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TITLE INTESTINAL MOTILITY AND INTESTINAL BLOOD CIRCULATION

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INTESTINAL MOTILITY AND INTESTINAL BLOOD CIRCULATION

by
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of the requirements for the degree of
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INTRODUCTION

The physiological importance of the interrelationship between the activity of any living organ and its blood circulation is well recognized. Since the early work of Claude Bernard (1858) on the blood flow in the salivary glands, and the introduction of the stromuhr by Carl Ludwig (1856) for quantitative measurements of the blood flow and his methods for perfusion of surviving organs, numerous investigations have been carried out on the flow of blood in various organs, both isolated and intact. Such quantitative determinations of the blood supply to the different tissues have demonstrated that the volume flow of blood varies widely according to the degree of activity of the tissue and also from one organ to another. The following table presents approximate values of volume flow of blood to several tissues and emphasizes the marked difference between these values:

Minute Volume per 100 Grams Tissue

	cc.	
Posterior extremity	5	Tschuewsky
Skeletal muscles	12	"
Heart	16	Bohr and Henrique
Head	20	"
Stomach	21	Burton-Opitz
Liver (arterial)	25	"
Portal organs (combined)	30	"

Minute Volume per 100 Grams Tissue (Cont.)

	cc.	
INTESTINE	31	Burton-Opitz
Spleen	58	"
Liver (venous)	59	"
Pancreas	80	"
Liver (total)	84	"
Brain	136	Jensen
Kidney	150	Burton-Opitz
Suprarenal	490	"
Thyroid	560	Tschuewsky
Thyroid	355	Knowlton, Dooley and Curtiss

In the above table, it is noteworthy that the small intestine receives about twice as much blood per 100 grams tissue as the heart and nearly 2 1/2 times as much as skeletal muscles.

It is of interest, however, that while the literature contains a great volume of information regarding the relationship between the intestinal and the systemic circulation, there has been no direct experimental investigation of the interrelationship between the motility of the small intestine and its intrinsic circulation except for the limited early work of Mall (1896) and more recently that of Anrep (1934). The inherent power of the intestinal musculature to contract spontaneously, together with the peculiar anatomical relationship between the different layers of the intestinal wall and its vascular bed, point to the possibility of the existence of a distinct and a basically important functional relationship between the motor activity of this organ and the movement of blood through its walls. Furthermore, because of

the fact that the intestinal smooth muscles are peculiarly sensitive to mechanical stimulation, sudden alterations in the blood pressure may induce changes in the activity of this tissue.

In view of the paucity of the existing data regarding these aspects further experimental evidence from direct blood flow measurements through the intestine is called for. To supply such data the experiments presented in this study, were undertaken. The great majority of these experiments were performed on isolated loops of dog's small intestine perfused with heparinized dog's blood; in addition a few experiments were performed on the gut in situ with the nerve supply intact. The general outline followed in this study including the methods employed and the order in which the experimental data and their interpretation are presented, are as follows:

SECTION I

METHODS.

SECTION II

INTERRELATIONSHIP BETWEEN INTESTINAL MOTILITY AND INTESTINAL CIRCULATION.

I Effect of Intestinal Motility on Intestinal Blood Flow

1) Individual rhythmic contractions and blood flow

2) Tonic contractions and blood flow

3) General motor activity and blood flow

II Effect of Alterations in Blood Pressure on Intestinal Motility

1) Arterial pressure changes

2) Venous pressure changes

3) Arterial and venous occlusions

III Vascular Reactions to Alterations in Perfusion Pressure

IV Influence of Pulsatile Perfusion Pressure on Blood Flow and on Intestinal Motility Activity

V Influence of Alterations in Intralumenary Pressure on Blood Flow and on Intestinal Motor Activity

SECTION III

INFLUENCE OF CARBON DIOXIDE, LOW OXYGEN AND ACETYLCHOLINE ON INTESTINAL MOTILITY AND BLOOD FLOW.

I Effect of Changes in Carbon Dioxide Tension in Arterial Blood

II Effect of Low Oxygen Tension in Arterial Blood

III Effect of Acetylcholine

SECTION I

METHODS

In the various experiments called for in the program outlined above, the venous outflow, arterial inflow, intestinal motility, intestinal volume, venous and arterial pressures were continuously recorded on the kymograph. The methods employed for these different recordings were as follows:

I RECORDING OF BLOOD FLOW

1) Venous Outflow

Two methods were used for measurement of the venous outflow: (a) drop method by displacement and (b) the thermopile method.

(a) Drop Method by Displacement: In this method the outflow of venous blood from the tissue is collected in thin-walled rubber balloon reservoirs B, fig. 1, previously emptied of all air and supported as shown, in an appropriate container A, filled with water to the exclusion of all air. The flow of blood into these balloons displaces an equal volume of water from the container which in turn displaces an equal volume of concentrated salt solution from bottle C. This displaced salt solution is led through a metal orifice D from which it drops on a platinum contact and serves to close the primary circuit of the relay R by means of which a signal

magnet S is activated to record each drop on the kymograph.

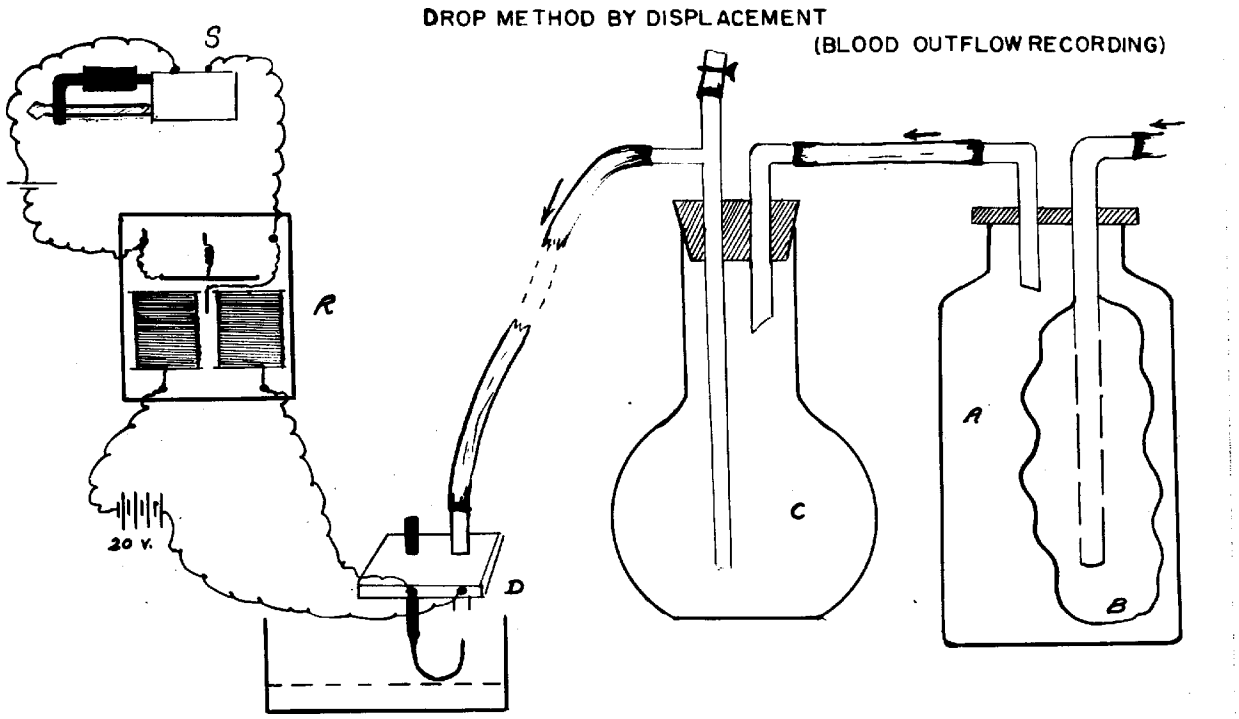


Figure 1. Schematic representations of the apparatus used for recording the venous outflow by the drop method of displacement. A container; B thin rubber balloon reservoir for receiving venous blood; C bottle containing concentrated salt solution; D drop recorder; R relay; S signal magnet. Arrows point to the direction of the flow of blood, water and concentrated salt solution.

This method proved entirely satisfactory and offered an accurate means for quantitative measurement of the venous outflow of blood. Furthermore, with all air carefully excluded from the system, the time lag is negligible. The balloon reservoirs serve to collect the venous blood flowing from the tissue for further use if needed.

(b) Thermopile Method: This method is essentially the same as that originally described by Gesell and Bronk (1926) but in which various changes have been made to adapt it for the

experimental purposes and to improve its sensitivity. In this method a thermopile modified after Wilson and Epps (1920) is employed.

The operation of this apparatus is, in principle, as follows: The blood, the flow of which is to be determined, is led through a tube of high thermo-conductivity (silver) enclosed in a water jacket of low thermo-conductivity (lucite) through which a steady flow of water of constant temperature is maintained. The inflow water to this jacket passes over

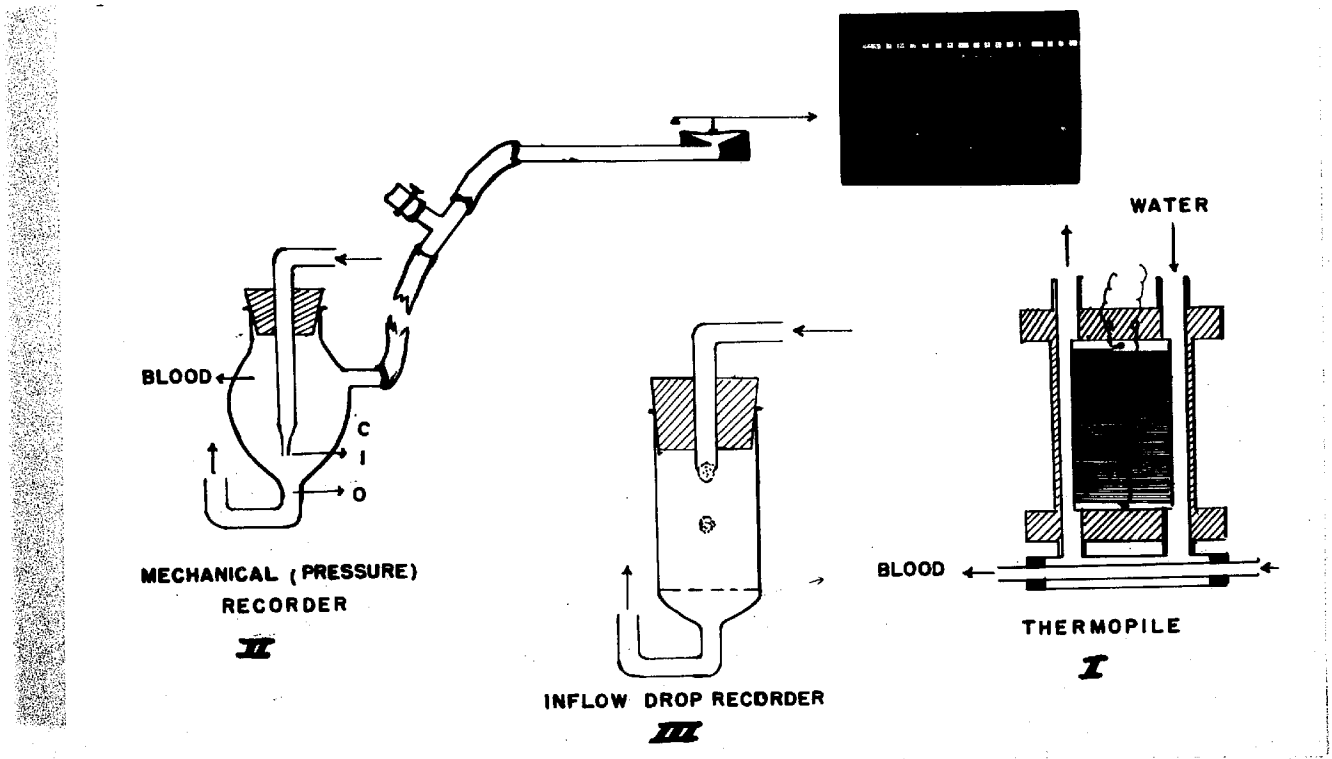


Figure 2. Diagramatic representations of the three methods of blood inflow recording. I thermopile unit; II mechanical pressure recorder consisting of C central chamber, I inlet tube and O outlet tube; III inflow drop recorder. Graphic record in upper right corner shows pressure variations consequent upon changing rate of outflow from central chamber of mechanical pressure recorder as recorded by membrane tambour; numbers refer to simultaneous changes of outflow and pressure.

the cold junctions of the thermopile (I, fig. 2) then into the water jacket where it is warmed by the flowing blood and then passes over the warm junctions and out through a narrow pinhole orifice (not shown in figure). An increase of the blood flow raises the temperature of the jacket water, thus increasing the temperature difference between the cold and warm junctions of the thermopile with the resultant increase in electrical potentials which are continuously recorded by a potentiometer.

(The details of construction of this thermopile and the conditions which must be met to insure reliable functioning of the method are described in the footnote.*)

---

*I. Construction of Thermopile

The two metals used in the thermopile unit as thermocouples are advance wire No. 40 and the same metal plated with silver. The number of turns used were 120 and 160 (120 and 160 metal junctions). The sensitivity of these thermopiles proved very satisfactory for the experimental purpose, and the lag varied from 2-4 seconds.

The procedure for the plating and advance wire was that adopted by Gesell and Bronk (1926). The advance wire No. 40 is wound on a rectangular piece of formica 2 mm. thick, 22 mm. wide and 37 mm. long. The wire is then cleaned thoroughly with alcohol and distilled water and its resistance is determined. On one side of the turns the wire is covered with paraffin, except for a trough in which all half turns are exposed for a stretch of about 1/3 inch. The paraffin covered half turns include also the part of wire on one-half of the thickness of the formica strip.

The plating solution used has the following composition:

AgCN	22.3	grams
NaCN	26	grams
NH_4Cl	3.7	grams
Water	500	cc.

In the early experiments of the present study, in which this method was employed, the potential changes were continuously recorded on the kymograph by manual operation of a type-K (Leeds and Northrop) potentiometer. Although this method was satisfactory for recording slow changes of the blood flow, it was not sufficiently rapid for accurately following

---

For plating, the half turns covered with paraffin are used as cathode, a rectangular plate of silver being used as the anode. To insure electrical connection of all the half turns, the paraffin "trough" is filled with mercury, thus eliminating potential drop. The surface of the plating solution is arranged so that only the half turns not covered with paraffin are immersed in the solution.

The current used for plating is 3-4 milli-amperes to insure smooth plating (stronger currents cause deposition of granulated silver). The total quantity of electricity to be used is calculated on the basis that a layer of silver of minimum 1/3 of the diameter of advance wire is deposited on the half turns.

The following is a sample calculation (Gesell and Bronk, 1926).

Thermopile: 160 turns (No. 40 Advance wire)
diameter of wire = 0.079 mm.
cross sectional area of wire
$= 0.0395^2 \times 3.1416$
$= 0.00487$ mm.^{2}
length plated = 160 x 23
= 3680 mm.
minimum cross sectional area of silver coating
$= \frac{\text{area}}{3}$
$= 0.00162$ mm.^{2}
$= 0.0000162$ cm.^{2}
quantity of silver to be deposited
= 3680 x 0.0000162 x 10.5
= 0.062596 grams
Coulombs required for plating
$= \frac{0.062596}{0.001118}$
=56.01 or 4 amps. for about 4 hours
Resistance before plating
= 768.3 ohms
Resistance after plating
= 432.5 ohms

the more rapid changes of blood flow during individual rhythmic contractions. This method was, therefore, replaced by a G.E. photoelectric potentiometric recorder which was adapted to record continuously on smoked paper (fig. 4).

The half plated wire is then mounted into a special frame shown in fig. 2.

The significance of using a silver tube for the flow of blood is that silver has greater conductivity than other usable metals or glass.

II. Conditions necessary for proper functioning of thermopile: 1) constant rate and 2) temperature of water delivered to thermopile unit.

1) To insure a constant rate of delivery of water to the thermopile, two factors should be taken into consideration. The first is the maintenance of a uniform and constant head of pressure and this is insured by using a big Mariotte bottle (40 litres capacity). The second factor is the maintenance of a constant resistance to the flow; this is controlled by properly adjusting the outflow orifice. If the latter is made so small in comparison with the rest of the water system, the main resistance will be offered by this outflow orifice, which is of course constant. Precautions should be taken to keep the outflow orifice (usually about a fraction of a mm. in diameter) free of any dirt which may actually hamper the flow of water or even stop it. For this reason the entire water system should be thoroughly clean and distilled water used. Under such conditions a constant flow of water can be maintained for long periods of time.

2) To insure a constant temperature of the water, the following precautions are necessary:

a. Equilibrating the distilled water to room temperature so as to keep the gradient between the water temperature and the exterior at a minimum with minor fluctuations in room temperature. For this, the reservoir bottle should be filled with distilled water at least 24 hours prior to its use.

b. The water reservoir should be of a large capacity to minimize temperature fluctuations.

c. Thorough insulation of reservoir and tubing system to provide protection against rapid changes in temperature.

2) Arterial Inflow

For the measurement of the arterial inflow the thermopile method described above for the outflow was employed.

As a second method for continuous recording of the variations of arterial inflow a mechanical pressure recorder was devised (II, fig. 2). This apparatus consists of a central chamber C with inflow and outflow tubes as indicated I and O, the inlet orifice being of distinctly smaller diameter than that of the outlet, but not so small as to interfere with the free flow of blood into the artery. The principle upon which this apparatus functions is dependent upon this difference of the inflow and outflow orifices. Thus, with a constant flow of blood into the artery a state of pressure equilibrium will be established in the central chamber. However, with any sudden acceleration of the arterial inflow, the outflow from the chamber will increase momentarily above the chamber inflow; the resultant momentary decrease of the chamber pressure is recorded with a sensitive tambour (fig. 2). With a sudden diminution of the inflow into the artery, the reverse occurs, i.e. the pressure in the chamber will increase momentarily. Similarly if there occurs a regurgitation of blood from the artery this will increase the chamber pressure.

This device served, then, as an accurate indicator of the movement and the direction of the blood flow change in the artery. Its proper functioning is dependent upon the suddenness of the arterial inflow change; gradual changes will not

be satisfactorily recorded by this method, since in this case the pressure change in the central chamber will be less pronounced. Further, to obtain best results the central chamber and the greater part of the tubing connected to the tambour should be filled with blood.

This method served also as an excellent check on the time relations between the intestinal contractions and the blood inflow changes recorded by the thermopile method.

A third method which was used for recording the arterial inflow is a modification of the above apparatus and provides a quantitative measurement of the inflow by drops. For this purpose the apparatus (III, fig. 2) is constructed with the central chamber a little longer than that used in the previous method, and the inlet and outlet orifices are of equal diameter. Instead of extending the inlet tube to the bottom of the chamber, an air space is left through which the blood falls in drops. As originally planned, this was to have been used as an electric drop recorder, each drop closing a relay circuit activating a signal magnet at the kymograph. In the few experiments in which this method was employed, however, the drops were signaled manually by a signal magnet.

II RECORDING OF INTESTINAL CONTRACTIONS

Intestinal contractions were recorded by tambours connected at each end of the intestinal loop (fig. 3). In a few cases, however, contractions from one end only were recorded. This method was found preferable to the use of

distended balloons introduced into the intestinal lumen.

The intestinal loop is cannulated at both ends with short wide glass cannulae which are connected to vertical tubes 1 and 1' of a special air and water tight container (fig. 3). These vertical tubes are directly connected to the recording tambours 6 and 10, as shown in the diagram.

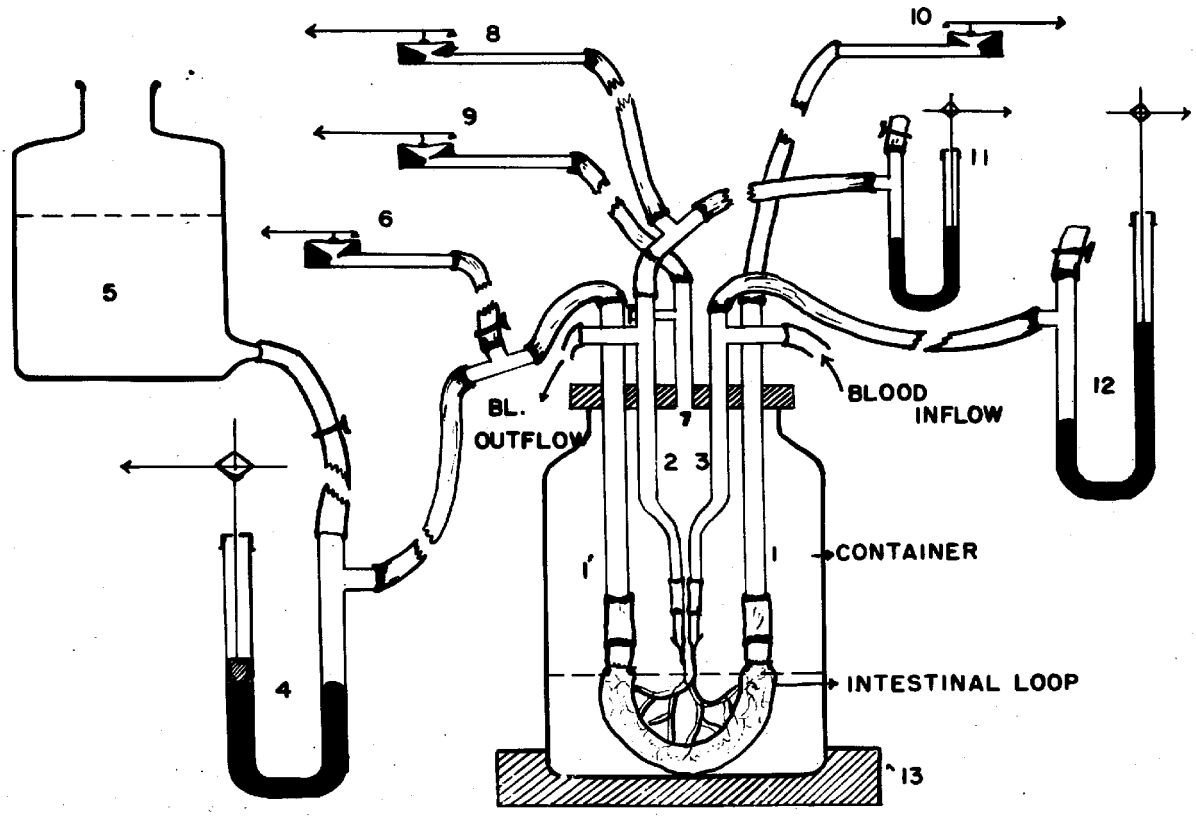


Figure 3. Diagramatic representation of apparatus used for recording intestinal contractions, intestinal volume, intralumenary pressure and arterial and venous pressure. 1 and 1' vertical tubes to which the intestinal loop is connected; 2 and 3 inflow and outflow tubes of blood; 4 Hg manometer for intralumenary pressure recording; 5 intralumenary pressure bottle containing Tyrode's solution; 6 and 10 tambours for recording intestinal contractions; 8 and 9 tambours for recording venous pressure and intestinal volume changes; 11 and 12 Hg manometers for venous and arterial pressure; 13 lead base attached to container to keep it submerged in water baths (not shown in figure).

