro-intestinal tract to the eye. Am. J. Physiol. 1927, 82, 56-58.

342. Pearcy, J.F. and Van Liere. Reflexes from the colon. Reflexes to the stomach. Am. J. Physiol. 1926, 78, 64-73.

343. Pendergrass, E.P., Ravdin, I.S., Johnston, C.G. and Hodes, P.J. (1) Studies of the small intestine. (2) The effects of foods and various pathological states on the gastric emptying and the small intestine pattern. Radiol. 1936, 26, 651-662.

344. Peters, J.P. and Van Slyke, D.D. Quantitative clinical biochemistry. 1931, Vol. 1, page 751.

345. Peters, J.P. Salt and water metabolism in nephritis. Medicine, 1932, 11, 435-455.

346. Pierce, H.B., Haege, L.F. and Fenton, P.F. The rate of emptying of the rats stomach following the intragastric administration of glucose solutions. Am. J. Physiol. 1941-42, 135, 526-530.

347. Plant, O.H. and Miller, G.H. Effects of morphine and some other opium alkaloids on the muscular activity of the alimentary canal. (1) Action on the small intestine in unanesthetized dogs and man. J. Pharmacol. 1926, 27, 361-383.

348. Pommerenke, W.T. A study of the sensory areas eliciting the swallowing reflex. Am. J. Physiol. 1928, 84, 36-41.

349. Prasad, B.N. The carbohydrate metabolism of gut muscle. J. Physiol. 1935, 85, 239-248.

350. Prasad, B.N. The mechanical activity of gut muscle under anaerobic conditions. J. Physiol. 1935, 85, 249-266.

351. Pudenz, R.H. J.A.M.A. 1938, 111, 2253.

352. Puestow, C.B. Intestinal motility and postoperative distention: experimental and clinical studies. J.A.M.A. 1942, 120, 903-908.

353. Quigley, J.P. Action of insulin on the gastric motility of man. Proc. Soc. Exper. Biol. & Med. 1929, 26, 769-770.

354. Quigley, J.P. and Hallaran, W.R. The independence of spontaneous gastro-intestinal motility and blood sugar levels. Am. J. Physiol. 1932, 100, 102-110.

355. Quigley, J.P., Highstone, W.H. and Ivy, A.C. A study of the propulsive activity of a Thiry-Vella loop of intestine. Am. J. Physiol. 1934, 108, 151-158.

356. Quigley, J.P., Johnson, V. and Soloman, E.I. Action of insulin on the motility of the gastro-intestinal tract. (1) Action on the stomach of normal fasting man. Am. J. Physiol. 1929, 90, 89-98.

357. Quigley, J.P. and Meschan, I. Action of fats introduced into the duodenum on the pyloric sphincter and adjacent portions of the gut. Am. J. Physiol. 1937, 119, 386-387.

358. Quigley, J.P. and Meschan, I. The role of the vagus in the regulation of the pyloric sphincter and adjacent portions of the gut, with special reference to the process of gastric evacuation. Am. J. Physiol. 1938, 123, 166.

359. Quigley, J.P., Read, M.R., Radzow, K.H., Meschan, I. and Werle, J.M. The effect of hydrochloric acid on the pyloric sphincter, the adjacent portions of the digestive tract and on the process of gastric evacuation. Am. J. Physiol. 1942, 137, 153-159.

360. Quigley, J.P., Zettleman, H.J. and Ivy, A.C. Analysis of the factors involved in gastric motor inhibition by fats. Am.J. Physiol. 1934, 108, 643-651.

361. Raiford, T.S. and Mulinos, M.G. Studies in gastro-intestinal motility. Arch. Surg. 1936, 33, 276-296.

362. Rake, G.W. A case of annular muscular hypertrophy of the esophagus (achalasia of the cardia without esophageal dilatation). Guy's Hosp. Rep. 1926, 76, 145-152.

363. Rake, G.W. On the pathology of achalasia of the cardia. Guy's Hosp. Rep. 1927, 77, 141-150.

364. Rankin, F.W. and Learmonth, J.R. Section of the sympathetic nerves of the distal part of the colon and the rectum in the treatment of Hirschsprung's disease and certain types of constipation. Ann. Surg. 1930, 92, 710-720.