Both the vertical tubes and the intestinal loop are filled with Tyrode's solution while the connecting tubes and the recording tambours are filled with air; the intralumenary pressure will, therefore, be equal to the column of fluid in the vertical tubes and can be regulated by raising or lowering the leveling bottle (5) filled with Tyrode's solution. The intralumenary pressure is recorded by a mercury manometer (4).

The container, with the suspended intestinal loop, is partially filled with oxygenated Tyrode's solution so as to cover only the dependent part of the tissue which is slightly touching the bottom. In this way any possibility of buoyancy of the loop which might result in kinking of the blood vessels or intestinal lumen is avoided. Tubes 3 and 2 passing through the top of the container serve for the inflow and outflow of perfusion blood respectively. In order to keep the container which consists simply of a large glass jar submerged in the temperature constant (37-38° C.) water bath (fig. 4) a heavy lead base is attached to the jar; the water-tightness of the container prevents any contamination of the Tyrode's solution inside by water from the bath. In some experiments changes in the intestinal volume were recorded by means of a sensitive tambour (9) connected to tube (7) of the container (fig. 3).

Because of its simplicity and the absence of any possible interference with the continuity of the intestinal loop or with the patency of the blood vessels, this method was used

throughout this experimental study. In those experiments which were performed on the gut in situ with its nerves intact, the loop was perfused without its removal from the abdominal cavity.

III PERFUSION METHODS

Two methods were used for perfusion: (a) a direct and (b) a displacement method.

(a) Direct Method

This method was used in the earlier experiments in which perfusion was limited to normal blood. The apparatus consists of a thermally insulated Mariotte bottle (one liter capacity) which serves as the arterial blood reservoir. This is connected to a coil of glass tubing immersed in the constant temperature water bath. The height of the Mariotte bottle determines the perfusion pressure which can be altered by raising or lowering this bottle. Undue loss of gases from the perfusion blood is prevented by means of a thin supernatant layer of mineral oil.

(b) Displacement Method

This method as shown diagramatically in fig. 4, was used in the majority of experiments. Aside from the fact that it eliminates any possible undue alterations of gaseous content of the blood, it furnishes a satisfactory means of maintaining a constant (identical) head of pressure on shifting from one blood to another, e.g. from normal blood to that with a low content of oxygen.

The blood reservoirs B consist of thin-walled rubber balloons suspended from glass tubes passing through the stoppers of the air-tight reservoir containers (2) which are completely filled with water (fig. 4). The blood reservoirs are filled with the desired blood to the exclusion of all air, extreme care being exercised not to distend them in the least degree. The reservoir containers are connected to the Mariotte bottle and submerged into the constant temperature water bath. In this system, water from the Mariotte bottle displaces blood from the reservoirs, pushing it at the maintained pressure head through the cannulated artery into the tissue.

In the experiments where the inflow mechanical pressure recording device is used, this is submerged in the water bath as shown in fig. 4 (3). When the thermopile method is used every precaution is taken to insulate the thermopile vessels and the flow tubes with cotton wool.

In order to apply pulsatile pressure to the perfusion blood, a simple valveless piston pump, with modifiable stroke and rate, is connected by a T-tube to the outflow line from the pressure (Mariotte) bottle.

Arterial (perfusion) pressure is continuously recorded by a mercury manometer connected by a T-tube to the perfusion system as shown in figures 3 and 4. The venous pressure was also recorded in some experiments either by a membrane tambour calibrated in mm. of mercury or by a mercury manometer,

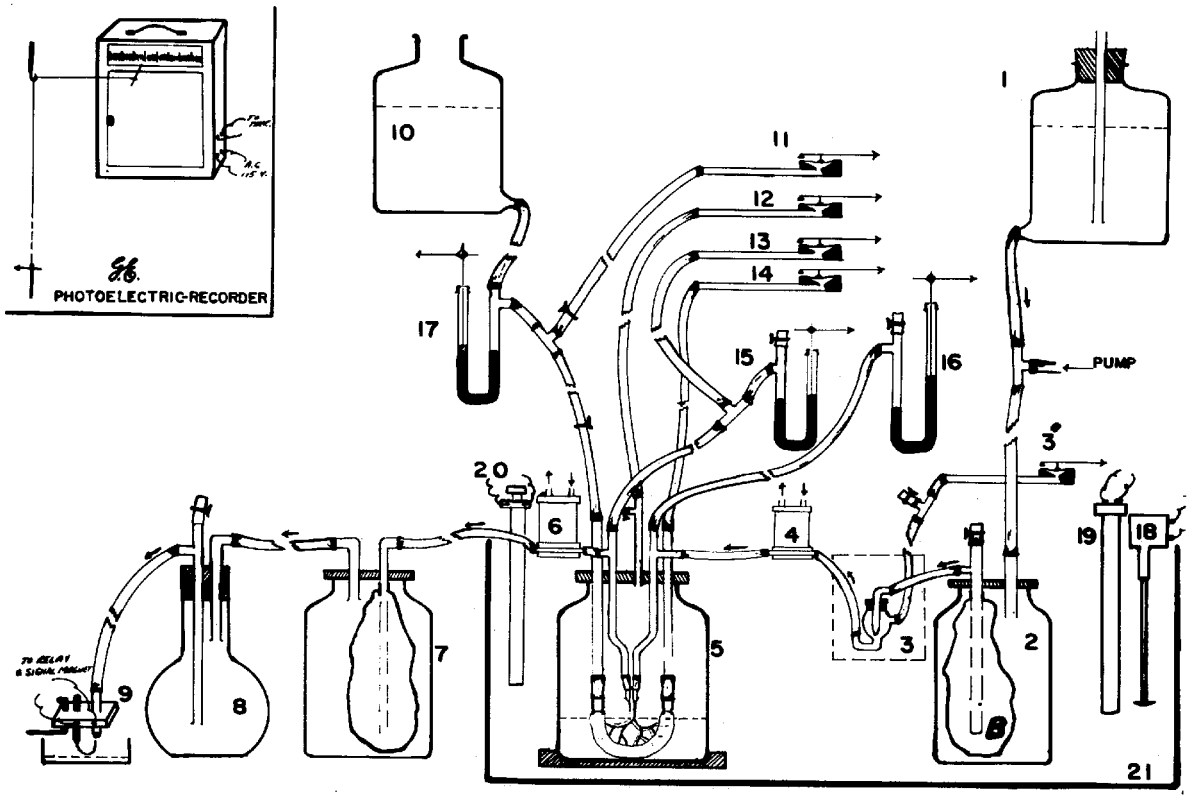


Figure 4. Diagramatic representation of complete perfusion apparatus. 1 Marriotte bottle for perfusion pressure; 2 container with arterial blood reservoirs (B); 3 mechanical pressure recorder connected in circuit only for special cases; 4 arterial thermopile unit; 5 loop container; 6 venous thermopile unit; 7 venous blood reservoir; 8 bottle with concentrated salt solution; 9 drop recorder; 10 bottle for intralumenary pressure regulation; 11 and 14 tambours for recording intestinal contractions; 12 and 13 tambours for recording intestinal volume and venous pressure respectively; 15, 16 and 17 Hg manometers for venous, arterial and intralumenary pressures; 18 electric stirrer; 19 electric heating element; 20 thermostat unit. Diagramatic representation of G.E. photoelectric-recorder shown in upper left corner.

or both; the first method has the advantage of being sensitive to small variations in the venous pressure. In both systems the tubes from the tissue to the manometer are filled with physiological salt solution (saline) to the exclusion of all air.

IV COLLECTION AND EQUILIBRATION OF PERFUSION BLOOD

In all experiments the intestinal loops were perfused with heparinized dog's blood withdrawn from the animal immediately preceding the removal of the intestinal loop; however, in some cases additional amounts of blood were obtained from donor dogs.

The experimental animals, 12-15 kilos in body weight, were anesthetized with sodium pentothal administered intravenously. Usually about 8-12 cc. of a 4% solution of the drug in saline, administered slowly, sufficed to adequately anesthetize the animal to prepare it for operation; additional amounts were administered throughout operative procedure if necessary. This anesthetic was preferred to urethane and morphine and other drugs because it proved to have no pronounced effect on the intestinal motility and also because its anesthetizing effect is of a short duration.

The anesthetized animal was repeatedly hemorrhaged from the carotid or the femoral artery then reinjected with equal volumes of 5% glucose-saline solution. In this way 600 to 800 cc. of diluted blood were obtained.

The pooled diluted heparinized blood was then divided into portions which were equilibrated with the desired gas mixtures, previously prepared in large pressure tanks and then analyzed by a Haldane-Henderson gas analyzer to determine accurately their percentage composition.

The blood was thoroughly equilibrated in tonometers of

large volume continuously and slowly rotated in a constant temperature bath (38° C.) by a motor for at least 20 minutes, during which time frequent renewal of the gas mixtures in the tonometers was made.

V OPERATIVE PROCEDURE

While the blood was being equilibrated as described above, the loop of intestine was selected and isolated with its mesenteric blood vessels with the animal still under anesthesia. The operative steps taken towards the isolation of the loop were as follows:

a) The trachea was cannulated in order to avoid the aspiration of regurgitated fluids into the bronchial system.

b) An incision 5 inches long was made in the abdomen along the linea alba and the various layers of the abdominal wall reflected. The edges of the incision and the external surface of the abdomen were covered with gauze which was kept moistened with warm Tyrode's to prevent drying, cooling and unnecessary contamination of the loop during its isolation. The omentum was then reflected and the small intestine gently inspected for the selection of an appropriate loop, about 5 inches long, from the upper third of the jejunum (about 1 foot below the duodenum). Only loops with distinct blood supply, i.e. single artery of supply and single draining vein were chosen. The selected loop was carefully withdrawn from the abdominal cavity while the rest of the viscera

were kept within. The loop was heavily wrapped in gauze continuously moistened with warm Tyrode's solution.

All the mesenteric attachments of the selected loop to the adjacent segments were tied off with double ligatures to avoid any undue hemorrhage and then carefully cut between these ligatures. The artery and vein supplying the loop were carefully dissected from the surrounding tissue for a length of about 1/2 inch, and each vessel ligated and cannulated with small cannula previously filled with a dilute solution of heparin; extreme care was taken to avoid introduction of any air into the artery. Throughout this procedure the loop was supplied by blood through the anastomosis with adjacent segments. Before the final isolation of the loop, the blood which was by this time thoroughly equilibrated, was transferred to the respective reservoirs and arrangements made for prompt perfusion.

Final isolation of the loop was accomplished by double ligation of the gut and sectioning. Each end of the loop was cannulated with a large glass tube. In this procedure of isolation the tissue was deprived of its blood supply for not more than 3 minutes and the isolated loop with its cannulated blood vessels was then quickly transferred to the container and its lumen flushed. The intestinal vessels were then connected with the perfusion system and perfusion begun promptly. (The complete connections for the perfusion system are shown in fig. 4.)

SECTION II

INTERRELATIONSHIP BETWEEN INTESTINAL MOTILITY AND INTESTINAL CIRCULATION

I EFFECT OF INTESTINAL MOTILITY ON INTESTINAL BLOOD FLOW

The question as to how muscular contraction affects the flow of blood through the muscle tissue, has attracted the attention of physiologists as far back as a century ago. Thus, Ludwig and Schmidt (1868), Sadler (1869), Burton-Opitz (1903), and more recently Rein (1930), Anrep (1934), and others have investigated the relationship between muscular contraction and blood flow in cardiac and skeletal muscle. In contrast to this, there has been no systematic study of the influence of smooth muscle contraction (in small intestine) on the blood flow through this tissue except for the few experiments by Mall (1896) and Anrep (1934).

In our study we have investigated some of the fundamental relationships between the contraction of the intestinal smooth musculature and the flow of blood in the intestinal wall by means of the perfusion methods described above. For purposes of convenience these experiments together with the results derived therefore are presented under three groups:

1) Relation between individual rhythmic contractions and blood flow.

2) Relation between tonic contractions and blood flow.

3) Relation between general motor activity of the intestine and blood flow.

1) Individual rhythmic contractions and blood flow:

An examination of the records, especially those obtained during the early parts of the experiments reveals that with the

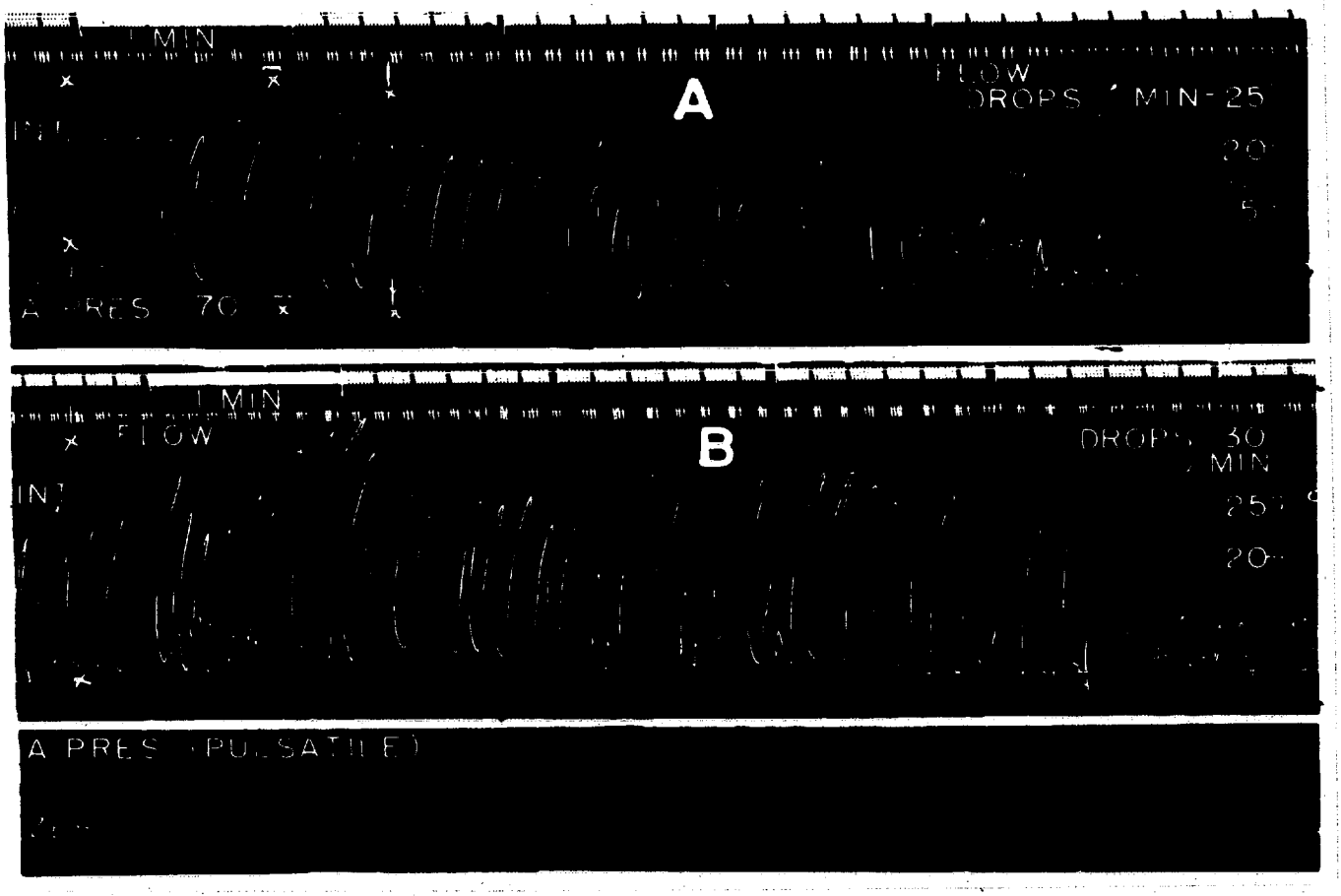


Figure 5. Illustrating relationship between rhythmic contractions and venous outflow. Perfusion of the loop carried out under constant A, and pulsatile pressure B.

Tracings from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; INT. intestinal contractions; A. PRES. arterial pressure (70 mm. Hg in both A and B); Zero line for arterial pressure in B. Simultaneous ordinates marked by X.

institution of rhythmic activity of the intestinal loop the venous outflow became distinctly intermittent. This intermittence of the outflow was found to be definitely related to the rhythmic contractions as shown in fig. 5 in which the outflow was recorded by the drop method. In part A of this figure the intermittent pattern of the outflow consisted of periodic augmentations during the contraction phases alternating with periods of complete outflow arrest during relaxation. As can be seen in this figure, such intermittance of the outflow gradually gave place to a steady form of dropping as the rhythmic contractions of the loop gradually diminished in strength. Further, it is to be observed that the mean outflow (plotted curve) diminished gradually with the decrease of motor activity. Similar results are shown in part B of this figure, where perfusion was carried out under pulsatile pressure.

For further illustration of the time relationships between the outflow and the intestinal rhythmic contractions, a similar record was obtained on a faster moving drum, fig. 6. In this figure the accurate time relations of the outflow changes and the rhythmic contractions are brought out by superimposing the outflow drops directly on the contraction curve. It is thus clearly demonstrated that the augmentation of the outflow occurs during the contractile phase and may extend into the early part of relaxation, i.e. while the muscle is still in a state of partial contraction. An

equally important observation in this figure is that the venous pressure curve shows undulations, the rising phases of which coincide with the intestinal contractile phases and the periods of augmented venous outflow. Such venous pressure waves are also shown in fig. 17 which demonstrates that they are coincident with the rhythmic contractions and disappear during decreased activity of the loop. The magnitude of these venous pressure changes varied from 6-12 mm. of water according to the amplitude of gut contractions.

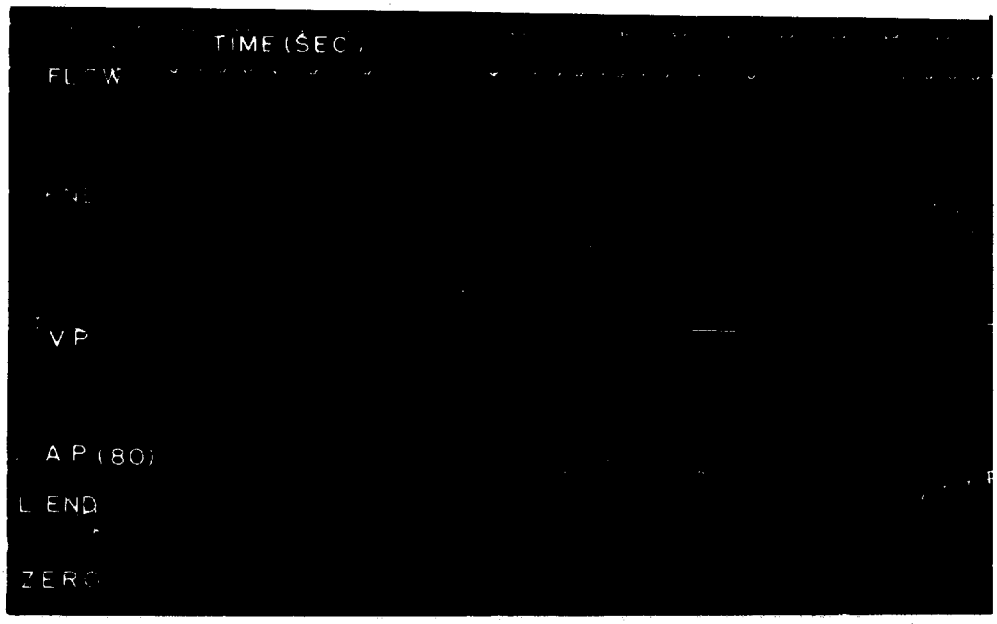


Figure 6. Illustrating relationship between rhythmic contractions and venous outflow (on a fast drum).

Tracings from above downward: time in seconds; venous outflow drops; U. END intestinal contractions from upper end of loop; V.P. venous pressure changes by tambour; A.P. arterial pressure; L. END intestinal contractions from lower end of loop; zero line for arterial pressure. Simultaneous ordinates marked by X.

Venous outflow (drops) superimposed directly on contraction curves.

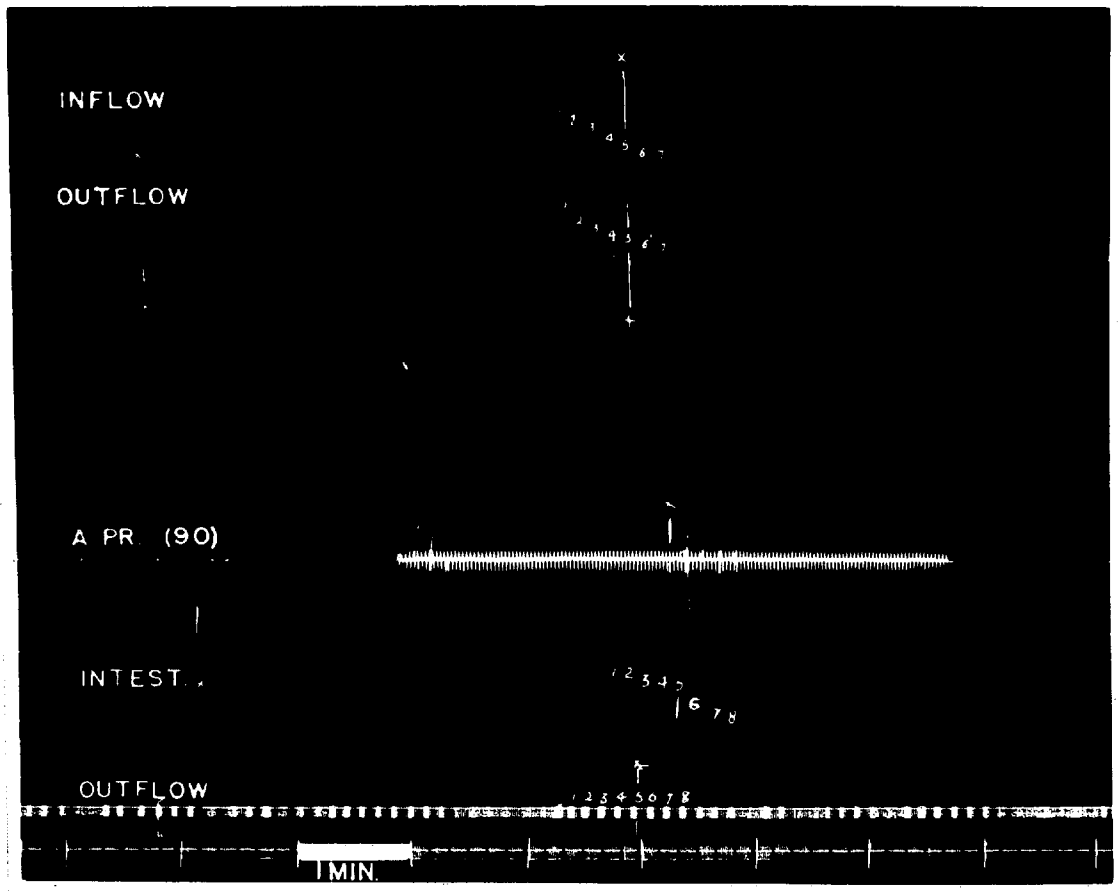


Figure 7. Illustrates relationship between intestinal rhythmic contractions and venous outflow. Tracings from above downward: inflow by thermopile; outflow by thermopile; A.PR. arterial pressure (90 mm. Hg); INTEST. intestinal contractions; zero line; outflow drops; and time in minutes. Numerals refer to simultaneous changes in arterial inflow, venous outflow and intestinal contractions. Simultaneous points marked by X. Lag of thermopile 3 sec.