365. Ranson, A.W. and Billingsley, P.R. Studies on the sympathetic nervous system. J. Comp. Neurol. 1918, 29, 305.

366. Ranson, S.W. and Clark, S.L. The anatomy of the nervous system. Its development and function. 1947, eighth edition.

367. Ravdin, I.S., Pendergrass, E.P., Johnston, C.G. and Hodes, P.J. The effect of foodstuffs on the emptying of the normal and operated stomach, and the small intestine pattern. Am. J. Roentgenol. 1936, 35, 306-315.

368. Reid, P.E., Ivy, A.C. and Quigley, J.P. Spiral propulsion of a bolus in the intestine. Am. J. Physiol. 1934, 109, 483-487.

369. Ringer, S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J. Physiol. 1883-84, 4, 29-42.

370. Rives, J.D. and Strug, L.H. Treatment of Hirschsprung's disease by spinal anesthesia. A preliminary report. New Orleans, M. & S. J. 1935, 88, 81-84.

371. Roberts, W.M. The effect of oils on gastric secretion and motility. Quart. J. Med. 1931, 24, 133-152.

372. Robertson, H.E. and Kernohan, J.W. The myenteric plexus in congenital megacolon. Proc. Staff Meet., Mayo Clin. 1938, 13, 123-125.

373. Rogatz, J.L. Roentgen ray studies of stomach function. Am. J. Dis. Child. 1924, 28, 53-68.

374. Rogers, F.T. and Hardt, L.L.J. Contributions to the physiology of the stomach. (26) The relation between the digestive contractions of the filled and the hunger contractions of the empty stomach. Am. J. Physiol. 1915, 38, 274-284.

375. Rosenbrueth, A. The chemical mediation of autonomic nervous impulses as evidenced by summation of responses. Am. J. Physiol. 1932, 102, 12-38.

376. Rosenbrueth, A. and Cannon, W.B. Adequacy of chemical theory of smooth muscle excitation. Am. J. Physiol. 1936, 116, 414-429.

377. Rosenbrueth, A., Davis, H. and Rempel B. The physiological significance of the electric responses of smooth muscle. Am. J. Physiol. 1936, 116, 387-407.

378. Ross, J.P. Selection of cases of megacolon for sympathectomy. Proc. Roy. Soc. Med. 1939, 32, 1148-1149.

379. Rusk, H.A. Changes in serum potassium in certain allergic states. J.A.M.A. 1939, 112, 2395-2398.

380. Scandola, C. Possibility of recuperation of intestine in strangulation hernia. J.A.M.A. 1915, 64, 2029.

381. Schmidt, C.L.A. The extra-hepatic functions of bile. Physiol. Rev. 1927, 7, 129-150.

382. Schrader, G.A. et al. Symptomatology and pathology of potassium and magnesium deficiencies in the rat. J. Nutrition, 1937, 14, 85-110.

383. Schwartz, H.G. Reflex activity within the sympathetic nervous system. Am. J. Physiol. 1934, 109, 593-604.

384. Scott, W.J.M. and Morton, J.J. J. Clin. Invest. 1931, 9, 247.

385. Scudder, J. Surgery, 1937, 1, 74.

386. Scudder, J. Shock; Blood studies as a guide to therapy. Lippincott, Philadelphia, 1940.

387. Shay, H. and Gershon-Cohen, J. Experimental studies in gastric physiology in man. (2) A study of pyloric control. The roles of acid and alkali. Surg. Gynec. Obst. 1934, 58, 935-955.

388. Shay, H. and Gershon-Cohen, J. Experimental studies in gastric physiology in man; the mechanism of gastric evacuation after partial gastrectomy as demonstrated roentgenologically. Am. J. Digest. Dis. & Nutrition, 1935, 2, 608-613.

389. Sheehan, D. The effect of cortical stimulation on gastric movements in the monkey. J. Physiol. 1934, 83, 177-184.

390. Sheehan, D. Some problems relating to the dorsal spinal nerve roots. Yale J. Biol. Med. 1935, 7, 425-440.

391. Sheehan, D. The hypothalamus and gastro-intestinal regulation. Res. Publ. Ass. Nerv. Ment. Dis., 1940, 20, 589-616.

392. Sheehan, D. Relationship of the hypothalamus to the large bowel. Am. J. Digest. Dis., 1942, 9, 361-363.

393. Sheehan, D. and Labate, J.S. Effect of nicotine on uterine responses to hypogastric nerve stimulation. Am. J. Physiol. 1942, 137, 456-458.