In addition to the drop method the thermopile was also employed to record the outflow, whereby a continuous recording of the outflow changes was obtained as shown in fig. 7. Here, where both the inflow and outflow were recorded, the tracing of the outflow exhibited waves, the rising phases of which (increased flow) coincided exactly with the

rhythmic contraction phases of the loop. This relationship has been illustrated further by indicating simultaneous changes in a portion of the record with identical numbers. It is also noted that the magnitude of the outflow changes increased with the increase in the strength of the contractions, e.g. the flow change simultaneous with contraction #6 was much greater than that simultaneous with the weaker contraction #1. The figure also shows that the same outflow-contraction relationship obtains under both constant and pulsatile perfusion pressure.

The data thus far indicate that during each individual rhythmic contraction the outflow is increased and during relaxation it is decreased.

Our experimental results also demonstrate that there is a characteristic relationship between the rhythmic contraction and the arterial inflow. Such relationship is clearly shown in figures 7 and 8. In the latter figure, the inflow was recorded by the mechanical pressure recorder (curve A where the upstroke indicates a decreased inflow), and also by the thermopile (curve B where the downstroke indicates a decreased inflow). Each of these curves (A and B) shows distinctly that the arterial inflow decreased during the individual contraction phases of the intestinal loop whereas the outflow, recorded by drops, increased. This relationship has, as in fig. 7, been illustrated further by the use of identical numbers designating simultaneous changes. Two significant features can also be seen by close

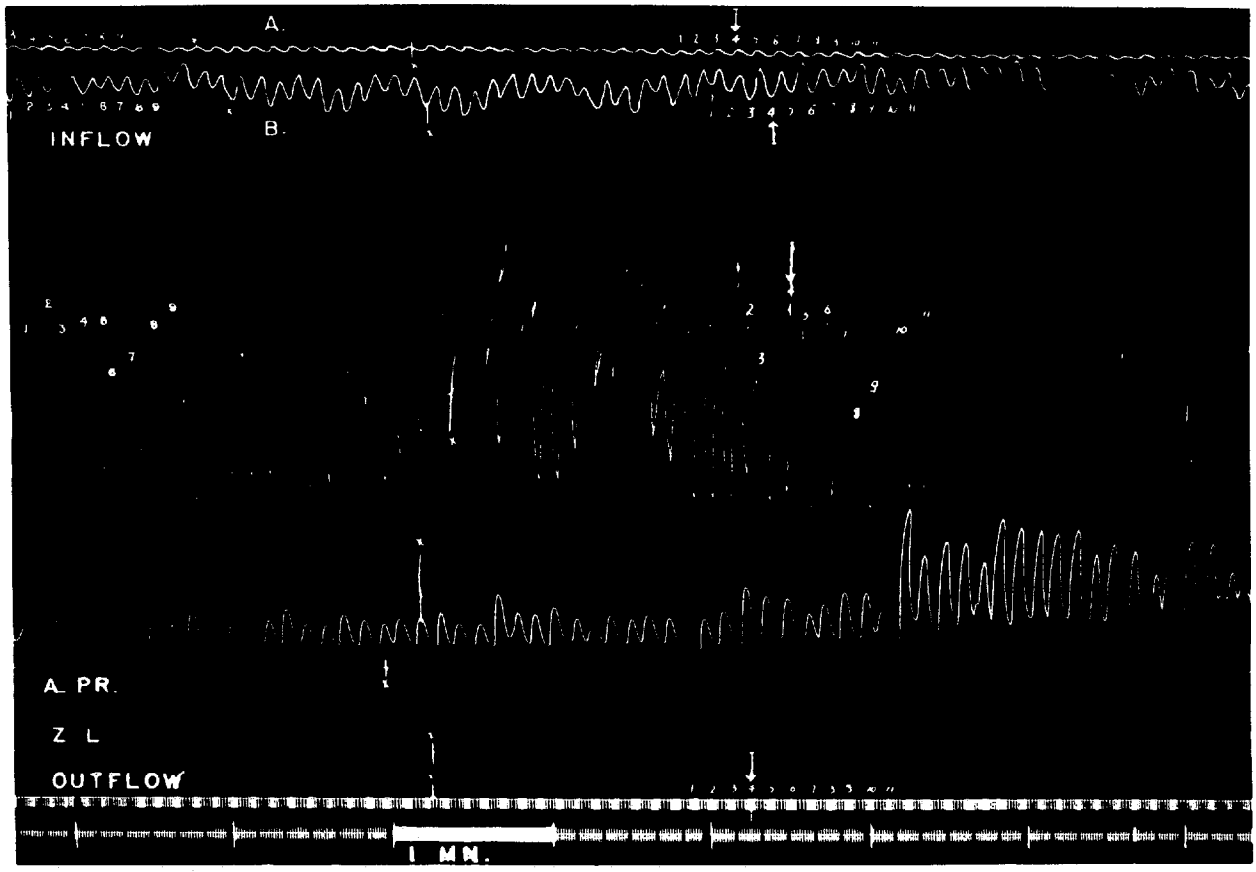


Figure 8. Illustrates relationship between intestinal rhythmic contractions, arterial inflow and venous outflow. Tracings from above downward: A arterial inflow as recorded by mechanical pressure recorder (upstroke indicates decrease); B arterial inflow by thermopile (upstroke indicates an increase); intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; Z.L. zero line; outflow drops; and time per minutes. Numerals refer to simultaneous changes in arterial inflow, venous outflow and intestinal contractions. Simultaneous ordinates marked by X. Thermopile lag 3 seconds.

examination of this record (fig. 8), namely: (1) the inflow tracing (A) of the mechanical pressure recorder exhibited asymmetrical upstrokes and downstrokes (waves 4, 5, 6 and 7), the former being markedly the steeper, and (2) the arterial pressure tracing showed distinct waves corresponding to the rhythmic contractions. Both of these observations point

to the possibility of the occurence of an arterial regurgitation during the contraction phases.

The same relationship between the intestinal rhythmic contractions and the blood inflow and outflow is further illustrated on a more rapidly moving drum as shown in fig. 9; for convenience of comparison, the outflow drops have been plotted in a portion of the record and all the simultaneous changes numbered to clarify such relationship. In this

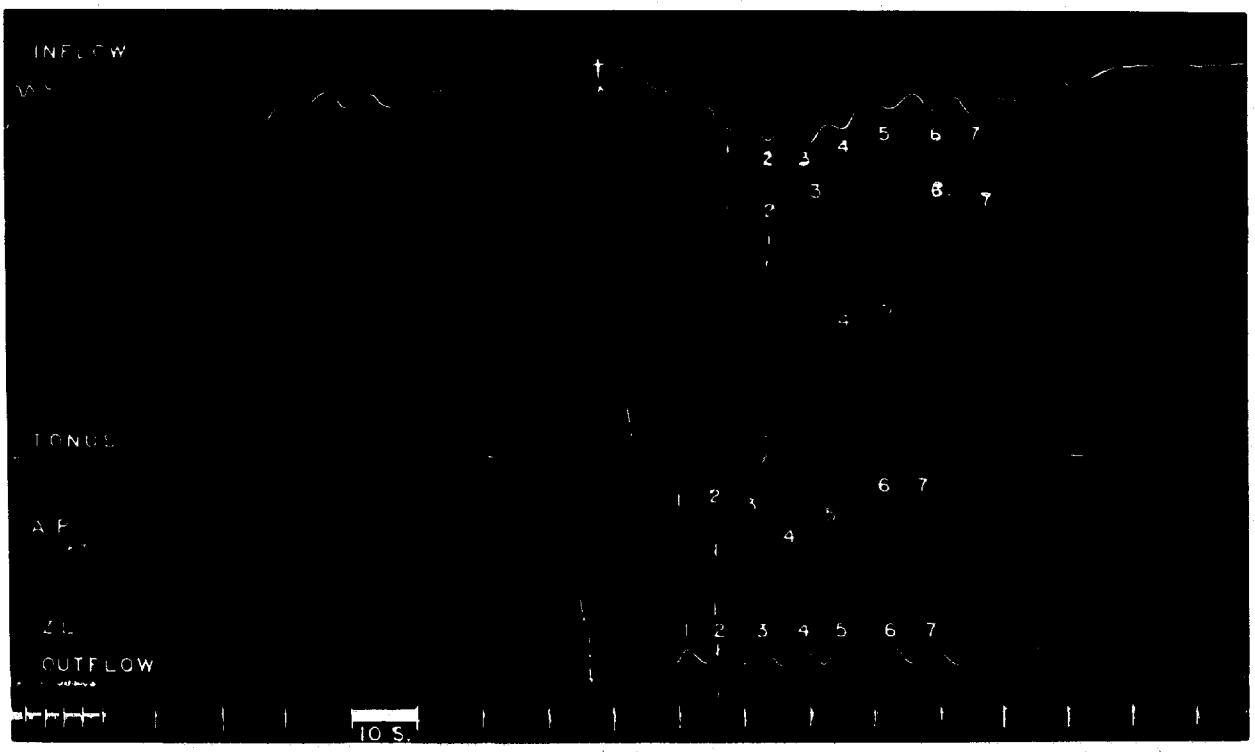


Figure 9. Illustrates relationship between intestinal rhythmic contractions, arterial inflow and venous outflow, on a fast-moving drum. Tracings from above downward: arterial inflow by thermopile; intestinal contractions from upper end of loop; schematic representation of tonic changes; A.P. arterial pressure (67 mm. Hg); intestinal contractions from lower end of loop; Z.L. zero line; venous outflow in drops; time in 10 sec. intervals; numerals refer to simultaneous changes in arterial inflow, venous outflow and intestinal contractions. Thermopile lag 3 1/2 secs.

figure, in which simultaneous points are also indicated by a broken line, it is seen that while the rhythmic contraction phase decreased the inflow, it increased the outflow.

(2) Tonic Contractions and Blood Flow:

The experimental results concerning the relationship between the intestinal tonic contractions and blood flow are divided into: a) effect of tonic contractions on the blood flow, and b) after-effect of tonic contractions.

a) Effect of tonic contractions on the blood flow: The predominant effect of tonic contractions, especially when strong and relatively sustained, was to diminish both the venous outflow and the arterial inflow. This is illustrated in fig. 10, in which each of the tonic contractions shown

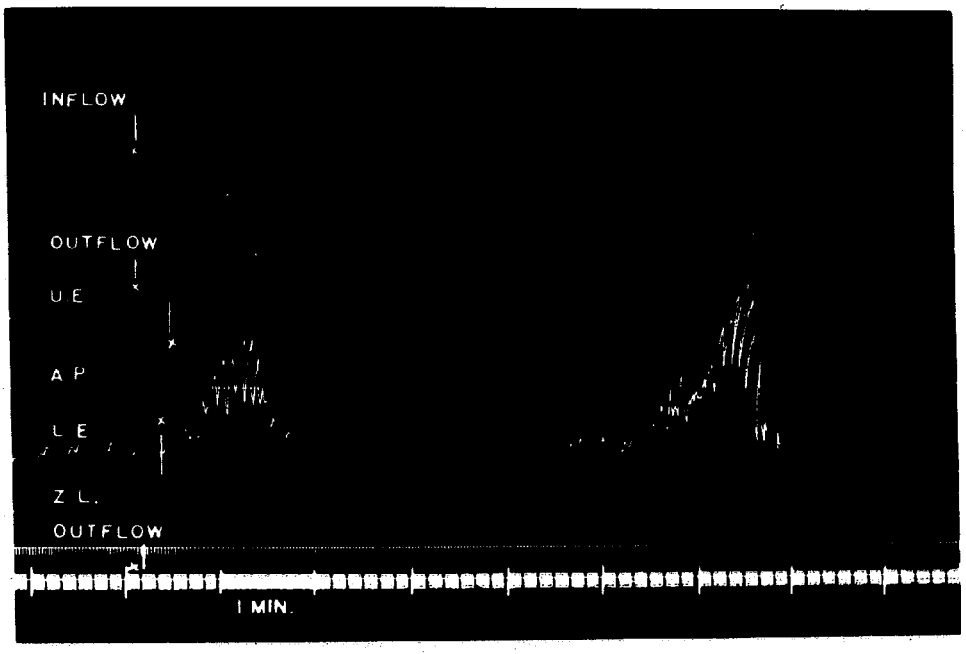


Figure 10. Illustrates relationship between tonic contractions and intestinal blood flow. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; U.E. intestinal contractions from upper end of loop; A.P. arterial pressure; L.E. intestinal contractions from lower end of loop; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

caused a well pronounced drop in the blood flow followed by a gradual return to the normal level upon the gradual decline of tonus. It is also noteworthy that strong tonic contractions induced by acetylcholine affect the blood flow in a manner similar to that of the spontaneous tonic contractions described above. Thus, in fig. 59 strong tonic contractions resulting from intra-arterial injections of acetylcholine caused a marked reduction in both the arterial inflow and venous outflow in spite of the vasodilator action of this drug (cf.).

While the preceding description represents the most common finding, particularly in the case of the arterial inflow, there occasionally occurred certain variations in the effect of tonic contractions on the venous outflow. Thus, in fig. 11 the sudden institution of the tonic contraction caused a sharp increase in the outflow and a simultaneous decrease in the inflow, both of which changes attained the maximal and minimal values respectively at the point of highest tonus. Upon the onset of decline of the tonic state the outflow diminished, first abruptly, then more gradually; the inflow, on the other hand, increased rapidly to attain a supra-normal value at the end of the tonic relaxation then gradually returned to normal. It is of interest to note, in this figure, that the changes in both the inflow and outflow during the tonic contractions resemble greatly those induced by each individual rhythmic contraction phase

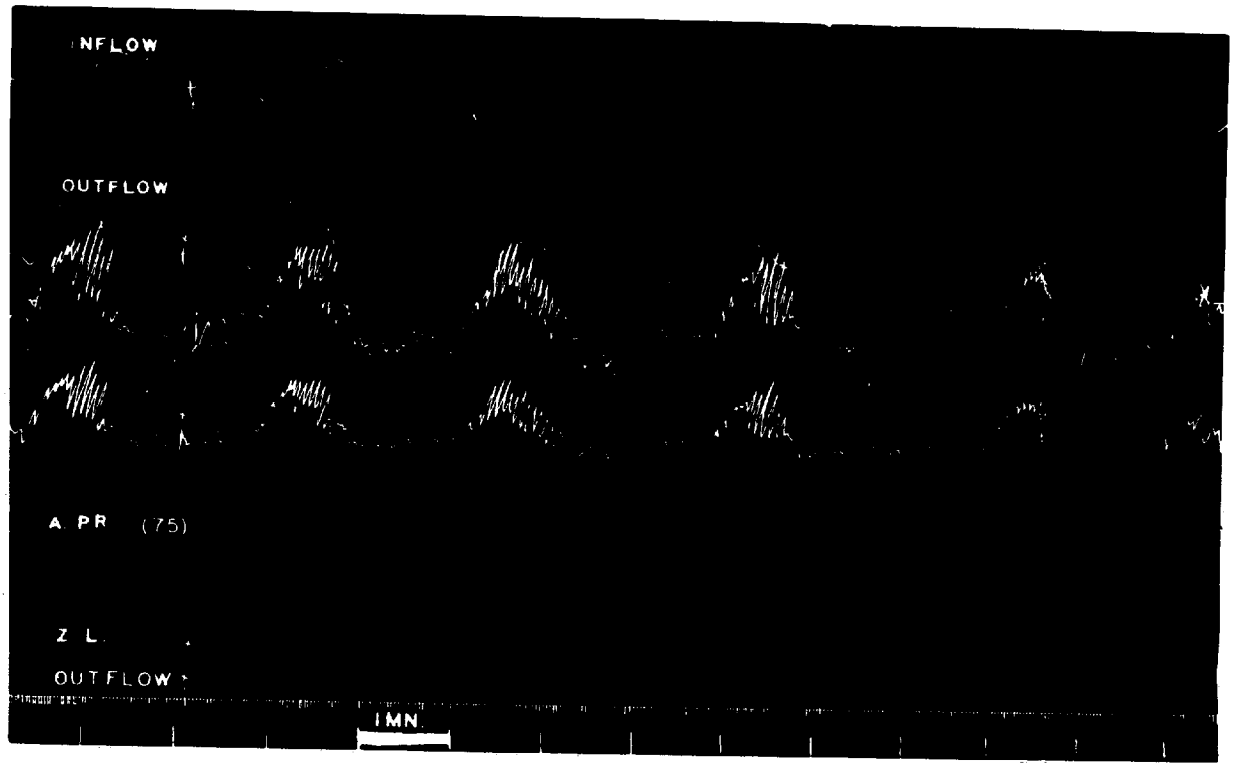


Figure 11. Illustrates relationship between intestinal tonic contractions, arterial inflow and venous outflow. Tracints from above downward: arterial inflow by thermopile; venous outflow by thermopile; intestinal contractions from upper, and lower ends of loop; A.PR. arterial pressure (75 mm. Hg); Z.L. zero line; venous outflow drop; time in minutes. Simultaneous ordinates marked by X.

described above (figs. 8 and 9). This resemblance points to a common factor responsible for flow changes induced by the two types of contraction.

Figure 12 shows another effect of the tonic contraction on the venous outflow (inflow was not recorded) similar to that seen in fig. 11 except that, here, the initial increase in the outflow was followed by a diminution before the tonus began to decline. Upon relaxation there occurred further decrease of the flow to below normal and subsequent return to the pre-tonic value. The intestinal volume decreased

with each tonic contraction. The diminution of the outflow before the onset of the decline in tonus, which was missing in fig. 11, may be attributed to the more prolonged sustained tonus in this case (fig. 12).

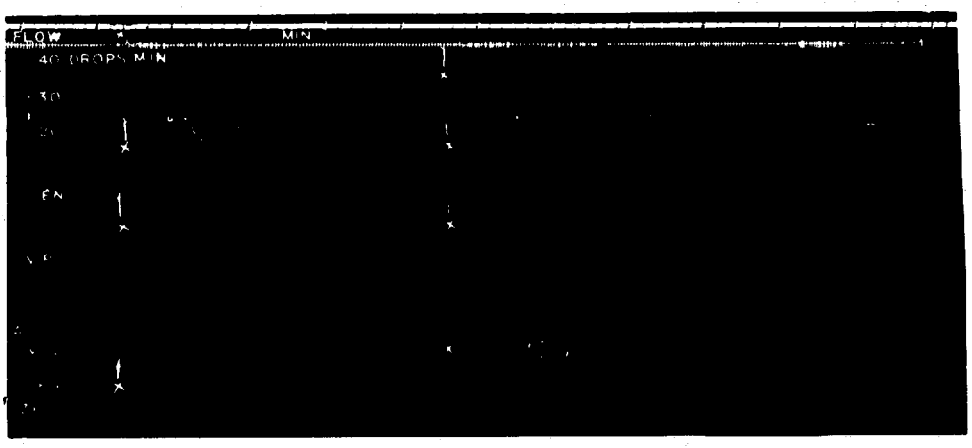


Figure 12. Illustrates relationship between tonic contractions and venous outflow. Tracings from above downward: time in minutes; venous outflow drops; plotted curve for venous outflow in drops per min. (11 drops = 1 cc.); U.END intestinal contractions from upper end of loop; V.P. venous pressure by tambour; A.P. arterial pressure; I.VOL. intestinal volume; L.END. intestinal contractions from lower end of loop; zero line. Simultaneous ordinates marked by X.

From the above figures (10, 11 and 12) it is evident that tonic contractions lead to a predominant decrease in both the arterial inflow and venous outflow; the outflow, however, occasionally shows an initial increase which is then followed by a decrease with the maintenance of the high tonus. This initial increase in the outflow may be attributed to the suddenness of the tonus rise, which, under such condition, acts in a manner similar to that which occurs during the contractile phase of rhythmic movements.

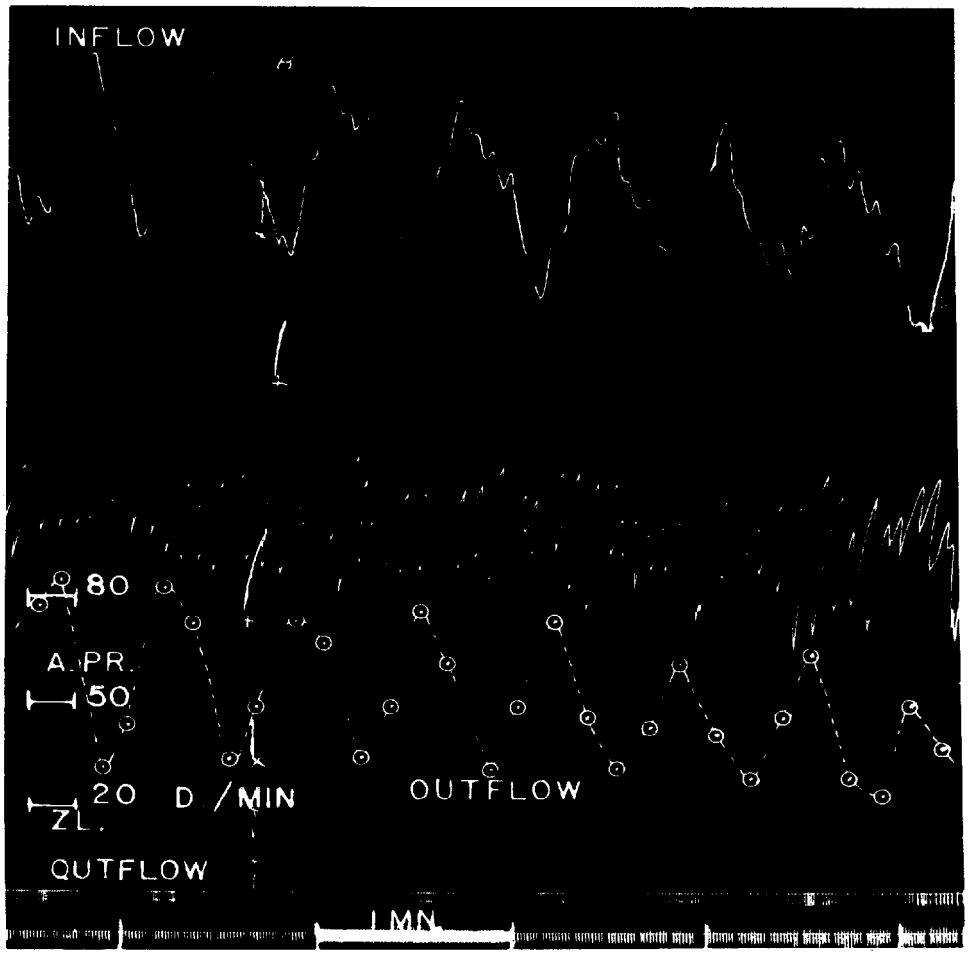


Figure 13. Illustrates relationship between intestinal contractions and blood flow. Tracings from above downward: B Arterial inflow by thermopile; intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; venous outflow plotted in drops per min.; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

An interesting finding which merits special reference is shown in fig. 13. Here, the intestine exhibited irregular rhythmic contractions and, unlike the preceding figures, the tonic changes were poorly defined. Both the arterial inflow and venous outflow, on the other hand, showed remarkable rhythmical changes with no apparent relationship to the

indistinct tonic changes (especially in the left half of the record.) While it may be, that the flow changes were induced by some alterations in the tension of the gut musculature (not registered), this apparent disproportionality between the flow and tonic changes suggests that the marked rhythm of the flow had its origin in a mechanism other than the intestinal motility. Such a mechanism probably lies in inherent spontaneous changes in the vascular tone itself. However, this phenomenon seldom occurred in such a remarkable manner as shown in this figure.

b) <u>After-effect of tonic contractions</u>: In most instances the termination of a tonic contraction, especially when strong

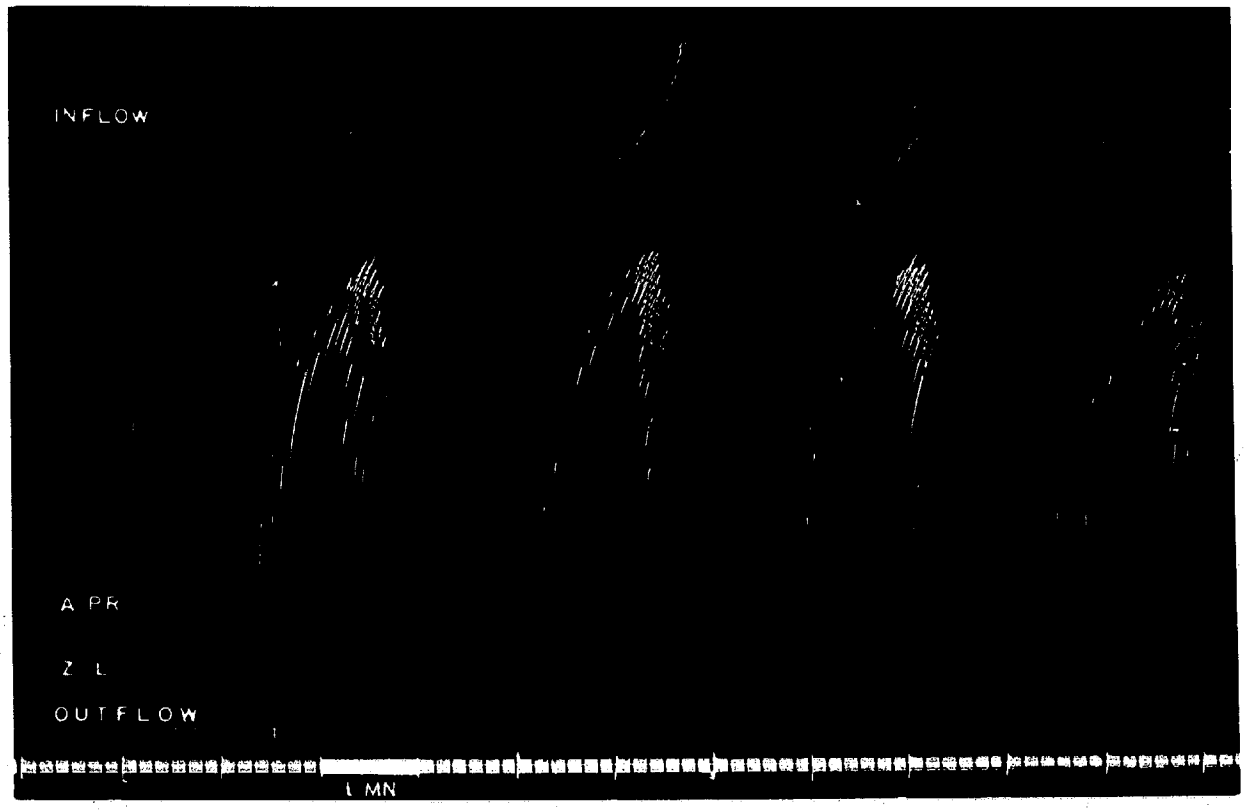


Figure 14. Illustrates after-effect of intestinal tonic contractions on the blood flow. Tracings from above downward: arterial inflow by thermopile; intestinal contractions from upper and lower ends of loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

and relatively sustained, was attended by a supra-normal flow of blood which persisted for some time thereafter as shown in fig. 14. In this figure, the rise of tonus upon which were superimposed strong rhythmic contractions, caused an initial distinct decrease in both the inflow and outflow (drops). Upon the onset of decline of tonus the flow was increased first gradually and then more sharply to well above the pre-tonic level, the maximum flow being attained only after the tonus had returned to normal. This post-tonic augmentation of the blood flow, then, gradually decreased toward normal until a new tonic contraction was initiated which caused repetition of these flow changes.

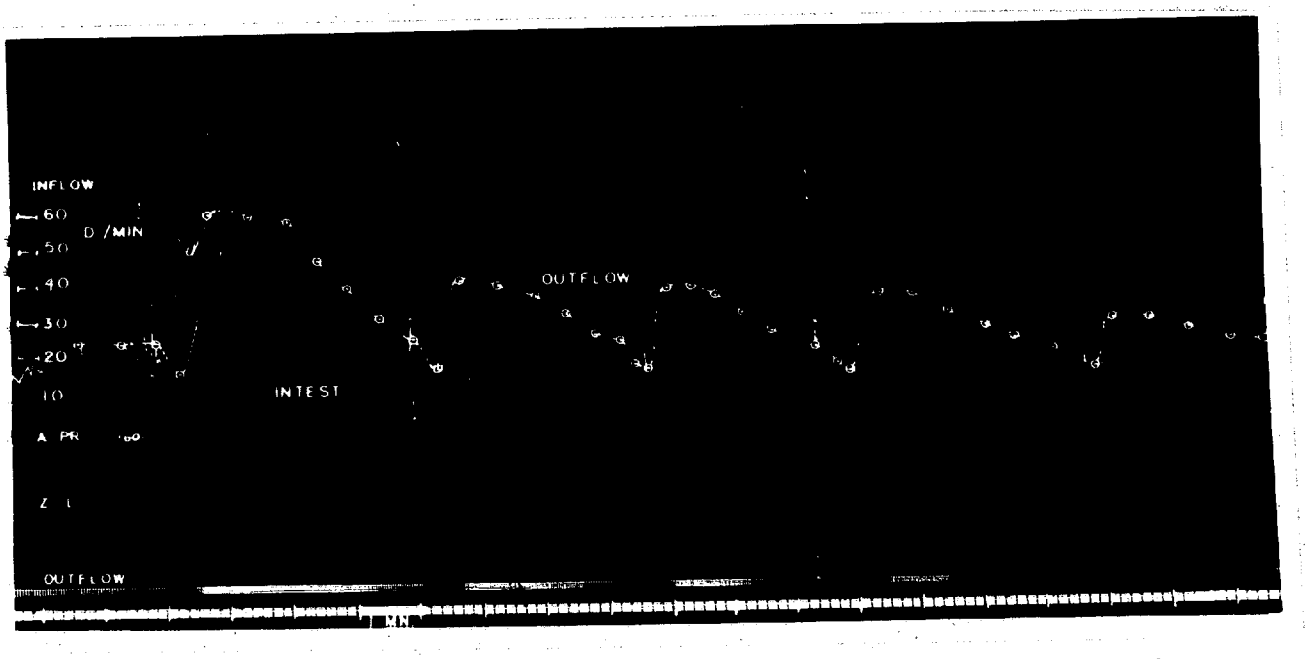


Figure 15. Illustrates after-effect of intestinal tonic contractions on blood flow. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted curve in drops per min.; INTEST. intestinal contraction; A.PR. arterial pressure (60 mm. Hg); Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

A well pronounced post-tonic effect is also seen in fig. 15. Here, as in fig. 14, the gut exhibited periodic tonic contractions during each of which both the outflow and inflow suffered a marked decrease. But, with the precipitous drop of tonus, the flow increased sharply to a level far in excess of normal then diminished steeply toward normal. With the onset of the succeeding tonic contraction, the flow was again sharply decreased and the rest of the cycle, as described in the first contraction, was repeated for this and the subsequent contractions. Two important features are to be noted in this figure: 1) the duration of the first tonic contraction was greater than that of the succeeding, and its after-effect on the flow was greater and more prolonged, 2) the magnitude of the last tonic contraction was markedly smaller (with little or no difference in duration) than that of the preceding, and its after-effect on the flow was much weaker. This relationship points to two distinct factors which determine the magnitude and duration of the post-tonic augmentation of blood flow, namely 1) magnitude and 2) duration of the tonic contraction, both of which operate in an additive manner.

The post-tonic augmentation of the blood fow, described in the above figures (14 and 15), may be attributed to the action of certain vasodilator metabolites which are released during the period of tonic activity. The hyperemic effect of such apparently potent substances is obscured, however,

during the period of high tonus, because of the prevailing vascular compression; but with the release of tonus and subsequent opening up of the vascular bed, the effect appears promptly and attains its full height when the loop is completely relaxed.

The occurrence of such a vasodilator after-effect has also been observed following the termination of prolonged tetanic contraction of skeletal muscle. It was first described by Gaskell (1877) and later confirmed by Rein (1930), Anrep (1934) and others who have attributed this after-effect (in skeletal muscle) to an action of vasodilator metabolites. There is, however, some difference of opinion regarding the exact time of release and action of these vasodilator substances. Rein believes that they are released into the skeletal muscle circulation only at the termination of the tetanic contraction, whereupon they produce the post-tonic dilatation. On the other hand, Anrep states that these substances are formed and liberated during the tetanic state, but because of the compression of the vascular bed within the muscle, they become effective only when the vessels are decompressed, i.e. at the end of tetanus.

The information regarding the nature of these vasodilator metabolites is, at present, limited. Gaskell, realizing the vasodilator properties of the acid products of the cell metabolism, investigated the effect of cH on the blood vessels.

He ascertained that lactic acid, one of the chief products of cell metabolism, is capable of producing vasodilatation. Other products, which have definite vasodilator properties, e.g. adenylic acid and carbonic acid, have been identified by other workers; but to what extent each of these substances contributes to the ultimate vasodilatation is not known.

In the present study, while no attempt was made to determine the exact nature of these specific vasodilator substances, reperfusion of venous outflow blood from the gut which might be expected to contain such substances, was performed in some experiments. In order to eliminate the effects of low O_2 and excess CO_2 of this venous blood, the latter was equilibrated with "normal" gas mixtures (CO_2 4%, O_2 30%) before it was used in reperfusion; some venous blood was also reperfused without such equilibration. The effects of venous blood, both equilibrated and non-equilibrated, are shown in fig. 16. In part A of this figure shifting from arterial to non-equilibrated venous blood caused a predominant increase in the blood flow (preceded by an initial decrease probably induced by the early slight tonic contraction). This predominant increase in the flow indicates an active vasodilatation which may be attributed to the effect of low O_2, excess CO_2 and specific metabolites. In part B of the figure, shifting from arterial to venous blood equilibrated to normal CO_2 and O_2 tensions, caused a similar but less pronounced vasodilatation. It is, therefore, reasonably concluded that

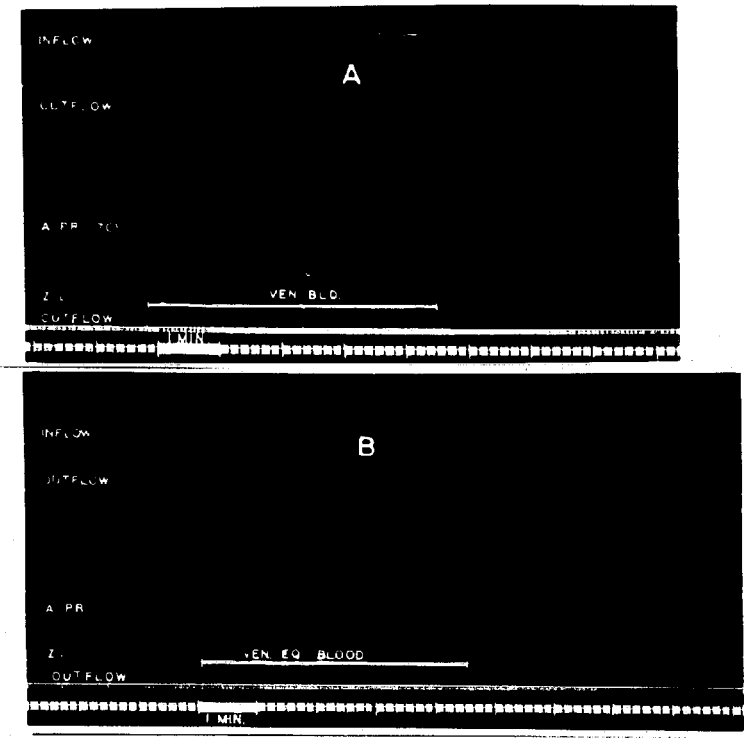


Figure 16. Illustrates effect of venous blood on intestinal blood flow. A. Effect of reperfusion of venous blood non-equilibrated (4 min. 40 sec.) B. Effect of reperfusion of venous blood equilibrated with "normal" gas mixture: CO_2 4% and O_2 30% (4 min. and 40 sec.) Tracings show: arterial inflow and venous outflow recorded by thermopile; A.PR. arterial pressure (70 mm. Hg); intestinal contractions from one end of the loop in A and from both ends in B; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

venous blood possesses a vasodilator property which is not attributable to an excess of CO_2 or to low O_2, and must be ascribed to certain substances released from the active tissue. Anrep (1934) carried out perfusion experiments in which he studied the effect of venous blood collected from a resting skeletal muscle and from a tetanic muscle. He found that the latter blood had a distinct vasodilator action, while venous blood from resting muscle had no such effect.

The magnitude and duration of this hyperemic after-effect is determined by the height and duration of the previous tonic contraction (fig. 15), the stronger the contraction and the longer it is sustained, the greater the potency of the vasodilator influence.

Another possible cause for the post-tonic vasodilatation is an anoxic effect directly on the vascular walls during the period of decreased blood flow consequent upon vascular compression.

DISCUSSION:

In the interpretation of the experimental results described above, a consideration of the findings of earlier workers, derived from other contractile tissue is of importance.

Surprisingly enough, considerable controversy still exists concerning the influence of skeletal and cardiac muscle contraction on the blood flow through these tissues notwithstanding the relatively extensive investigation which has been directed to the solution of this problem. The various results and conclusions of the earlier workers can be generally classified into two schools of opinion:

1. One school holds that during the increase of mechanical tension in tetanic contraction of skeletal muscle, there is a marked diminution or even an arrest of the arterial inflow, while the venous outflow is initially increased

then diminished. Similarly it is held that the coronary blood flow decreases during systole and increases during diastole.

2. The second viewpoint, on the other hand, holds that the increase in mechanical tension of skeletal muscle during tetanic contraction does not offer any interference to the blood flow through the muscle; on the contrary, it may even decrease the resistance offered by the intramuscular blood vessels to the flow. According to this view, cardiac systole is usually attended by an increase in coronary blood flow.

The first viewpoint is supported by the work of almost all of the early workers: Sadler (1869), Gaskell (1877), and others who measured the venous outflow from a muscle during contraction, and Dogiel (1871), Humilewski (1886) and Tschuewsky (1903) who measured the arterial inflow into the muscle, and Rebatel (1872) who carried out measurements of the coronary flow. Burton-Opitz (1903), using the Hurtle's stromuhr in the femoral vein, found that during tetanic stimulation of the motor nerve to the muscle, the venous blood flow first increased with the muscle shortening, then decreased during the continuation of the tetanic state of the muscle. He attributed the initial increase of the outflow solely to the increased pressure of the contracting muscle upon the blood contained in its vessels and concluded that the tetanically contracted muscle, therefore, was an obstacle to the

blood flow. Similarly, Verzar (1912) observed a stoppage of the venous outflow during tetanic contraction. Ganter (1928) measured the arterial inflow of skeletal muscle and found it to be considerably diminished during contraction. More recently Anrep (1934) measured the arterial inflow into skeletal, cardiac and smooth muscle (by his hot-wire anemometer) and found that during the contraction of these tissues there was a diminution or arrest of the inflow, and that during strong and rapidly developing contractions there occurred a regurgitation of blood into the supplying artery.

Further evidence in support of the findings of the foregoing authors was furnished by Heilemann (1902) who found, by direct microscopic observations of the musculus submaxillaris of the frog, that on tetanizing the muscle the blood flow in the finer venules and in the capillaries became greatly diminished, and that during strong contraction a backward movement of the blood column was observed in the arteries.

In contrast to the above school of thought, the work of Hochrein (1932) on the coronary blood flow and that of Rein (1930) on skeletal-muscle circulation support the second view viz. that muscle contraction does not interfere with the muscular blood flow, but rather augments it. Hochrein could find no exact time relation between the phases of cardiac cycle and the observed changes in the coronary flow;

however, he stated that there was generally a tendency of increased coronary flow during cardiac systole. Rein's results, obtained by the thermostromuhr, were to the effect that during short tetanic stimulation of the skeletal muscle (gastrocnemius of dog) there was a marked increase of the blood flow in the artery and vein. During prolonged tetanic contractions there occurred an initial increase of the inflow followed by a rapid decline to the original level, which was either maintained for the remainder of the tetanic state or showed a second gradual increase. Rein therefore concluded that, "the contraction of the skeletal muscle decreases the resistance of the intramuscular blood vessels to the flow of blood."

As anatomical evidence in support of his interpretation, Rein mentioned the findings of Spaltehol⁄z on the anatomical distribution of the blood vessels in skeletal muscle. According to Spaltehol⁄z (1924), the finer vessels and capillaries within the muscular tissue run parallel to the cylindrical muscle fibers; upon contraction the fibers become shorter and thicker and, therefore, the interspaces between them become wider so that a partial removal of the mechanical pressure on the blood vessels occurs, thus leading to decrease of the resistance to the blood flow.

Rein attributed the decreased blood flow observed by Anrep and others, during the indirect tetanic stimulation of the muscle, to a simultaneous stimulation of the

vasoconstrictor fibers to the muscle. He emphasized that in order to avoid stimulation of these vasomotor fibers the frequency of the stimulatory current should be higher than 300 cycles/sec. However, Anrep claimed he had excluded the possibility of such simultaneous stimulation of the vasoconstrictor fibers as being the responsible factor for the observed decrease of flow, because paralyzing these fibers by large doses of ergotoxine did not abolish the effect; curare, on the other hand, abolished the effect as it paralyzed the muscle without paralyzing the vasoconstrictor fibers themselves.

In his criticism of Rein's conclusions, Anrep emphasized the fact that Rein did not measure the blood flow through the specific muscle stimulated, but instead measured the total flow in the whole leg and foot. Anrep suggested that the observed increase of the flow under such conditions might have been due to a reflex vasodilatation in the non-stimulated muscles of the same leg and foot, and that such reflex vasodilatation might overshadow any decrease in the contracting muscle itself.

In contrast to the great volume of experimental studies on the effect of skeletal and cardiac muscle contraction on their intrinsic blood flow, the data pertaining to the effect of smooth muscle contraction on its blood flow is meager. Rein (1931) observed that the blood flow in the superior mesenteric vein exhibited characteristic undulations; however,

his experiments do not provide any data concerning the relationship between the intestinal contraction and the blood flow since he did not record the intestinal motility. Mall (1896) observed that during the rhythmic contractions of an isolated perfused loop of dog's small intestine, there was an augmentation of the venous outflow and a simultaneous increase in the venous pressure. He attributed these changes to the compression of the vascular bed by the contracting smooth muscles. Almost half a century later Anrep (1934) in supplementing his investigations on skeletal muscle blood flow, mentioned above, measured the arterial inflow in isolated short loops of small intestine and found that during each individual rhythmic contraction the inflow decreased, whereas upon relaxation of the loop the inflow returned to normal.

In interpreting our experimental results concerning the effect of the contraction of the smooth musculature of the small intestine on its intrinsic blood flow, a consideration of the anatomical relationships between the different layers of the wall and the vascular bed is of prime importance. In contrast to the rather simple arrangements of blood vessels in skeletal and cardiac muscle, the intestinal wall is far more complex in structure and its vascular bed is possessed of a characteristic anatomical arrangement. Mall (1896) found that the greatest vascularity in the intestinal wall is present in the submucosa; this layer contains dense venous plexuses (Veneballchen) which receive venous blood from both

the inner and outer layers. According to this author, the veins carrying the blood from these plexuses (long and short intestinal veins) to the outer mesenteric veins are provided with "valves" which are capable of withstanding high back pressures: "Such system of valves prevents any backward injection into the vein from going into the artery. The resistance is so great that the high pressure is more apt to rupture the mesenteric vein than to force the injecting material into the submucosal plexuses." This has been confirmed in our experiments in which attempts were made to perfuse the loop through its vein; it was found that pressures as high as 125 mm. Hg failed to push the blood from the venous side into the artery (arterial pressure zero), thus demonstrating the presence of some "barrier" preventing the backward flow of blood.

Spanner (1932) ascertained the presence of powerful sphincters in the "throttle" veins draining the submucosal venous plexuses. He also emphasized that the venous plexuses (or nests) play a prominent role in the circulatory adjustment in the small intestine of dog (and other carnivora); due to their considerable capacity (average surface area of venous nests is 45 sq. mm. in 100 sq. mm. of tissue) and their great capability of dilatation they may serve as voluminous blood depots. In addition to these dense venous plexuses of the submucosa, a rich venous anastomosis exists in the

other layers of the intestinal wall, e.g. mucosa, muscularis mucosa and the outer muscle layers between which there is a rich intermuscular venous plexus.

The arterial supply to the wall also exhibits a free anastomosis in all the layers. One important difference between the arterial supply and the venous drainage systems in the intestinal wall is that while the arterial system is freely intercommunicating so that a shift of the arterial blood path is possible between the adjacent segments of the intestine, such a free movement of venous blood is restricted by the valves in the draining veins which allow only a unidirectional flow of venous blood.