394. Sherrington, C.S. Schafer's textbook of physiology. 1900, vol. 2, Edingburgh.

395. Sherrington, C.S. Postural activity of muscle and nerve. Brain, 1915, 38, 191-234.

396. Simpson, S.L. et al. The presence of an excess of male (comb-growth and prostate stimulating) hormone in virilism and pseudo-hermaphroditism. Endocrinol. 1936, 20, 363-372.

397. Skinner, J.T. and McHargue, J.S. Response of rats to boron supplements when fed ration low in potassium. Am. J. Physiol. 1945, 143, 385-390.

398. Slaughter, D. and Gross, E.G. Some new aspects of morphine action; effect on intestine and blood pressure, toxicity studies. J. Pharmacol. & Exper. Therap. 1940, 68, 96-103.

399. Slaughter, D. and Lackey, R.W. Effect of morphine sulfate on serum choline esterase. Proc. Soc. Exper. Biol. & Med. 1940, 45, 8-10.

400. Slaughter, D. and Munsell, D.W. Some new aspects of morphine action, effects on pain. J. Pharmacol. & Exper. Therap. 1940, 68, 104-112.

401. Slaughter, D. and Parsons, J.C. and Munal, H.D. New clinical aspects of the analgesic action of morphine. J.A.M.A. 1940, 115, 2058-2060.

402. Smith, A.H. Effects on diet poor in inorganic salts on certain organs and blood of young rats. Am. J. Physiol. 1930, 94, 107-117.

403. Smith, O.N. and Chamberlin, G.W. Benzedrine sulfate, its effects on the motor function of the digestive tract, on gastric acidity, and on evacuation of biliary system. Radiol. 1937, 29, 676-682.

404. Smith, F.M. and Miller G.H. The refkex influence of the colon, appendix and gallbladder on the stomach. Arch. Int. Med. 1930, 46, 988-993.

405. Sollmann, T. A manual of pharmacology. 1942, 6th edition, W.B. Saunders Co., Philadelphia.

406. Sollmann, T., von Oettingen, W.F. and Shikawa, Y. The effects of bicarbonate buffers and of carbon dioxide on the motor functions of the excised small intestines of rabbits. Am. J. Physiol. 1926, 86, 661-674.

407. Spencer, W.H., Meyer, G.P., Rehfuss, M.E. and Hawk, P.B. Gastro-intestinal studies. (12) Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach. Am. J. Physiol. 1916, 39, 459-479.

408. Spurrell, W. R. Duodenal reflex. J. Physiol. 1935, 84, 4P-5P.

409. Stokes, J. and Wilder, T.S. Esophageal obstruction; a clinical and experimental study of its effect on life and growth. Am. J. Dis. Child. 1932, 43, 604-609.

410. Stucky, C.J., Rose, W.B. and Cowgill, G.R. Studies in the physiology of vitamins. (6) The effect of insulin on gastric motility in vitamin B deficiency. Am. J. Physiol. 1928-29, 87, 85-92.

411. Suckow, G.R. and Burget, G.E. The response of isolated segments of intestine and uterus to adrenalin at different pH levels of the bath. Am. J. Physiol. 1929, 88, 143-150.

412. Sunderman, F.W. et al. Studies in serum electrolytes. (50) Concentration of electrolytes and non-electrolytes in the serum during lobar pneumonia. J. Clin. Invest. 1926-27, 3, 37.

413. Telford, E.D. and Stopford, J.S.B. The autonomic nerve supply of the distal colon. An anatomical and clinical study. Brit. M. J., 1934, 1, 572-574.

414. Templeton, R.D. and Johnson, V. Further observations on the nature of hunger contractions in man. Am. J. Physiol. 1929, 88, 173-176.

415. Templeton, R.D. and Lawson, H. Studies in the motor activities of the large intestine; normal motility in the dog, recorded by the tandem balloon method. Am. J. Physiol. 1931, 96, 667-676.

416. Thomas, J.E. A further study of the nervous control of the pyloric sphincter. Am. J. Physiol. 1929, 88, 498-518.

417. Thomas, J.E. The mechanism of gastric evacuation. J.A.M.A., 1931. 97, 546-547.

418. Thomas, J.E. Gastric inhibition caused by amino acids in the small intestine. Am. J. Physiol. 1941-42, 135, 609-613.