On the basis of the above anatomical description, our findings on the blood flow changes accompanying the intestinal contractions can be adequately explained. Thus, it is apparent that the intermediate position of the dense and capacious venous plexuses of the submucosa between the outer muscle layers and the muscularis mucosa, renders this considerable portion of the vascular bed subject to variable degrees of mechanical tension exerted by the contraction or relaxation of the muscle fibers. Of perhaps even greater influence in this connection are the circular muscle fibers on both sides of the submucosa since the mechanical tension of their shortening will be directed centrally toward the lumen of the gut. Consequently, upon simultaneous contraction of

these circular muscle fibers, the submucosal tissue, including the venous plexuses, will be compressed. The immediate effect of such vascular compression is the expulsion of venous blood present in the venous plexuses and simultaneously a partial (or complete) blocking of the arterial inflow into the contracting segment of the loop. It is also probable that upon contraction of the muscular wall, not only the submucosal venous plexuses, but also the intermuscular plexuses, are compressed. Therefore, the increase of the outflow during each individual rhythmic contraction phase is attributed to the initial expulsion of the venous blood, while the simultaneous diminution of the inflow is due to the obstruction of the arterial paths.

During rhythmic activity of the gut, the periods of increased contractile tension are soon followed by relaxation, whereby, according to the above interpretation, the vascular bed is decompressed. The immediate effect of such vascular decompression is a prompt increase of the arterial inflow to normal, while the outflow will be decreased temporarily, for an interval of time necessary for the filling of the partially empty capacious venous plexuses. The occurrence of such compression and decompression of the vascular bed in a rhythmical manner, corresponding to the intestinal rhythmic contraction, will ultimately lead to the reciprocal rhythmic variations of the outflow and inflow already described (figures 5, 6 7, 8 and 9).

The strength and the rate of development of the muscular contraction distinctly influence the changes in the blood flow. Thus, during strong and rapidly developing contraction the arterial inflow diminution and the outflow augmentation are markedly accentuated. In fact, if the contraction is sufficiently strong and abrupt there may occur an actual regurgitation of the arterial blood into the supplying artery and in the perfusion system. This is suggested from a careful examination of fig. 8, where it has been observed that the waves of the inflow mechanical pressure recorder (tracing A) exhibited asymmetrical upstrokes and downstrokes. The fact that the upstroke (indicating an increase) is steeper than the downstroke (indicating a decrease) points to the possible occurrence of a sudden backward movement of the arterial blood into the central chamber of the recorder during the contraction of the loop. Also, the appearance of waves corresponding to the rhythmic contraction of the loop on the arterial pressure tracing indicates a backward movement of perfusion blood into the mercury manometer. In this case the inflow mechanical recorder may actually act as a partial one-way valve allowing the blood flow only in the direction of the tissue; any tendency for the flow to be reversed will lead to an increase in the pressure in the mercury manometer and in the chamber of the recorder.

Similarly, with increased strength of individual rhythmic

contractions the magnitude of the outflow increase may be accentuated as seen in fig. 7.

An important determinant of the pattern of the blood flow changes during rhythmic activity, is the length of the perfused loop. Thus, in relatively long loops, where two segments may be actively contracting, any asynchronism between the contraction phases in the two segments may alter the rhythmical pattern of the flow which is being measured in the entire loop. To further elucidate this point, if one segment of the loop is contracting while a contiguous segment is relaxing, the decrease in the arterial inflow induced by the contracting segment will be annulled, in part at least, by the increased inflow induced by the simultaneously relaxing segment. The venous outflow pattern may be affected in the same way, but to a lesser degree because of the presence of valves which prevent the movement of venous blood from one segment to the other. However, the fact remains, that the specific effect of contraction in any given segment is to diminish the arterial inflow and increase the venous outflow in this segment. The underlying factor here is the compression of the vascular bed during contraction.

If the duration of the increased contractile stress of the muscle is prolonged, e.g. as in <u>tonic contractions</u>, the initial increase in the outflow, consequent on the initial expulsion, is soon followed by a decrease. This is due to

the continuation of the vascular compression and the resultant decrease of the blood inflow. The diminution of both the outflow and the inflow are then maintained throughout the remainder of tonic contraction. Upon the decline of tonus, the vascular bed is decompressed and there results a prompt increase of the inflow which is followed shortly thereafter by the return of the outflow to normal.

The extent of diminution of both the inflow and outflow during the tonic contraction is determined by the strength of the contraction, since the latter will determine the extent of the vascular compression. The magnitude of the initial increase of the outflow at the beginning of the tonic contraction is determined by the degree of previous filling of the vascular bed. This filling is dependent upon the duration and the extent of relaxation in the muscle of the gut and its blood vessels, and upon the inflow pressure.

The nature of the tonic contraction may influence appreciably the pattern of the blood flow, particularly that of the venous outflow. Thus, in propagated tonic contractions, e.g. peristalic waves, there might occur a progressive vascular compression from one segment of the loop to the adjacent with a resultant progressive expulsion of venous blood from these segments. This phenomenon may ultimately lead to a maintenance of an increased outflow throughout the entire period of the propagated tonic contraction; this is suggested in fig. 11. Here, the inflow undergoes an initial but

temporary diminution consequent upon the vascular compression and as the elevated tonus begins to drop the vascular bed is decompressed whereby the inflow increases promptly, while the outflow decreases to the normal pretonic level.

3. General Motor Activity and Mean Blood Flow

That increased activity of an organ is attended by a parallel increase in the arterial blood supply to this organ is well known. This phenomenon has been demonstrated experimentally in many tissues including skeletal and cardiac muscle. Thus, as early as 1867, Chauveau and Kaufmann observed that the blood supply to the levator labii of the horse was increased by threefold during mastication over the resting value. More recently Rein (1930), Anrep (1934) and others, working on rhythmically contracting skeletal muscles (normally or electrically stimulated), have confirmed the above finding, namely that under such conditions of activity the blood flow is considerably increased above normal.

While on general principles, therefore, it might be expected that an increase in the intestinal motor activity would be associated with an increase in the mean blood flow, there has been, up to the present, no experimental demonstration of such phenomenon. However, the experiments in the present study demonstrate not only that individual rhythmic and tonic contractions have specific effects on the intestinal blood flow, as described above, but also that the general

motor activity plays a significant role in influencing the mean intrinsic blood flow. Thus, records illustrating the effect of increased general motor activity of the gut upon the blood flow are shown in fig. 17. In part A of this figure,

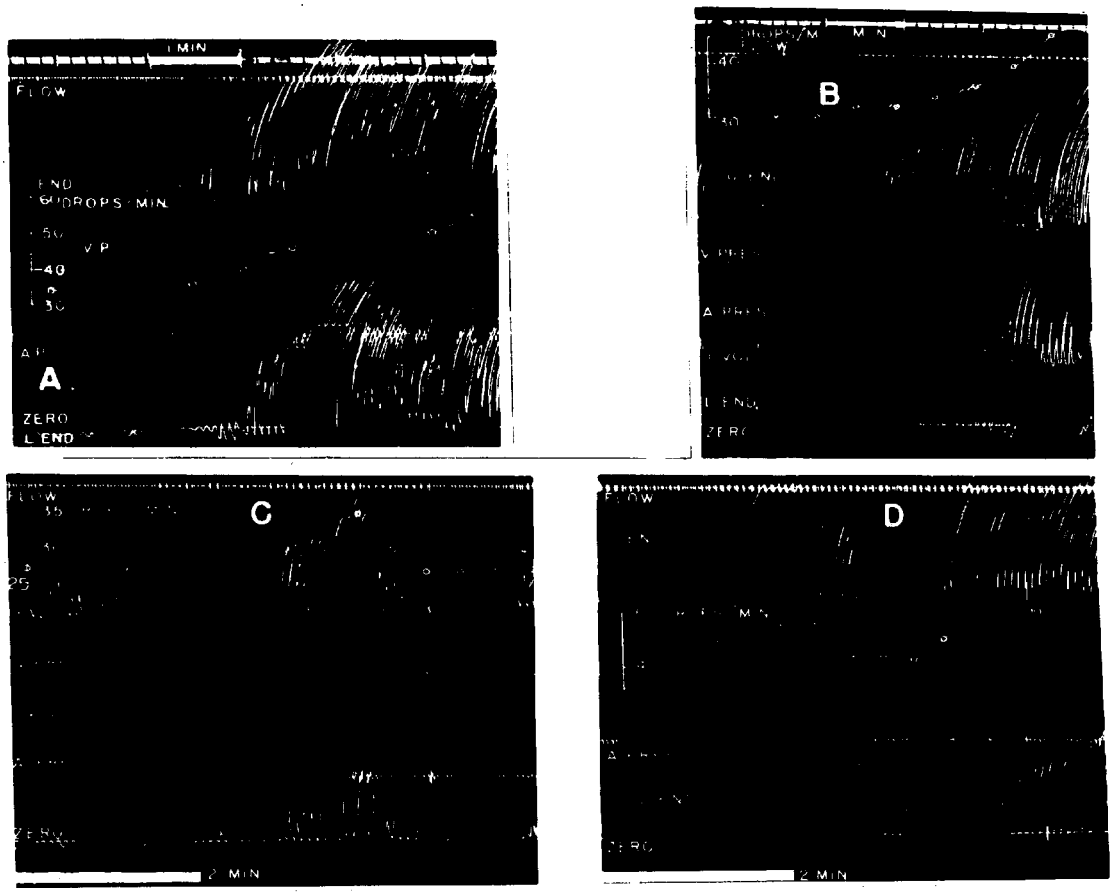


Figure 17. Illustrates influence of general intestinal motor activity on blood flow. In all parts of the figure venous outflow was plotted in drops per minute on curve with circles. Tracings also show: venous outflow drops (FLOW); intestinal contractions from upper end (U.END) and lower end (L.END) of the loop; V.PRES. venous pressure recorded by tambour; I.VOL. intestinal volume A.PRES. arterial pressure (pulsatile in A, C and D); and time in minutes.

the gut showed a gradual but steep increase in the amplitude of the rhythmic contraction and a rise in tonus; the blood outflow increased gradually to about 70% above the resting

value. In part B, the loop also showed a gradual increase mainly in its rhythmic activity which was attended by a parallel rise in the outflow of about 60% above the resting value. In parts C and D the gut exhibited periodic increase in the rhythmic motility, and here it is noted that the outflow increased during the periods of increased activity and decreased during the periods of lower activity. An interesting feature to be seen in parts B, C and D is that the synchronous venous pressure changes became more pronounced with the increase in the amplitude of the rhythmic contractions.

In figure 18, demonstrating the same relationship between the motor activity of the loop and the blood flow, both the

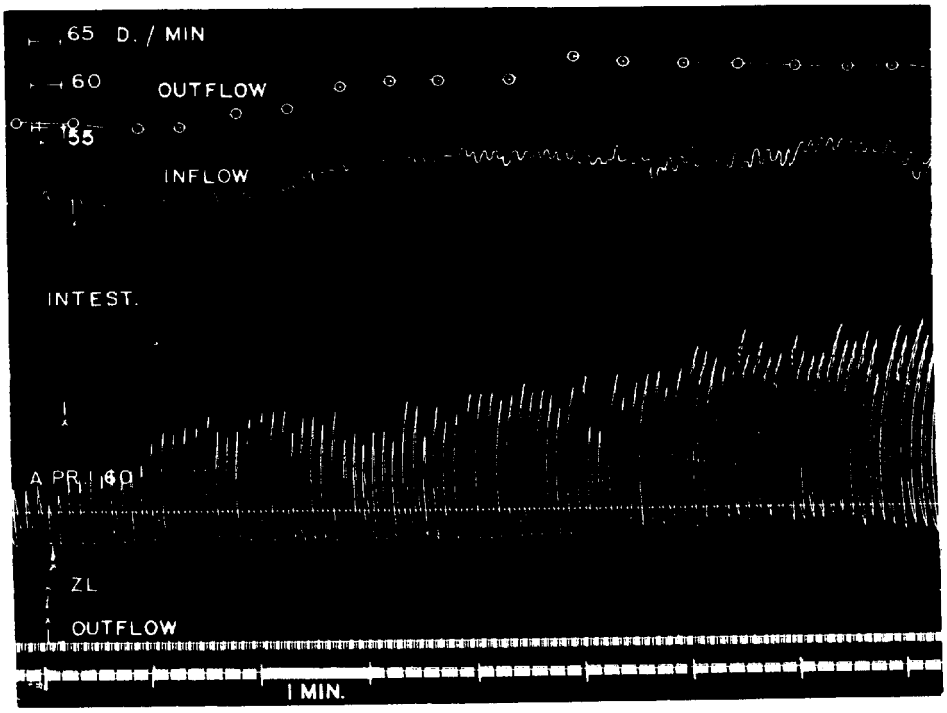


Figure 18. Illustrates influence of general intestinal motor activity on blood flow. Tracings from above downward: venous outflow plotted in drops per min.; arterial inflow by thermopile; INTEST. intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure (60 mm. Hg); Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

arterial inflow and the venous outflow were recorded. Here, the rhythmic contractions showed a gradual increase in amplitude accompanied by a parallel gradual increase in the inflow and outflow (plotted curve).

A significant feature common in these figures (17 and 18) is that the increase in the blood flow occurred subsequent to the increase in the motor activity. This observation, therefore, indicates that the changes in the gut motility were the cause rather than the effect of the observed changes in the blood flow.

Discussion:

The results presented above indicate clearly that the increase in the general motor activity of the gut caused an increase in the mean flow of blood through this tissue. Since these results were obtained in the isolated loop, they must be attributed solely to certain local mechanisms.

At present, the most generally accepted explanation for such local mechanisms is that the increased blood flow during activity results from the local action of vasodilator metabolites released in greater amounts during tissue activity.

This would appear to be an essential factor in the occurrence of an increase in the mean blood flow in the intestine as demonstrated in our experiments. However, it must be emphasized that during rhythmic contraction of the loop, these vasodilator metabolites become effective on the flow only during the

periods of muscle relaxation, when the vascular bed is released from compression. Thus, with gradual increase in the strength of the rhythmic contractions there is an increase of metabolic products which, acting additively, lead to a gradual increase in the blood flow provided adequate intervals of relaxation are present for these substances to exert their effect. If the rhythmic contractions occur at a fast rate so as to allow only for short inadequate periods of relaxation (and vascular decompression) the volume flow of blood to the tissue per unit time may suffer an actual diminution (fig. 7), in spite of the existing vasodilatation. Similarly, if the increase in the strength of rhythmic contractions is accompanied by a rise in the gut tonus, the latter may overcome the tendency for an increase in the blood flow by virtue of the vascular compression exerted by the high tonus (fig. 9). In those cases, where with longer loops only a small part of the tissue is tonically active while the rest is relaxed, such relaxation may permit the vasodilator substances to act resulting in an increase of the total blood flow in spite of a recorded tonus elevation.

Propulsive power of intestinal contractions on blood flow:

In addition to the effectiveness of the vasodilator metabolites in furnishing means for augmenting the blood flow through the loop, our experiments have demonstrated conclusively that the small intestine possesses another efficient

mechanism for aiding the flow of blood through its wall, namely the rhythmic propulsion of venous blood by the rhythmic contractions. Such rhythmic propulsion of blood constitutes an actual pumping mechanism which significantly facilitates the onward movement of an augmented arterial inflow (consequent on vasodilation) into the draining veins. The experimental evidence for this conclusion is found in the experiments in which the venous outflow was occluded while recording the arterial and venous pressures simultaneously. The results of such procedure are shown in fig. 19 where occlusion of the venous outflow caused two significant changes. First, the amplitude of the intestinal rhythmic contractions increased considerably for some time, then followed a period of depression and a subsequent increase; second, the venous pressure waves corresponding to, and caused by, the rhythmic contractions became distinctly accentuated (16 mm. Hg). The venous pressure was raised thereby and eventually exceeded the arterial pressure by 19 mm. Hg. To further illustrate this propulsive power of the rhythmic contractions, a one-way valve was placed between the venous manometer and the tissue. Results of such a procedure are shown in part B of the figure. Here, with venous occlusion, each rhythmic contraction caused a rise in the venous pressure in a step-like manner, until finally it exceeded the arterial pressure by 28 mm. Hg.

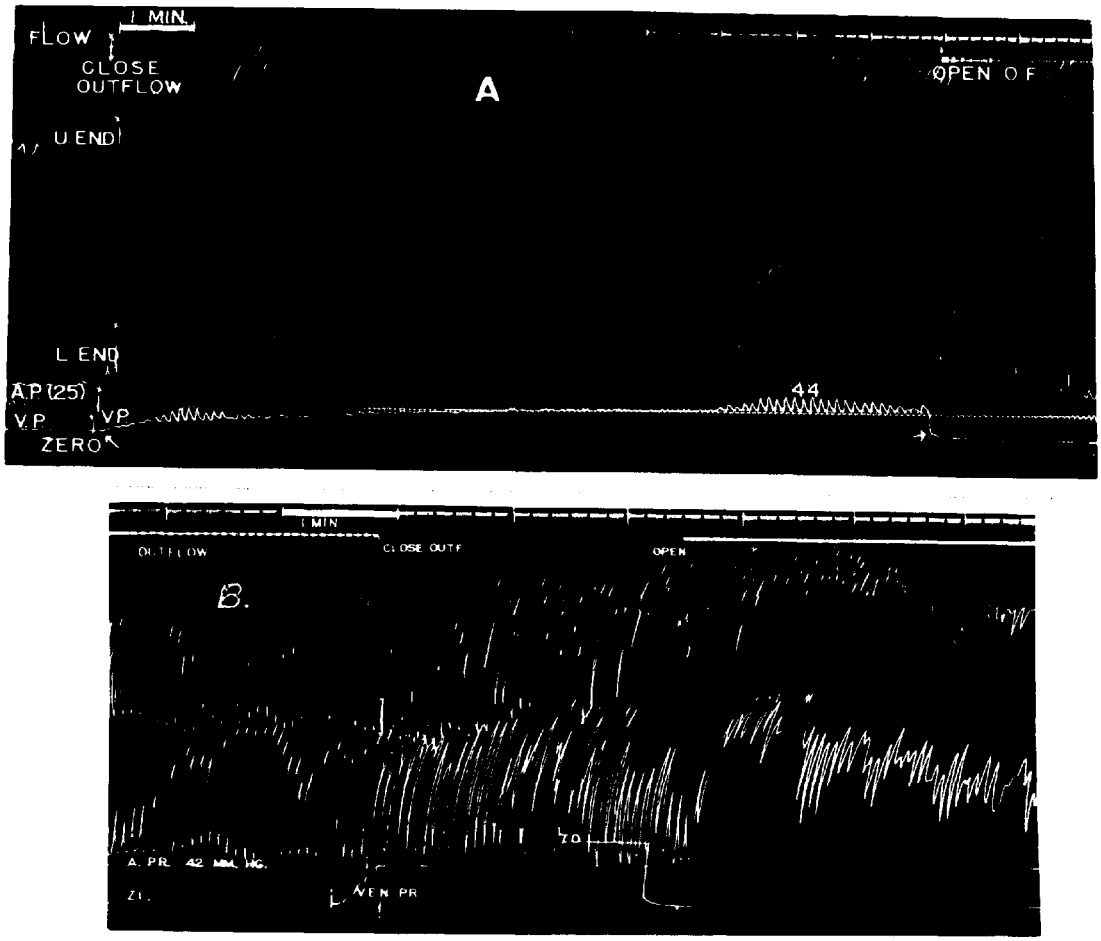


Figure 19. Illustrates propulsive power of the intestinal rhythmic contractions on the blood flow. In both A and B venous pressure is raised above the arterial pressure by the propulsive influence of rhythmic contractions. Tracings from above downward: time in minutes; venous outflow drops; U.END intestinal contractions from upper end of loop, and L.END from lower end; A.P. arterial pressure (25 mm. Hg, pulsatile in A; 42 mm. Hg, constant in B); V.P. venous pressure recorded by Hg manometer; Z.L. zero line for arterial and venous pressures. In B one-way valve placed between venous manometer and outflow tube.

The above experimental results indicate clearly then, that: (1) the propulsive power exerted by the rhythmic con-contraction on the outflow of blood is proportional to the strength of the contractions and (2) these rhythmic contractions are capable of pumping the blood into the veins against a

venous pressure higher than the arterial inflow pressure. This pumping mechanism is adequately provided for by the characteristic anatomical arrangement of the vascular bed: the presence of dense capacious venous plexuses in the submucosa and, the existence of a valvular system in the larger draining veins of the intestinal wall which insures a unidirectional flow of venous blood.

The possible significance of the intestinal rhythmic contractions in the propulsion of blood has been pointed out by Mall (1896). More recently Okea (1934) inferred from observations on mesenteric vein pressure variations, that the rhythmic contractions of the small intestine may serve as "a secondary peripheral heart."

It is evident from the above discussion that the pumping power of the intestinal rhythmic contractions, in conjunction with the vasodilator action of the metabolic products released during activity, constitute an efficient means for regulating the blood supply to the tissue and for facilitating the movement of venous blood. It should be re-emphasized, however, that in order that such means be effective the time intervals of vascular decompression during relaxation of the muscle must be long enough to allow for adequate filling of the vascular bed.

In summary of the results described above, concerning the effects of intestinal motility on the intestinal blood

flow, and the conclusions drawn therefrom, the following may be stated:

(1) During rhythmic activity of the intestine, the inflow decreases and the outflow increases during the contractile phases; during the relaxation phases this relationship is reversed.

(2) The increased outflow during the contractile phases of rhythmic activity is attributed to the sudden vascular compression resulting in the expulsion of venous blood, particularly from the submucosal venous plexuses; the simultaneous decrease in the inflow is due to the obstruction of the arterial paths during vascular compression.

(3) Tonic contractions cause a predominant decrease in both the inflow and outflow which is attributed to vascular compression. Occasionally the outflow increases initially upon the rise of tonus, especially when the latter is sudden and strong; this initial increase is attributed to the expulsion of venous blood consequent upon sudden vascular compression.

(4) Tonic contractions, especially when strong and relatively sustained, are followed by a post-tonic augmentation of both the inflow and outflow, which is attributed to the action of vasodilator metabolites released from the tissue during the high tonus. Such post-tonic vasodilatation may result in an augmented mean flow of blood.

(5) An increase in the general motor activity of the intestine, especially the rhythmic contractions, leads to an

increase in the mean blood flow (arterial and venous). This increase in flow is attributed to the action of vasodilator metabolites released in excess during increased activity.

(6) The rhythmic contractions of the intestine possess the power of pumping the blood through this tissue, thus furnishing a means to facilitate the movement of venous blood. This pumping power may actually propel the blood against a venous pressure higher than the arterial.

II EFFECT OF ALTERATIONS IN BLOOD PRESSURE ON INTESTINAL MOTILITY

Under normal conditions the small intestine is constantly subjected to the changes in the general blood pressure, as well as to changes in the blood flow consequent upon the circulatory readjustments throughout the body. Similarly, because of the direct connection of the mesenteric veins to the portal vein, the small intestine is subjected to the variations in the portal venous pressure. In the experiments described below, various procedures were carried out to determine the effects of arterial and venous pressure changes, as well as those of occlusion of the arterial and venous flows, on the activity and blood flow of the isolated perfused loop.

1) Effect of Alterations in Arterial Pressure:

The desired changes in the arterial pressure were applied by adjusting the height of the pressure bottle

(I, fig. 4) as described under methods.

Sudden elevation of the arterial pressure caused well pronounced reactions in the intestinal activity, as shown in fig. 20 A. Here, the perfusion pressure was suddenly

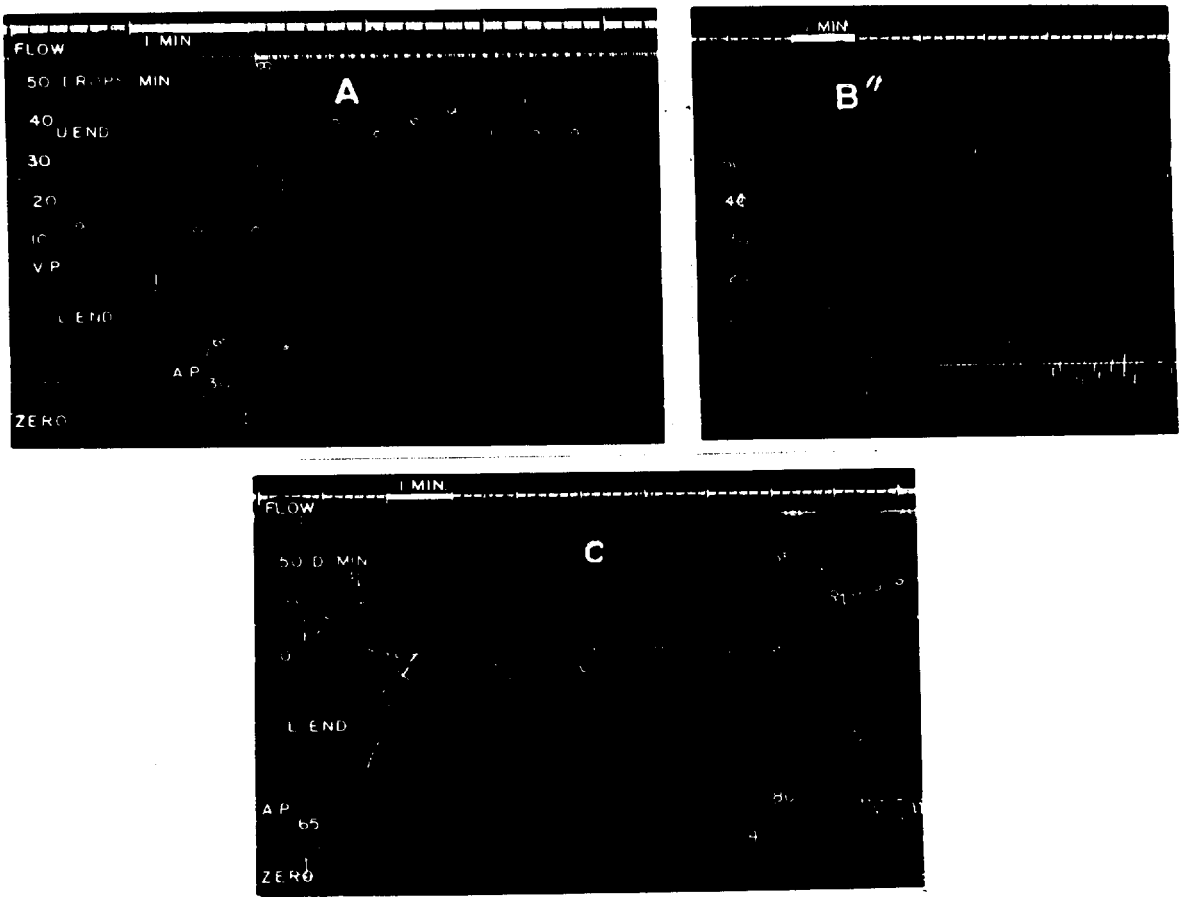


Figure 20. Illustrates effect of sudden elevation of arterial pressure. Tracings from above downward: time in minutes; venous outflow drops; intestinal contractions from upper end of loop; venous outflow plotted in drops per minute; V.P. venous pressure in A; A.P. arterial pressure; intestinal contractions from lower end of loop; zero line. In A, arterial pressure was raised suddenly from 30 to 65 mm. Hg; in B from 25 to 60 mm. Hg; and in C from 40 to 80 mm. Hg (at right hand side) and lowered from 60 to 40 (at left hand side).

raised from 30 to 65 mm. Hg, whereupon there occurred an immediate increase of the blood flow, and after a brief latency (5 seconds), the gut tonus showed a gradual but

distinct rise together with a gradual increase of strength of the rhythmic contractions. A similar result is shown in part B of this figure, where the arterial pressure was suddenly elevated from 25 to 60 mm. Hg. In both parts A and B of the figure, it is noteworthy that the gut maintained its high degree of activity and tonus throughout the period of the elevated arterial pressure.

Another frequent type of motor response of the gut to sudden elevations of the arterial pressure is shown in fig. 20 C (at right hand side). Here, the motor response consisted mainly of an initial sharp and sudden rise of tonus followed shortly thereafter by a drop to a level which was still well above the pre-elevation level.

An important finding concerning the motor reaction of the gut to arterial pressure elevation is that such reaction was conditioned, in part, by the magnitude of the pressure change. This is seen in fig. 21, where a sudden elevation of the arterial pressure from 55 to 70 mm. Hg failed to elicit any definite motor response, whereas a sudden elevation from 40 or 30 to 70 mm. Hg did evoke a well pronounced reaction. In this figure, another important feature is shown, namely that whereas a <u>sudden</u> elevation of the pressure from 30 to 70 mm. Hg elicited a distinct motor response, a <u>gradual</u> elevation of the same magnitude failed. This difference between the effectiveness of the sudden and gradual elevations may be attributed to, (1) the difference between the rate of the

pressure change per se, or (2) the difference between the attendant gradients of flow increase, or to both. However, it is noteworthy that while the gradients of the flow increase were identical for the sudden pressure elevation from 40 to

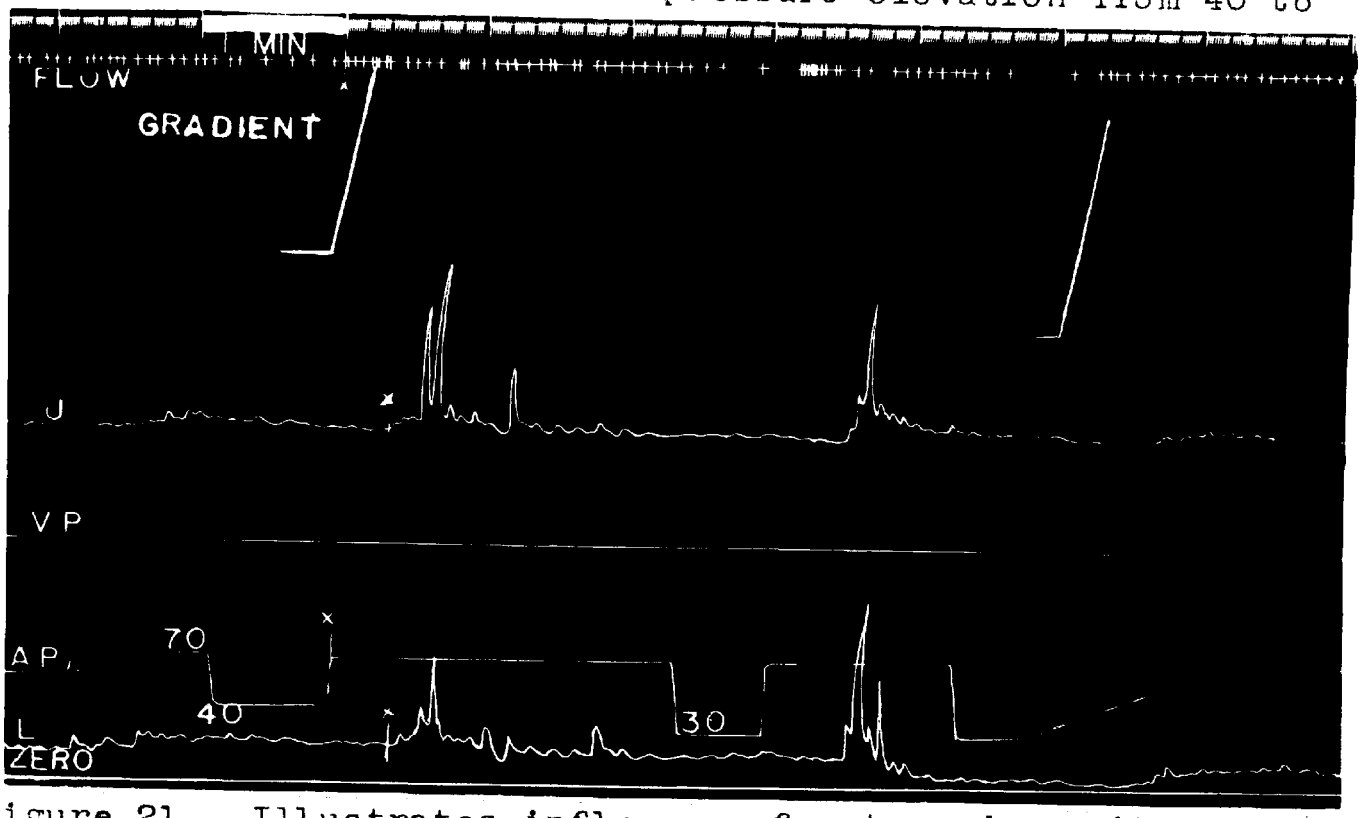


Figure 21. Illustrates influence of rate and magnitude of arterial pressure elevation on motor response of gut. Tracings from above downward: time in minutes; venous outflow drops; U. intestinal contraction from upper end of loop; V.P. venous pressure; A.P. arterial pressure; L. intestinal contractions from lower end of loop; zero line. Simultaneous ordinates marked by X. Gradients of blood flow change consequent upon sudden raising of arterial pressure from 40 to 70 mm. Hg and gradual elevation from 30 to 70 mm. Hg are shown below venous outflow drops.

70 and the gradual elevation from 30 to 70, as shown in the figure, a motor response was evoked only by the sudden elevation (the ultimate flow was almost the same after both elevations). From this, it would appear that the stimulating factor was the sudden change in pressure per se rather than

the attendant gradient of flow change.

Lowering of the arterial pressure, in contrast to pressure elevation, caused a predominant depression in the motor activity and tonus. This is shown in fig. 22, where lowering of the perfusion pressure from 115 to 70 mm. Hg caused an immediate cessation of all contractions of the loop together with a drop of tonus; the venous outflow also decreased by about 50%. The depressed motor activity of the gut lasted throughout the period of lowered pressure then gradually returned to normal upon raising the pressure to its previous level (which also caused an increase of the blood flow).

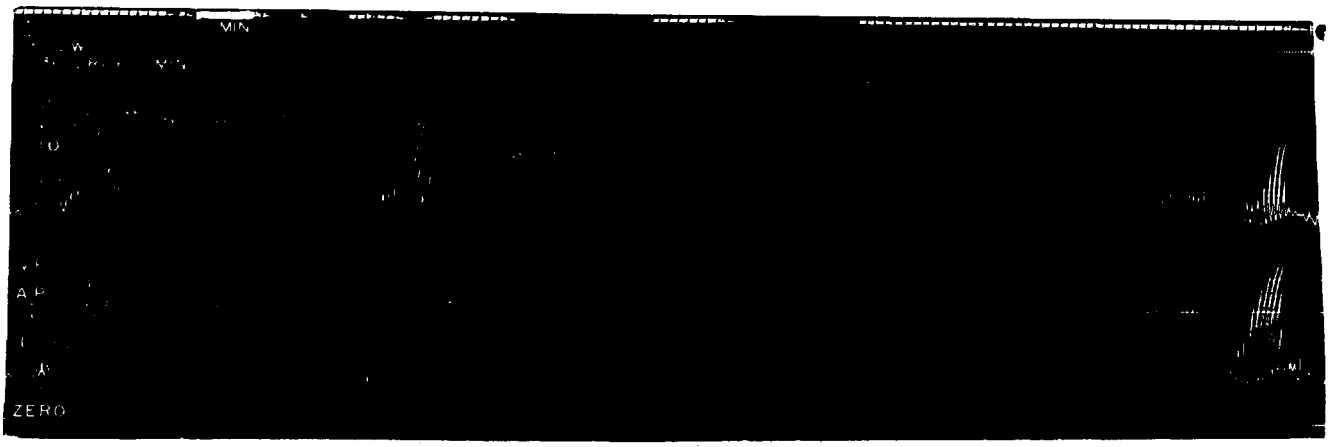


Figure 22. Illustrates effect of lowering of arterial pressure on gut motility. Tracings from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; U. intestinal contractions from upper end of loop; V.P. venous pressure; A.P. arterial pressure; L. intestinal contractions from lower end of loop; zero line. Arterial pressure lowered suddenly from 115 to 70 mm. Hg, then raised to 115 mm. Hg after 8 minutes.

This pronounced depression in motor activity consequent upon lowering the arterial pressure was commonly preceded by an initial transient stimulation of the gut with an increase in rhythmic contraction and tonus. This is illustrated in fig. 20 C (at left hand side), where a sudden lowering of the pressure from 65 to 40 mm. Hg caused a prompt and strong tonic contraction, followed by a drop of tonus to well below the pre-lowering level.

A similar initial stimulating action of sudden lowering of the arterial pressure is illustrated in fig. 23, A and B. In this figure, the motor response of the gut consisted of

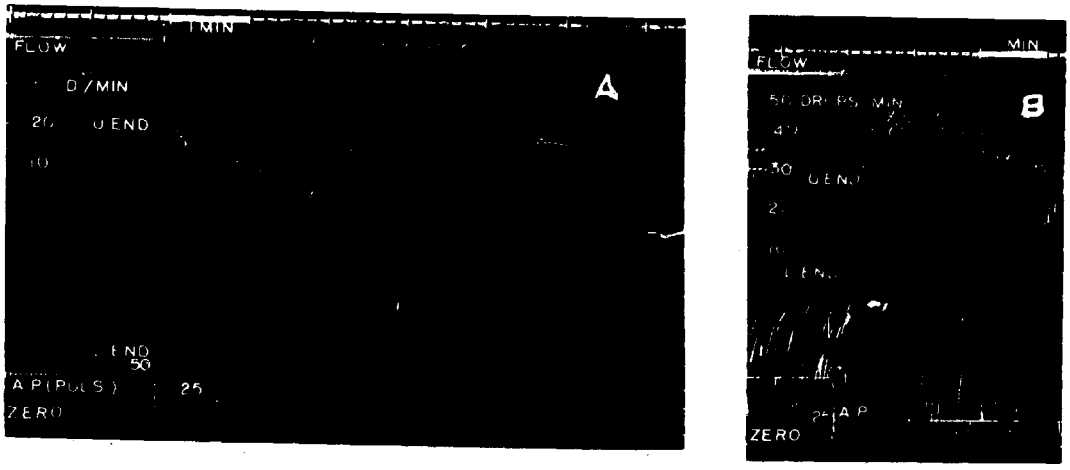


Figure 23. Illustrates intestinal motor response to sudden lowering of arterial pressure. Tracing from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; U.END intestinal contractions from upper end of loop, and L.END from lower end; A.P. arterial pressure (pulsatile in A and constant in B); zero line. Simultaneous ordinates marked by X. In A, arterial pressure lowered suddenly from 70 to 25 mm. Hg, and in B from 50 to 25 mm. Hg.

a pronounced initial temporary rise in tonus and an increase in the amplitude of the rhythmic contractions, followed by

depression to below the pre-lowering level.

The results described above, concerning the effects of sudden lowering of the arterial pressure and its maintenance at the low level, suggest that while the predominant depression in the gut activity under the low pressure may be due to the attendant decrease in the blood flow, the initial stimulation (figures 20 C and 23) may reasonably be ascribed to the stimulation inherent in the sudden lowering of the pressure per se. In this lowering, as was true for the raising of the arterial pressure, both the rate and the magnitude of the pressure change are significant factors in the elicitation of the motor response in the gut. This is shown in fig. 24, where sudden lowering of the pressure from 115 to 70 mm. Hg (first procedure in A) caused a sharp but transient increase in the gut activity and tonus; a gradual lowering of the pressure, however, (second procedure in A) evoked a definitely weaker and a more slowly developing motor reaction. In part B, a still more gradual lowering of pressure failed entirely to induce any motor response. Similarly, in part C a lowering of the pressure from 115 to 70 in sudden steps of 10-15 mm. Hg caused a very minor or almost negligible motor reaction in the gut. It is noteworthy in this figure, that the ultimate magnitude of the blood outflow decrease consequent upon the arterial pressure lowering was almost the same in all four procedures shown.

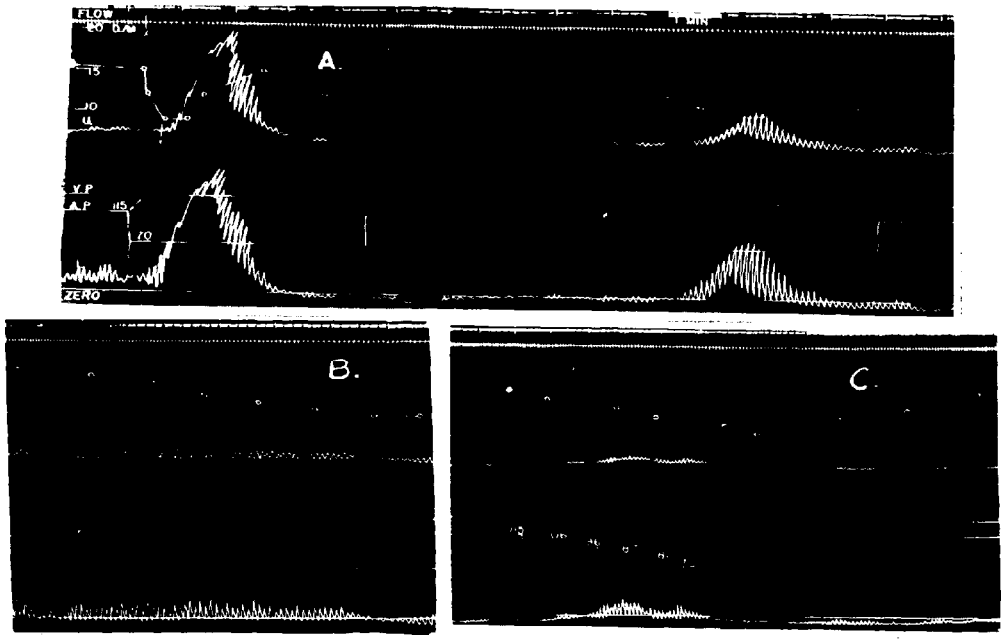


Figure 24. Illustrates influence of rate of change and magnitude of arterial pressure lowering on intestinal motor activity. Tracings from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; U. intestinal contractions from upper end of loop; V.P. venous pressure; A.P. arterial pressure; L. intestinal contractions from lower end of loop; zero line. In A arterial pressure lowered suddenly, and gradually (at arrows) from 115 to 70 mm. Hg; in B very gradually from 115 to 70, and in C in steps 115-106-96-87-80-70 mm. Hg.

It is also of interest in the above figure (24) that although the sudden pressure lowering induced a motor response, the sudden pressure elevation failed to cause any stimulation, whereas in fig. 21 the reverse was true.

In summary, the effects of alterations in the arterial pressure on the intestinal motor activity, as demonstrated by our experiments, are as follows:

(1) Elevation of the arterial pressure leads predominantly to enhancement of the motor activity and tonus of the gut.

(2) Lowering of the arterial pressure leads predominantly to depression of the motor activity and tonus of the gut.
(3) Sudden elevation or lowering of the arterial pressure causes an initial transient but well pronounced motor response in the gut. In this reaction, the rate of the pressure change as well as the magnitude is an important determining factor. While it cannot be denied that the gradient of the flow change may be a contributing factor in this response, the experiments provide evidence that the pressure change per se constitutes the stimulating agent.

2) Effect of Alterations in Venous Pressure:

Changes in the venous pressure were accomplished by a simple procedure of elevating or lowering the outflow orifice of the drop recorder, suddenly or gradually as desired.

Typical effects of venous pressure elevation on the gut motor activity are shown in fig. 25. In parts A, B and C of this figure, where the venous pressure was suddenly raised and maintained for short periods of time, there occurred well pronounced motor reactions in the gut. In part A, the motor response consisted mainly of a sharp and prolonged rise of tonus; a similar response was induced in part B but was preceded by an initial increase in the rhythmic contractions. In part C, there occurred chiefly an increase in the rhythmic activity which was maintained without much change in tonus, throughout the period of elevated venous pressure. In each of the above three procedures, the record of the venous outflow

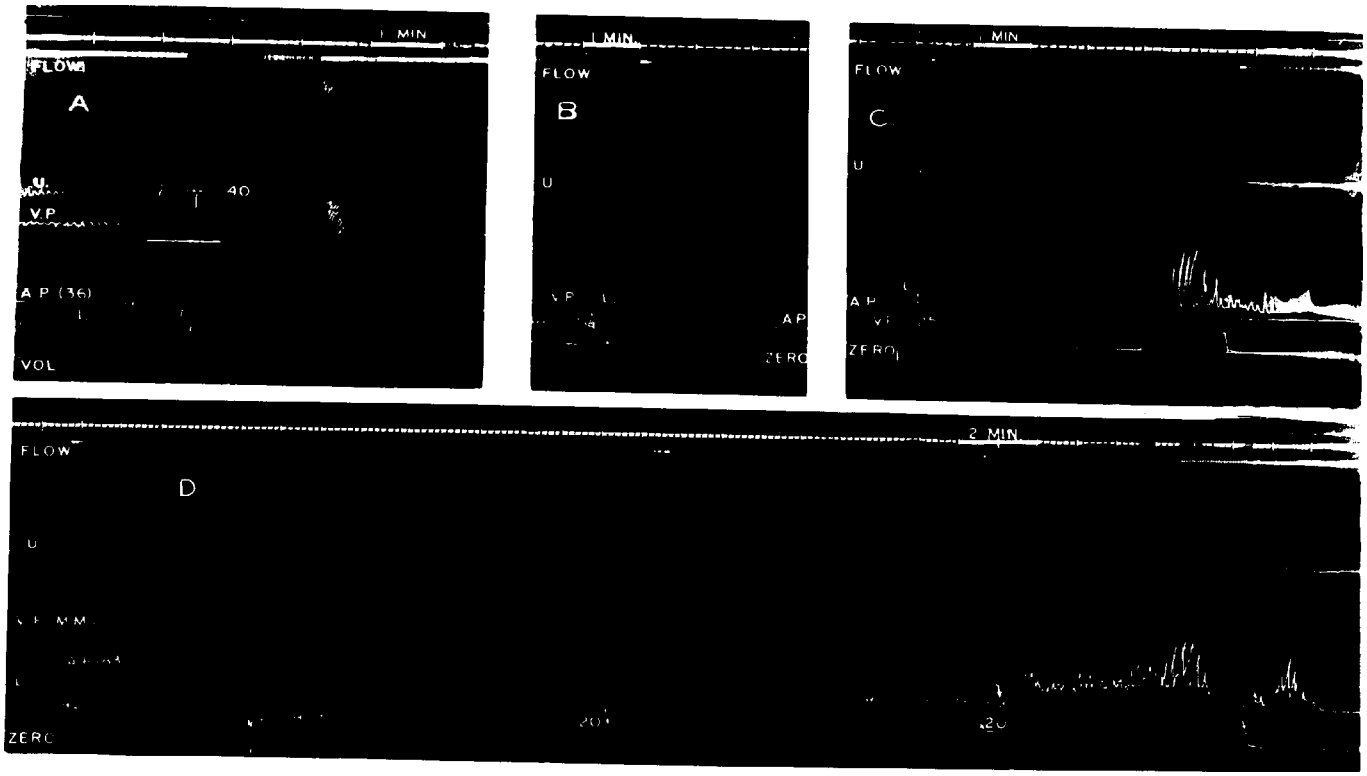


Figure 25. Illustrates intestinal motor response to sudden alterations in venous pressure. Tracings show: time in minutes; venous outflow drops; U. and L. intestinal contractions from upper and lower ends of the loop; A.P. arterial pressure; V.P. venous pressure recorded by membrane manometer in A and D, and by mercury manometer in B, C and D; zero line of arterial and venous pressures in B, C and D.

would seem to indicate a complete stoppage of the outflow. However, this does not necessarily follow since the raising of the outflow orifice (to raise the venous pressure) led to recession of the fluid level into the outflow tube and subsequent cessation of recording. The very rapid initial outflow which occurred upon lowering the venous pressure, as shown in the figure, is attributed to the accumulation of blood on the venous side. Such accumulation of venous blood

is due, in part, to that blood which had receded into the tube upon raising the outflow orifice and more significantly to that blood which was shifted from the arterial to the venous side by the strong tonic contractions elicited by the venous pressure elevation.