419. Thomas, J.E. and Crider, J.O. Inhibition of gastric peristalsis due to a substance found in commercial peptones. Proc. Soc. Exper. Biol. & Med. 1936, 34, 825-827.

420. Thomas, J.E. and Crider, J.O. The regulation of gastric emptying. Virginia M. Monthly, 1937, 64, 181-185.

421. Thomas, J.E., Crider, J.O. and Mogan, C.J. Studies of reflexes involving the pyloric sphincter and antrum and their role in gastric evacuation. Am. J. Physiol. 1934, 108, 683-700.

422. Thomas, J.E. and Kuntz, A. A study of gastro-intestinal motility in relation to the enteric nervous system. Am. J. Physiol. 1926, 76, 606-626.

423. Thomas, J.E. and Kuntz, A. A study of the vago-enteric mechanism by means of nicotine. Am. J. Physiol. 1926, 76, 598-605.

424. Thomas, R.H. Yale J. Biol. & Med. 1940, 12, 345.

425. Thorel, G. Contribution to the subject of ventricular membrane activity and innervation of the stomach. Am. J. Physiol. 1925, 75, 278.

426. Thorn, G.W. A study of the mechanism of edema associated with menstruation. Endocrinol. 1938, 22, 155-163.

427. Thorn, G.W. The effect of 17-hydroxycorticosterone and related adrenal cortical steroids on sodium and chloride excretion. Science, 1941, 94, 348-349.

428. Thorn, G.W. Desoxycorticosterone acetate therapy in Addison's disease. J.A.M.A. 1940, 114, 2517-2525.

429. Thorn, G.W. and Harrop, G.A. The sodium retaining effect of the sex hormones. Science, 1937, 86, 40-41.

430. Todd, T.W. Behavior pattern of the alimentary tract. 1930, (The Beaumont foundation lectures).

431. Trumble, H.C. The innervation and muscular activities of the distal colon: with a note on the surgical treatment of constipation. Brit. J. Surg. 1935, 23, 214-230.

432. Uprus, V., Gaylor, G.B., Williams, D.J. and Garmichael, E.A. Vasodilatation and vasoconstriction in response to warming and cooling the body: a study in patients with hemiplegia. Brain, 1935, 58, 448-455.

433. Veach, H.O. Studies on the innervations of smooth muscle. (4) Functional relations between the lower end of the esophagus and stomach of tne cat. Am. J. Physiol. 1926, 76, 532-537.

434. Vineberg, A.M. and Komorov, S.A. The influence of the vagus nerve on esophageal secretion. Am. J. Physiol. 1933, 104, 73-80.

435. Wade, R.B. and Royle, R.D. The operative treatment of Hirschsprung's disease: a new method. M. J. Australia, 1927, 14, 137-141.

436. Wallace, R., Ehrenfeld, I., Cowett, M., Joliffe, N., Shapiro, L. and Sturtevant, M. Motility of the gastro-intestinal tract. Am.J. Roentgenol. 1938, 39, 64-66.

437. Walton, F.E., Moore, R.M. and Graham, E.A. The nerve pathways in the vomiting of peritonitis. Arch. Surg. 1931, 22, 829-837.

438. Walzer, M., Gray, I., Straus, H.W. and Livingston, S. Studies in experimental hypersensitiveness in the rhesus monkey. (4) The allergic reaction in passively locally sensitized abdominal organs. J. Immunol. 1938, 34, 91-95.

439. Wang, S.C., Clark, G., Dey, F.L. and Ranson, S.W. Further study on the gastro-intestinal motility following stimulation of the hypothalamus. Am. J. Physiol. 1940, 130, 81-88.

440. Watts, J.W. The influence of the cerebral cortex on gastro-intestinal movements. J.A.M.A. 1935, 104, 355-357.

441. Watts, J.W. and Frazier, C.H. Cortical autonomic epilepsy. J. Nerv. Ment. Dis. 1935, 81, 168-175.

442. Watts, J.W. and Fulton, J.F. Intussusception--the relation of the cerebral cortex to intestinal motility in the monkey. New Engl. J. Med. 1934, 210, 383-896.

443. Waugh, J.M. Effect of fat introduced into the jejunum by fistula on motility and emptying time of the stomach. Arch. Surg. 1936, 33, 451-466.

444. Welch, C.S., Wakefield, E.G. and Adams, E. Function of the large intestine in man in absorption and excretion; study of a subject with an ileostomy stoma and an isolated colon. Arch. Int. Med. 1936, 58, 1095-1110.