That the rate of venous pressure change plays a prominent part in eliciting a motor response, as was true also for changes in the arterial pressure, is demonstrated by a comparison of the two procedures in part D. In the first procedure, the venous pressure was gradually raised to 20 mm. Hg and maintained at this level for 7 minutes. The gut showed only a slight increase in tonus which was probably due, in part, to distention of the intestinal wall by retention of venous blood. On the other hand, in the second procedure, where the venous pressure was raised suddenly to the same level, the gut responded by a sudden increase in tonus and rhythmic activity which was maintained throughout almost the entire period of increased venous pressure. Sudden lowering of the venous pressure induced a temporary increase of both tonus and rhythmic contractions followed by a return to pre-elevation quiescence.

3) Effect of Arterial and Venous Occlusions

In an attempt to further determine the influence of alterations in the blood pressure and blood flow on the intestinal motility, experiments were carried out in which

the arterial inflow and venous outflow were occluded singly or together.

a) Arterial Occlusion:

Occlusion of the arterial inflow led invariably to a predominant reduction in the motor activity and tonus of the gut as shown in fig. 26, A and B. In part A of this

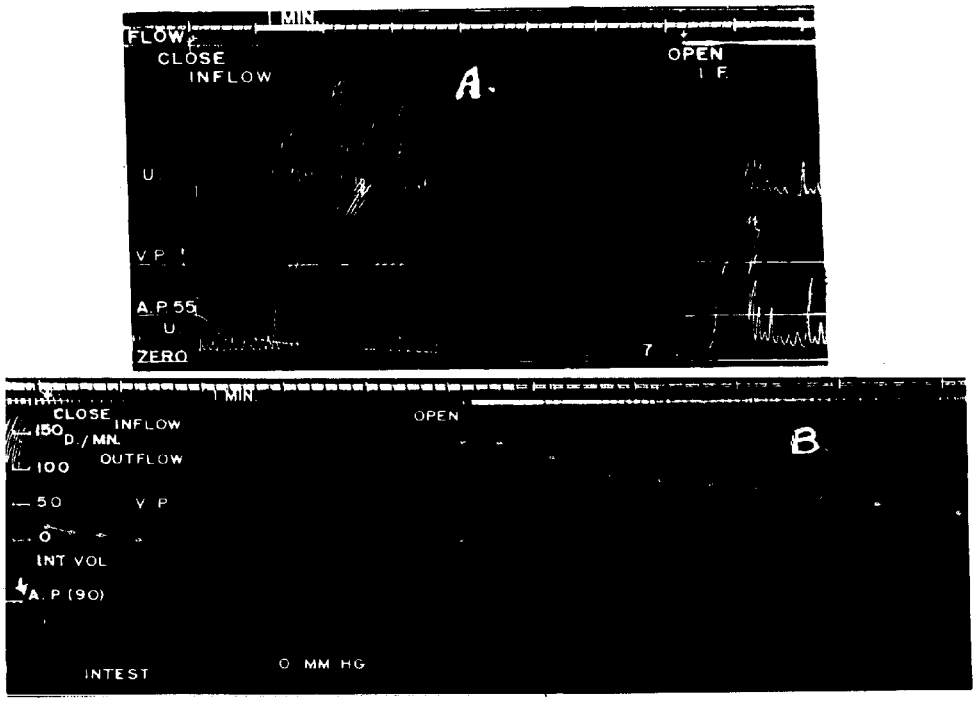


Figure 26. Illustrates effect of arterial occlusion on intestinal motor activity. Tracings from above downward: time in minutes; venous outflow drops; U. intestinal contractions from upper end of loop; V.P. venous pressure; INT.VOL. intestinal volume in B; A.P. arterial pressure; intestinal contractions from lower end of loop; zero line. In B, interrupted curve represents venous outflow plotted in drops per minute; the contractions from the upper end of the loop went off the record upon arterial de-occlusion.

figure, however, stoppage of the blood inflow caused, after a latency of about 50 sec., a marked but temporary stimulation

of the gut motility and rise of tonus followed by profound quiescence which was maintained for the remainder of the occlusion period. In part B, the initial stimulatory effect was absent. The common features in both parts of the figure were an immediate but gradual drop of the intra-arterial pressure following occlusion of the inflow, and, surprisingly enough, a continuation of the venous outflow for sometime after the occlusion until it stopped entirely. The intra-arterial pressure eventually reached 7 mm. Hg in A and zero in B. De-occlusion of the arterial inflow caused an immediate rise of arterial pressure to normal, and return of the venous outflow initially at a considerably higher rate than that previous to the occlusion; in part B this post-occlusion outflow reached a value about 600% of the pre-occlusion value, then gradually decreased toward normal. After a brief latency the gut responded to this de-occlusion by a vigorous rise of tonus and reappearance of rhythmic contractions; such response was of a much longer duration in B, but was followed in both cases by a return to pre-occlusion level. It is also of interest that arterial de-occlusion caused (in B) a sharp and temporary rise of the venous pressure above normal.

The experimental results presented in the above figure indicate, therefore, that occlusion of the arterial inflow to the intestine causes a predominant depression of gut activity which is frequently preceded by an initial transient

stimulation. Such predominant reduction in motor activity may reasonably be attributed to the attendant arrest of the arterial supply to the tissue (anoxic effect). The frequent initial stimulation may also be explained as due to an anoxic effect; however, the drop of arterial pressure per se, consequent upon occlusion of the inflow, may participate in the elicitation of this initial motor response, as already described. Restoration of the arterial supply to the intestine upon arterial de-occlusion leads to a return of the motor activity while the initial temporary tonic rise may be attributed, in part at least, to the attendant sudden rise of arterial pressure per se, (compare with effects of sudden elevation of arterial pressure described above, (fig. 20 C).

The post-occlusion supra-normal blood flow indicates a vascular dilatation induced, during the period of arterial occlusion, by vasodilator metabolites released from the anoxic tissue. This phenomenon resembles greatly that commonly referred to as reactive hyperemia.

b) Venous Occlusion:

In contrast to the predominant quiescence of the gut induced by arterial occlusion, the occlusion of the venous outflow caused a predominant augmentation of the motor activity as shown in fig. 27. In part A of this figure, venous occlusion led to a gradual increase in the height of the rhythmic contractions and a slight rise of tonus. Accompanying the increase of

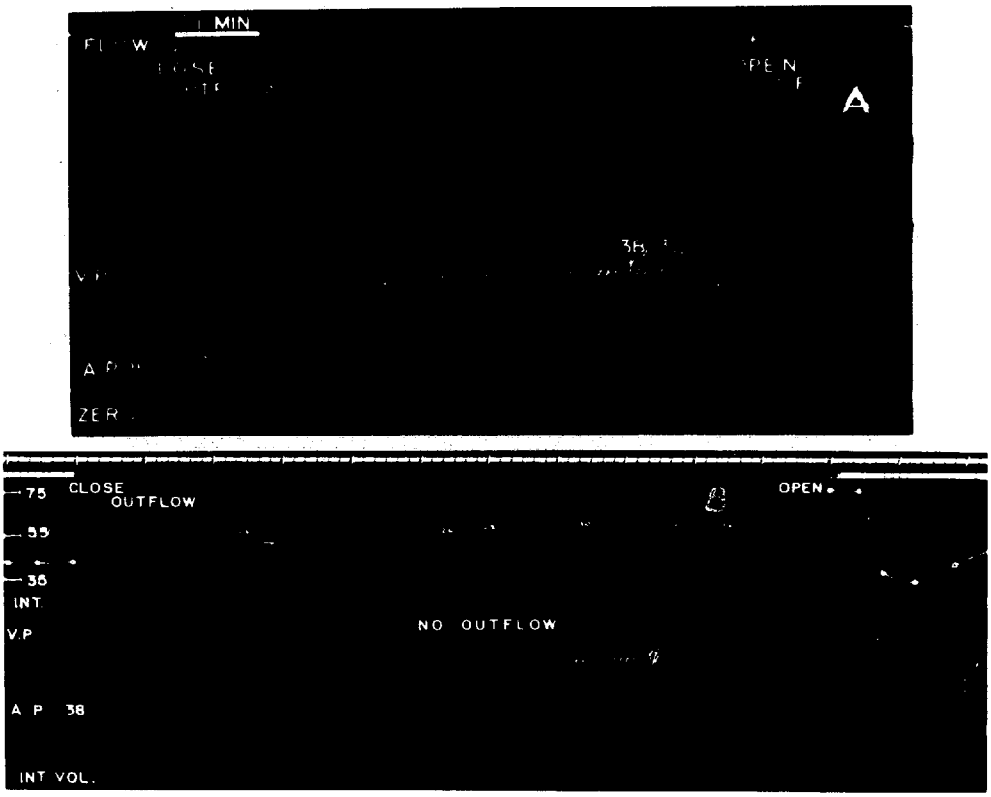


Figure 27. Illustrates effect of venous occlusion on intestinal motor activity. Tracings from above downward: time in minutes; venous outflow drops; U. intestinal contractions from upper end of loop; V.P. venous pressure recorded by membrane manometer; A.P. arterial pressure; L. intestinal contractions from lower end of loop; INT.VOL. intestinal volume in B.

the gut activity, the venous pressure tracing showed a gradual rise upon which there appeared marked undulations synchronous with the strong rhythmic contractions of the loop. This rise of the venous pressure eventually reached a level well in excess (13 mm. Hg) of the maintained perfusion pressure. This phenomenon constitutes, as already described above, conclusive evidence that the propulsive force of the rhythmic contractions may serve under some conditions

as an important contributor to the movement of blood against an unduly high pressure in the mesenteric or portal veins. Upon de-occluding the vein, the venous pressure dropped immediately to the normal level, the gut activity initially declined but shortly thereafter gave way to a temporary period of increased rhythmic contraction and tonus. The venous outflow, upon de-occlusion, was initially fast, but rapidly decreased to the pre-occlusion level. In fig. 27 B, the gut responded vigorously to both occlusion and de-occlusion of the venous outflow; shortly after the venous occlusion the gut exhibited a marked tonic contraction which lasted for about three minutes, then followed by a return to the normal tonic level and subsequent increase mainly in the rhythmic contractions. Upon de-occlusion, there occurred another vigorous motor reaction very similar but of shorter duration than that evoked by occlusion.

c) Combined Arterial and Venous Occlusion:

The reactions of the gut to simultaneous arterial and venous occlusion resembled to a great extent those induced by simple occlusion of the arterial inflow. Thus, it is shown in fig. 28 that shortly after the combined occlusion, the tonus rose very abruptly to beyond the limits of the recorder then fell to a subnormal level, with almost complete quiescence which persisted for the remainder of occlusion. During this period of double occlusion, it is noteworthy that the intra-arterial pressure decreased

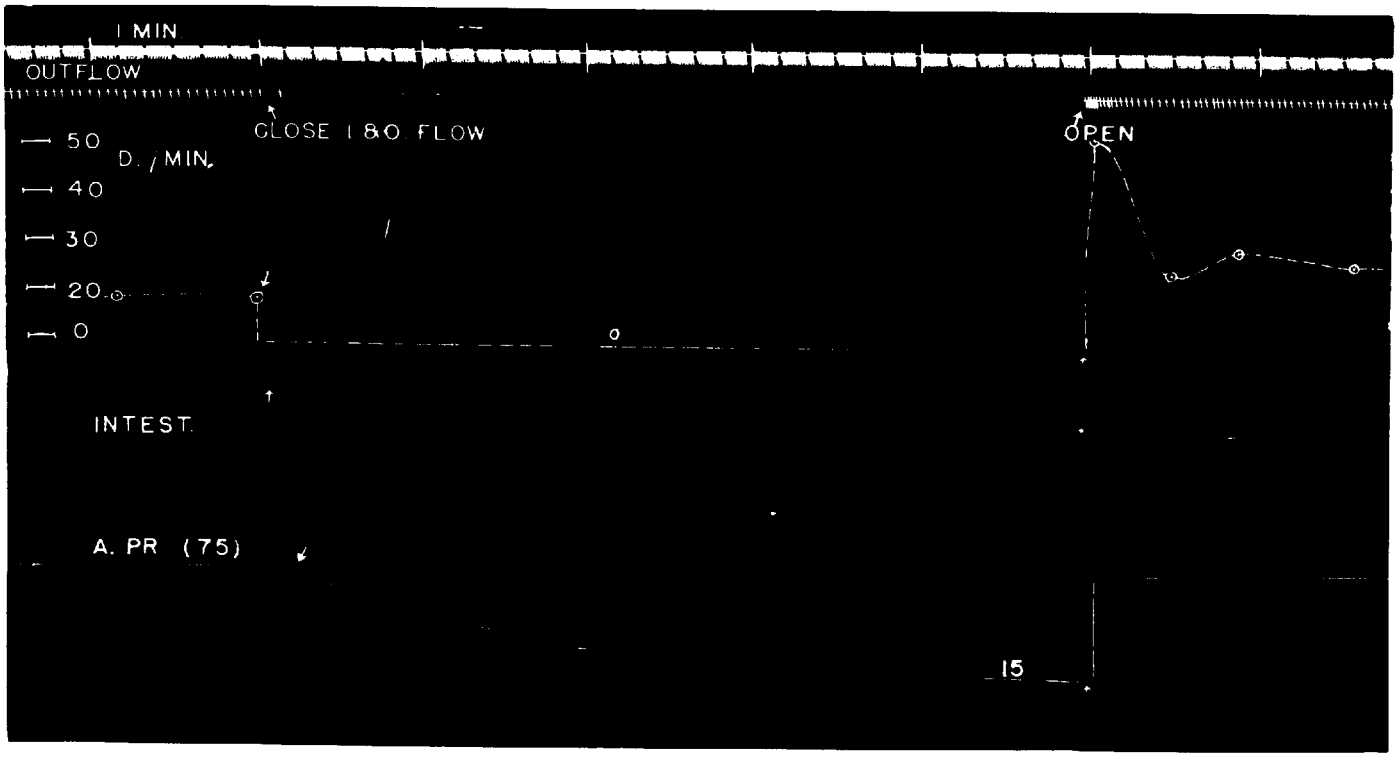


Figure 28. Illustrates effect of combined arterial and venous occlusion on intestinal motor activity. Tracings from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; INTEST. intestinal contractions; A.PR. arterial pressure. Simultaneous ordinates marked by arrows.

gradually from 75 to 15 mm. Hg. Upon simultaneous arterial and venous de-occlusion, the gut, after a brief latency, resumed its motor activity with a decided increase in the strength of the rhythmic contractions above normal, and the venous outflow returned initially at a supra-normal rate then gradually decreased to almost the pre-occlusion level.

Another record of combined venous and arterial occlusion is shown in fig. 29. Here, unlike the effects seen in fig. 28, there was no initial motor reaction to the occlusion; however, the gradual drop of intra-arterial pressure was

evident, as it was in fig. 28, in spite of the fact that there were neither venous outflow from the loop, nor arterial inflow into the loop (except for the small volume from arterial manometer). The double occlusion also caused an immediate but temporary rise of the venous pressure which coincided with the onset of the gradual drop of the intra-arterial pressure. This temporary elevation of the venous pressure is to be attributed to a transmission of blood from the arterial to the venous side as a consequence of the arterial

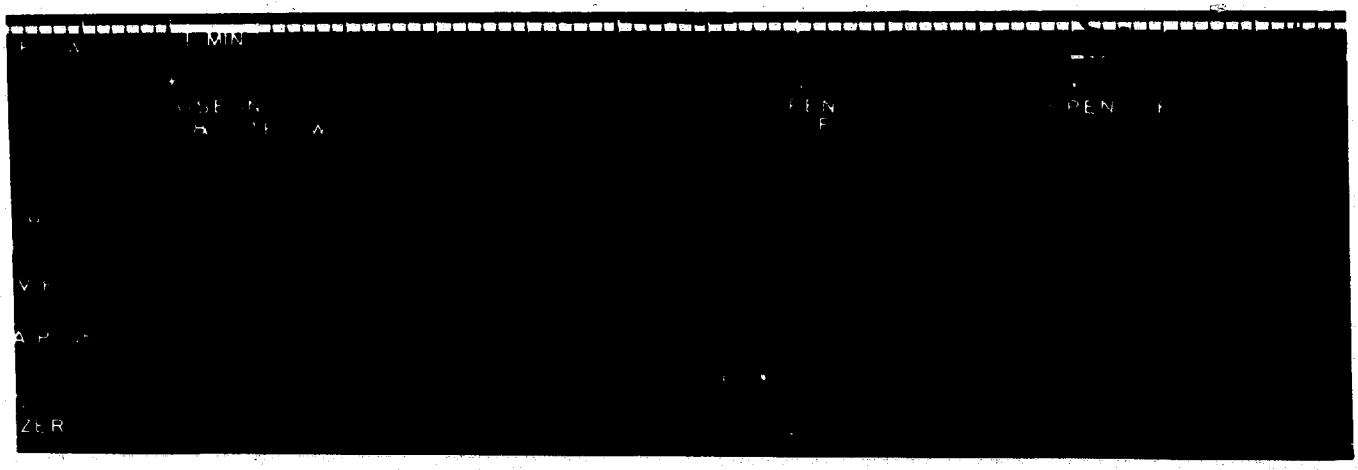


Figure 29. Illustrates effect of combined arterial and venous occlusion on the intestinal motor activity. Tracing from above downward: time in minutes; venous outflow drops; signal line; U. intestinal contractions from upper end of loop; V.P. venous pressure recorded by membrane manometer; A.P. arterial pressure; L. intestinal contractions from lower end of loop; zero line. Simultaneous ordinates marked by X.

tonus. Soon after the arterial pressure reached an almost steady level, the venous pressure also gradually declined to a subnormal level. This secondary drop in venous pressure may be ascribed to a vasodilatation limited to that portion

of the venous system beyond the valvular region of the submucosal venous plexuses, or to loss of fluids from the blood into the tissue. A careful examination of the figure also reveals that there occurred a very slow and slight decrease in the arterial pressure during the later stages of occlusion. This may be attributed to a dilatation of the vascular bed, to the gradual decline of tonus or to loss of fluids from the blood or to all three factors.

De-occlusion of the arterial inflow, while maintaining venous occlusion, caused an immediate return of the perfusion pressure to normal and a sudden, almost simultaneous steep increase of the gut tonus and rhythmic contractions; the venous pressure rose sharply to a level considerably higher than normal. De-occlusion of the venous outflow (three minutes later) caused an immediate drop of the venous pressure to normal, the gut tonus gradually decreased and the rhythmic contractions increased in strength to above normal. The blood outflow returned immediately, first at a markedly supranormal rate, then decreased very gradually toward normal.