445. Werle, J.M., Brody, D.A., Ligon, E.W., Read, M.R. and Quigley, J.P. The mechanics of gastric evacuation. Am. J. Physiol. 1940-41, 131, 606-614.

446. Wheelon, H. and Thomas, J.E. Rhythmicity of the pyloric sphincter. Am. J. Physiol. 1920-21, 54, 460-473.

447. Wheelon, H. and Thomas, J.E. Observations on the motility of the antrum and the relation of the rhytnmic activity of the pyloric sphincter to that of the antrum. J. Lab. & Clin. Med., 1920-21, 6, 124-143.

448. Wheelon, H. and Thomas, J.E. Observations on the motility of the duodenum and the relation of duodenal activity to that of the pars pylorica. Am. J. Physiol., 1922, 59, 72-96.

449. White, H.L., Rainey, W.R., Monaghan, B., and Harris, A.S. Observations on the nervous control of the ileocolic sphincter and on intestinal movements in an unanesthetized human subject. Am. J. Physiol. 1934, 108, 449-457.

450. Wiggers, C.J. Physiology in health and disease. 1945, 4th edition, Lea Febiger, Philadelphia.

451. Wilder, R.M. et al. Intake of potassium, an important consideration in Addison's disease. Arch. Int. Med. 1937, 59, 367.

452. Williams, R.D. The effect of cellulose, hemicellulose and lignin on the weight of the stool; a contribution to the study of laxation in man. J. Nutrition, 1936, 11, 433-449.

453. Williams, R.D. The manner in which food controls the bulk of the feces. Ann, Int, Med., 1936, 10, 717-727.

454. Williams, R.D. and Olmsted, R.H. A biochemical method for determining indigestible residue, (crude fiber) in feces; lignin cellulose, and non-water soluble hemicelluloses. J. Biol. Chem. 1935, 108, 653-666.

455. Williams, T.B. Vascular studies of the pylorus. Anat. Rec. 1928, 38, 273-291.

456. Wilder, R.L. and Schultz, F.W. The action of volatile fatty acids on the gastric motor mechanism in dogs. Proc. Soc. Exper. Biol. & Med., 1929, 26, 624-625.

457. Wilson, M.J., Dickson, W.H. and Singleton, A.C. Rate of evacuation of various foods from the normal stomach. Arch. Int. Med. 1929, 44, 787-796.

458. Winkler, A.W. and Hoff, H.E. Potassium and the cause of death in traumatic shock. Am. J. Physiol. 1942-43, 139, 686-692.

459. Winkler, A.W. and et al. Renal excretion of potassium salts. Am. J. Physiol. 1942-43, 138, 94.

460. Wislocki, G.B. and O'Connor, V.J. Experimental observations upon the ureters, with special reference to peristalsis and antiperistalsis. Bull. Johns Hopkins Hosp., 1920, 31, 197-202.

461. Wolf, S. and Wolff, H.G. Evidence on the genesis of peptic ulcer in man. J.A.M.A., 1942, 120, 670-675.

462. Woolworth, R.S. Studies in the contraction of smooth muscle. Am. J. Physiol., 1900, 3, 26-44.

463. Young, A.W. The movements of the isolated small intestine and the action of various drugs and extracts upon them. Quart. J. Exper. Physiol., 1915, 8, 347.

464. Zwemer, R.L. Factors affecting human potassium tolerance. Proc. Soc. Exper. Biol. & Med., 1936, 35, 424-426.

465. Zwemer, R.L. The importance of corticoadrenal regulation of potassium metabolism. Endocrinol., 1937, 21, 40-49.

466. Zwemer, R.L. Ann. Surg., 1938, 107, 161.

467. Zwemer, R.L. Surgery, 1938, 4, 510.

468. Moody, R.O., Van Nuys, R.S. and Chamberlain W.E. Position of the stomach, liver and colon. Results of a roentgenological study in six hundred healthy adults. J.A.M.A. 1923, 81, 1924-1931.

469. Ferguson, J.H. Effects of vagotomy on the gastric functions of monkeys. Surg. Gynec. Obst., 1936, 62, 689-700.

470. Herrin, R.C. and Meek, W.J. Distention as a factor in intestinal obstruction. Arch. Int. Med., 1933, 51, 152-168.

McGILL UNIVERSITY LIBRARY
IXM 1D84·1948
UNACC.