The fact that de-occlusion of the arterial inflow, during the maintenance of venous occlusion and apparent stoppage of flow, caused a stimulation of the gut motility would appear to constitute conclusive evidence that this motor reaction was due to the stimulating factor of the sudden blood pressure elevation. However, there still remains the

possibility of an actual arterial inflow, following arterial de-occlusion, sufficient to distend the dilated vessels. In order to investigate this point quantitative determinations of the arterial inflow during the period of venous occlusion were carried out by the drop method (III, fig. 2). The results are shown in fig. 30 A. Here, the arterial manometer tube was closed off preceding the occlusions in order to

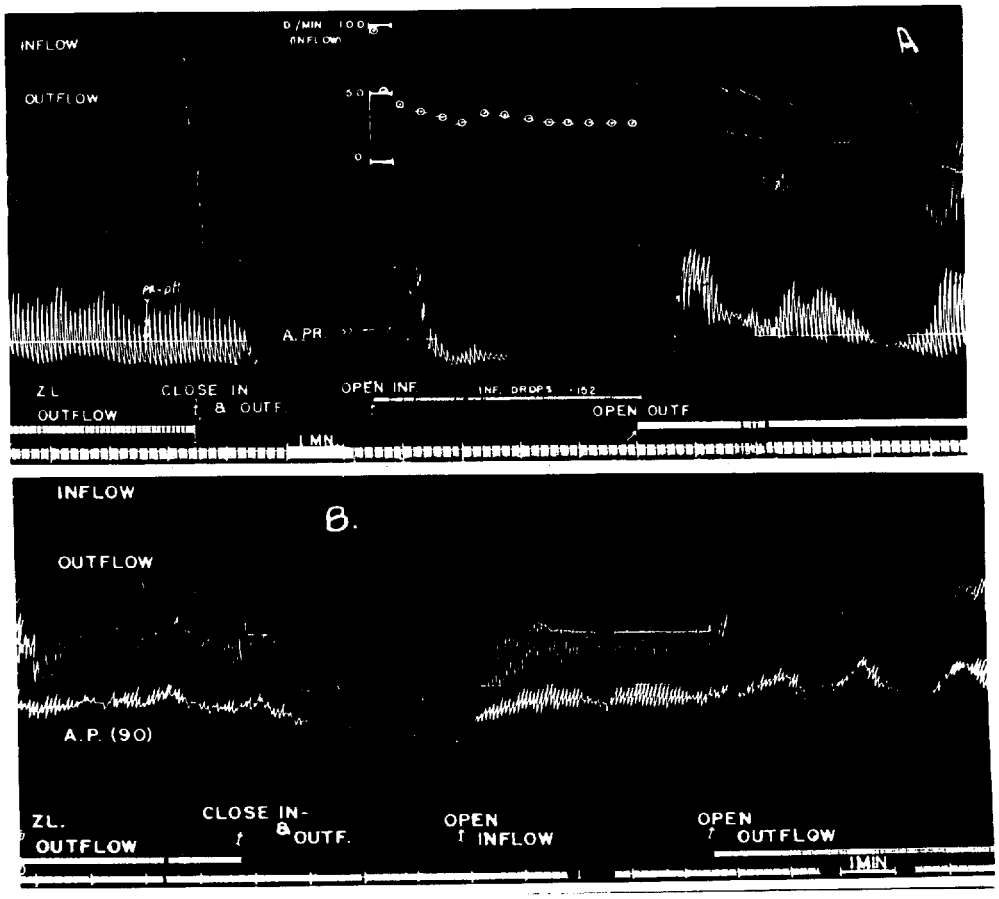


Figure 30. Illustrates occurrence of arterial inflow during maintenance of venous occlusion. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; intestinal contractions from both ends of loop; A.PR. arterial pressure (arterial manometer tube was closed off previous to the occlusions and de-occlusions); ZL. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. In A, arterial inflow was also followed by drop recorder during a part of the procedure; the inflow drops (22 drops = 1 cc.) are shown on zero line and were plotted on curve (with circles) shown at top of record. Upon combined arterial and venous occlusion the thermopile tracings, in both A and B, dropped to their base lines (off scale).

prevent any movement of fluid out of or into the manometer upon arterial occlusion or de-occlusion, respectively. Combined arterial and venous occlusion under these conditions led to quiescence of the gut, to decrease of tonus and to an immediate drop of both the arterial and venous flows (beyond the scale of thermopile recorders). Upon de-occluding the artery (OPEN INF.) there occurred an almost immediate stimulation of the gut; however, while no inflow was registered by the thermopile (off scale), the drop recorder showed an actual arterial inflow into the loop even though the vein was still occluded. This inflow (plotted in the figure) was initially very high then dropped rapidly to a fairly steady low level. A similar result is also seen in fig. 30 B where, with the venous outflow still occluded, the thermopile inflow curve registered an actual temporary flow of arterial blood into the tissue upon arterial de-occlusion. However, the inflow decreased gradually to beyond the scale of the recorder, but in all probability this does not represent complete cessation of inflow as suggested in part A.

These experimental data indicate, therefore, that while the motor response induced in the gut by sudden arterial de-occlusion may be attributed to a stimulus inherent in the sudden pressure change (venous and arterial), it cannot be denied that the attendant inflow of blood may also be a contributing factor in the elicitation of this motor response.

The occurrence of an actual inflow of arterial blood

despite the maintenance of venous occlusion might represent the blood required to fill the vessels previously dilated as a result of the preceding double occlusion. In this case one might expect that once the vessels were filled, the inflow would stop. It is of interest to note, however, that in fig. 30 A, this inflow persisted for a relatively long period (6 minutes). From this, one may tentatively conclude that the arterial inflow upon arterial de-occlusion (with vein occluded) does not simply represent the blood necessary to fill the previously dilated vessels, and that it must be explained on some other basis. In support of this conclusion are the results of experiments in which the inflow was measured by drops immediately following and throughout a period of simple venous occlusion. Such results are shown in fig. 31, which demonstrates that while the arterial inflow decreased markedly but gradually, it did not cease entirely but continued at a low and relatively steady level throughout the period of venous occlusion (6 minutes). The continuation of the inflow under such conditions raises another important question, namely, where does it go? Three possible explanations can be cited in answer to this question: (1) it may be due to some vasodilatation occurring continuously during the period of occlusion, (2) it may be due to a continuous fast seepage of fluids from the blood into the tissue consequent upon the rise of venous pressure, (3) it may be due to progressive opening up of more vessels especially in

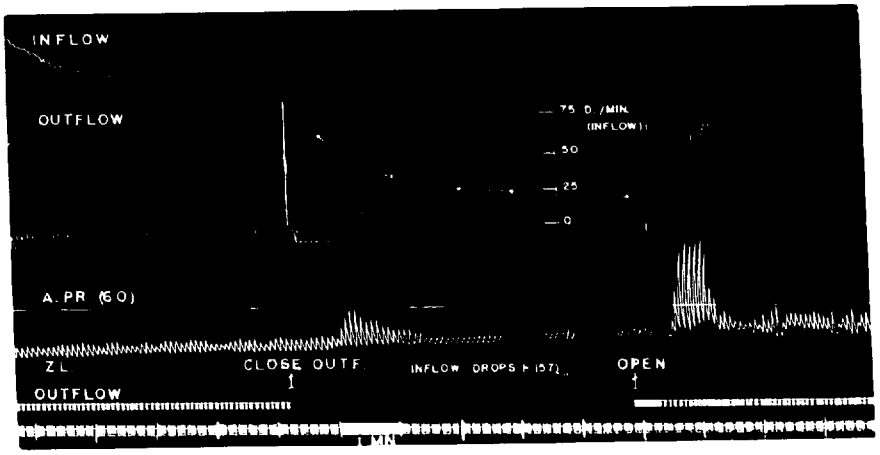


Figure 31. Illustrates continuation of arterial inflow following venous occlusion. Tracing from above downward: arterial inflow and venous outflow recorded by thermopile; intestinal contractions from upper end of loop; A.PR. arterial pressure; intestinal contractions from lower end of loop; ZL. zero line; venous outflow drops; time in minutes. Arterial inflow was also followed by drop method, the inflow drops are plotted on interrupted curve. Arterial and venous thermopile tracings went off scale upon venous occlusion.

submucosal venous plexuses with resultant pooling of blood therein.

Discussion:

Arterial Pressure Variations: With the exception of Mall's work on the perfused isolated loop of the dog's small intestine, almost all of the experimental investigations reported in the literature concerning the effects of variations in the arterial pressure on the intestinal motility were carried out on the tissue 'in situ'. Van Liere et al (1944) observed a significant increase in the motility of the dog's small intestine upon hemorrhaging the animal; they attributed this to a stimulation of the parasympathetic system by

hemorrhage, rather than the sympathetic. On the other hand, Hamilton et al (1944), using unanesthetized dogs with chronic duodenal fistulae, found that reduction of the general blood pressure to 54 mm. Hg by hemorrhage caused a sharp reduction in the duodenal tonus, and at about 40 mm. Hg peristaltic movements were usually abolished. Wakim and Mayson (1945) also observed that during bleeding, and for some time thereafter, the movements of small intestine of unanesthetized dogs diminished gradually until all activity ceased upon withdrawal of about 80% of the blood volume. None of the above authors, however, attempted to determine the various factors involved in influencing the intestinal motility during hemorrhage viz: extrinsic nervous and humoral factors as well as factors of intrinsic origin in the tissue itself. Mall (1896) observed that sudden lowering or raising the perfusion pressure induced characteristic responses in perfused isolated loops of the small intestine of dog consisting mainly of temporary rise of tonus; however, he offered no explanation for such motor responses.

Our experimental results on the isolated perfused loop point to the existence of two distinct but separate factors which participate in influencing the motor activity of the tissue upon altering the arterial pressure: (1) variations in the volume flow of blood consequent upon the pressure change, and (2) the change in the arterial pressure *per se*.

Thus, the predominant increase or depression of the

motor activity consequent upon raising or lowering the arterial pressure respectively may be attributed to the attendant increase or reduction in the volume flow of blood to the tissue. But, the initial transient motor responses immediately following sudden raising or lowering the arterial pressure (figures 20 C, 21 and 23) are best explained as due to a mechanical stimulating influence inherent in the blood pressure change. That this should be the case, is not surprising in the light of the physiological properties of smooth muscles of the tissue to respond to the various mechanical stimuli. In support of such a conclusion the following experimental evidence is of importance:

1) The rapidity of the onset of increase in the motor activity, following arterial pressure elevation, (fig. 20 A) is highly suggestive that the stimulation is one of mechanical type rather than due to the attendent increase in the blood flow. If this be so we may, then, attribute at least the initial increase in the motor activity to a mechanical stimulation induced by the sudden pressure change; the maintenance of such increased activity under the elevated pressure (fig. 20 A and B) may be ascribed to the added influence of the continuation of the augmented volume flow of blood.

2) The sharpness and transiency of initial motor and tonic increase resulting from the sudden elevation of the arterial pressure (figures 20 C and 23) also point to the involvement of a strong, rapidly acting and transient mechanical stimulation.

This transiency of the initial motor response is in accord with the well pronounced adaptive power of the intestinal muscle to mechanical stimuli. Further, it is of prime significance to note, in fig. 20 C, the distinct similarity between the motor response to sudden lowering and to sudden raising of the arterial pressure. Such motor responses can hardly be explained on the basis of the attendant alterations in the blood supply since they were evoked by both increasing and decreasing the blood flow.

3) The fact that the magnitude of the motor response is conditioned by the rate of change (or gradient) in the perfusion pressure (figures 21 and 24) stands in opposition to the interpretation that such response is due solely to the change in volume flow of blood. Thus, the results shown in figures 21 and 24 indicate that with a slow rate of change of arterial pressure adaptation occurred so there was little or no motor response, whereas a sudden change elicited a pronounced response even though the ultimate value of the blood flow was nearly the same under both conditions. However, while this explanation might appear to eliminate the blood supply as the essential causative agent, and is highly suggestive that it is the mechanical factor in the gradient of pressure change which is the essential feature, it does not dismiss the gradient in blood flow as a contributing cause. That the latter is highly unlikely, however, is demonstrated by the results shown in fig. 21 where it is

seen that, although the gradients of change in the blood flow were the same for both a gradual and a sudden pressure elevation, a motor response was elicited only by the rapid blood pressure elevation. In this case, therefore, the blood flow gradient could not have been the exciting factor and may be ruled out, and the motor response must then be attributed to the mechanical influence of the pressure gradient.

Venous Pressure Variations: In the interpretation of the effects of alteration in venous pressure on the intestinal motor activity, we find experimental evidence similar to that described above for arterial pressure variations. Thus, just as in the case of arterial pressure changes, sudden elevation and lowering of the venous pressure (fig. 25 D) evoked a motor response in the gut, while gradual change failed to do so. Further, it is noteworthy that aside from the initial stimulatory action of sudden elevation of venous pressure, the maintenance of the high pressure maintained the gut activity at a supranormal level. Because of the fact that during the period of elevated venous pressure the blood flow diminished, the increase in gut activity cannot be ascribed to an increase in the blood supply. Therefore, it may reasonably be concluded that the venous pressure per se constitutes an important influence on the motor activity of the intestine. This phenomenon may be of extreme significance in the intact animal since a rise in the portal

venous pressure would cause an enhancement of the gut movements. Such enhancement would, in turn, as has already been shown, lead to an increase in the propulsive (pumping) force of the intestinal rhythmic contraction on the blood flow against the high pressure in the portal vein.

From the foregoing considerations, then, it is evident that, while fully recognizing the importance of the attendant changes in the volume flow of blood, the experimental evidence is highly indicative that alterations either in the arterial or venous blood pressure per se evoke characteristic motor reactions in the gut, and that in these motor responses both the rate and the magnitude of the pressure change are important determinants. Such responses may arise from stimulation of the myenteric plexuses. The work of Thomas and Kuntz (1922) and others have demonstrated that these plexuses are highly specialized local reflex centers for the intestine. It may be, however, that such motor responses to blood pressure changes are entirely of myogenic origin.

Arterial and Venous Occlusions: In the interpretation of the effects of arterial and venous occlusions, singly or together, the motor responses of the gut may be attributed to the same determining factors as those described above for alterations in venous and arterial blood pressure, namely: (1) the attendant changes in the volume flow of blood, and (2) the arterial or venous pressure changes per se.

Arterial Occlusion: The predominant depression of the motor activity induced by arterial occlusion is ascribed mainly to the stoppage of the arterial supply to the tissue. Similarly, the initial transient increase in gut activity subsequent to arterial occlusion (fig. 26 A) may be attributed to an initial temporary stimulation induced by anoxemia of the tissue; however, here, the attendant decrease in the arterial pressure per se may also participate in the elicitation of this initial stimulation. On the other hand, the initial increase in the motor activity consequent upon arterial de-occlusion is, in all probability, due mainly to the mechanical stimulus inherent in the sudden elevation of arterial pressure. The promptness, sharpness, and transiency of this initial motor response to de-occlusion are strikingly similar to those of the response induced by sudden elevations of the arterial pressure described above (fig. 20 C). The maintenance of the normal activity of the gut following arterial de-occlusion is attributed here to the restoration and maintenance of the normal blood supply to the tissue.

Venous Occlusion: In the light of the evidence described above, concerning the effects of venous pressure alterations (fig. 25) the increase in gut activity resulting from venous occlusion, may best be attributed to a stimulating effect of the elevation of venous pressure <u>per se</u>. The great similarity between the effects of venous occlusion (fig. 27 B) and those of sudden elevation of venous pressure (fig. 25)

lend further support to the contention that the stimulation of gut activity during venous occlusion is induced by the rise of venous pressure per se. That this maintained increase in gut activity cannot be due to the attendant reduction in the blood flow is indicated by the finding that a similar reduction in the arterial flow induced by other means, e.g. lowering the arterial pressure, usually, not only failed to elicit any similar response, but also led to predominant depression of the gut activity and tonus.

The striking difference between the motor response induced by venous occlusion (predominant enhancement) and that evoked by arterial occlusion (predominant depression) may be of particular significance in relation to possible differences in the excitability of the tissue under these conditions. It is well recognized that tension on muscle alters its excitability; it may be then, that the maintained tension within the blood vessels (by arterial pressure) during venous occlusion serves to elevate, or at least to maintain, the excitability of the gut to its inherent rhythmic stimulus, whereas during arterial occlusion the excitability decreases because of the absence of the tension in the blood vessels.

Combined arterial and venous occlusions: The motor reactions of the gut to simultaneous venous and arterial occlusion and de-occlusion (fig. 28) are attributed to the same factors described above for simple arterial occlusion, namely (1) the cessation of arterial supply to the tissue, and (2) the

arterial pressure changes *per se*.

In the explanation of the motor responses induced by de-occluding the arterial supply only, (vein still occluded) after a period of double occlusion (fig. 29), three factors may be considered viz. (1) sudden rise of venous pressure to strikingly supra-normal levels and its maintenance there until venous de-occlusion, (2) sudden rise of arterial pressure, and (3) limited inflow of blood. Thus, the initial stimulation of the gut upon arterial de-occlusion may be ascribed to the sudden rise of arterial or venous pressure, or to both. The maintained activity during the venous occlusion is, in all probability, due to the maintained supra-normal venous pressure and the possible resultant enhancement of excitability. The possibility that the very limited arterial inflow following arterial de-occlusion may contribute to this motor response cannot be categorically denied. But, it is of particular interest that, while the motor activity and tonus during this maintained venous occlusion is distinctly supra-normal (fig. 29), the inflow is almost nil . This is highly suggestive that the blood pressure (venous and arterial) are the main responsible factors.

In summary then, the experimental data, described and discussed above, indicate that the motor activity of the gut is markedly modified by arterial and venous blood pressure alterations *per se*, as well as by alterations in the blood flow. It is also of particular significance that the increase

in the rhythmic contractions, consequent upon the rise of venous pressure (during venous occlusion) leads, in turn, to further elevation of the venous pressure by virtue of the increased propulsive power exerted upon the venous blood flow.

III VASCULAR REACTIONS TO ALTERATIONS IN PERFUSION PRESSURE

In addition to inducing motor reactions in the gut, our experimental results indicate that sudden alterations in the arterial pressure also evoked reactions in the intestinal vascular walls. Thus, in fig. 32 A, sudden elevation of the arterial pressure from 48 to 72 mm. Hg caused an immediate increase in the blood outflow of about 400%. This increased flow of blood under the elevated pressure was maintained for about one minute then gradually diminished, in three and one-half minutes, to a steady level only slightly higher than that obtaining previous to the pressure application. The gut activity, which was relatively weak throughout this record, was not apparently affected by the pressure elevation except for a very slight and very gradual rise of tonus, followed again by return to exactly the pre-elevation level. The changes in the blood flow following the arterial pressure elevation, therefore, cannot be ascribed to any changes in the motor activity or tonus of the gut. Under these conditions, the fact that the blood flow had returned to almost the pre-elevation level in spite of the maintenance of the higher arterial pressure, can only mean that the

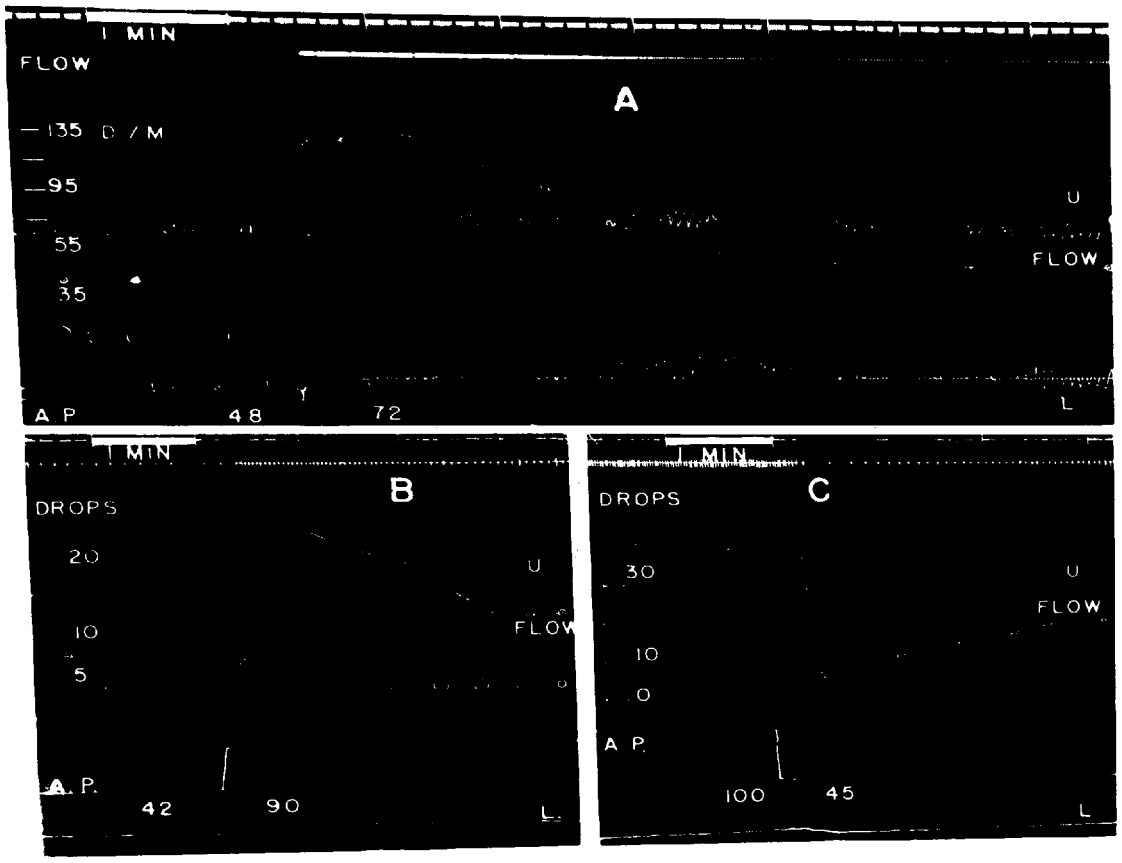


Figure 32. Illustrates vascular reactions to alterations in perfusion pressure. Tracings from above downward: time in minutes; venous outflow drops; U. intestinal contractions from upper end of loop; venous outflow plotted in drops per minute; diagrammatic representation of vascular caliber (circles); A.P. arterial pressure; L. intestinal contractions from lower end of loop. In A, arterial pressure was raised suddenly from 48 to 72 mm. Hg, in B from 42 to 90 mm. Hg. In C, arterial pressure was lowered from 100 to 45 mm. Hg.

blood vessel caliber has decreased to less than that obtaining before the pressure elevation.

Similar results from another experiment are shown in part B of the figure. Here, sudden elevation of the arterial pressure from 42 to 90 mm. Hg caused an initial marked increase (about 300%) in the blood flow, which, as in part A,

then gradually decreased to a steady level slightly higher than the pre-elevation level. Here, too, the gut was quiescent throughout the procedure except for only a slight increase in tonus upon the pressure elevation, which observation again excludes any change in gut activity as an essential causal factor for this secondary decrease of the blood flow during the maintained elevation of the pressure.

Typical effects of a sudden lowering of the arterial pressure are illustrated in fig. 32 C. Here, a sudden drop of the pressure from 100 to 45 mm. Hg caused an immediate precipitous decrease of the venous outflow to about one-fifth of the pre-lowering value. This low flow was maintained for about 30 seconds, then gradually rose to a new steady level of about one-half the original value. Here, as in parts A and B of the figure, the pressure lowering did not cause any significant change in the gut activity except for a slight drop in tonus which may represent a passive change in the gut volume resulting from the lowered arterial pressure. Any possibility that the secondary increase in the blood flow might be due to alterations in the gut activity or tonus is, therefore, ruled out and such changes in the flow must be attributed to a gradual increase in the vessel caliber.

Discussion:

The question of whether the blood vessels react passively to alterations in the arterial pressure or are capable of active tonic responses to such pressure alterations, has

long been debated. Bayliss (1902) in experiments on strips of carotid artery, as well as in plethysmographic experiments on the small intestine and hind limb of the dog, claimed he had demonstrated an active vasoconstrictor response to an elevation of the intra-arterial pressure. He stated that the musculature of the arterial walls reacted according to the intra-vascular pressure; they relaxed when the pressure was decreased and constricted when the pressure was increased.

v. Anrep (1913), however, maintained that these responses, described by Bayliss, were due to the release of humoral and chemical substances into the blood. Thus, he attributed the vasoconstriction following the elevation of the arterial pressure to a stimulation of the suprarenal glands and subsequent discharge of adrenalin in the circulation which then caused the observed constriction; in his experiments he found that extirpation of the suprarenals led to the disappearance of this vasoconstrictive reaction. He attributed the vasodilatation following the lowering of the arterial pressure to an asphyxial effect induced by the attendant decrease of the blood supply and the resultant formation of vasodilator metabolites.

In our experiments it is evident that any vasoconstrictor influences ascribed, in the intact animal, to adrenalin have been excluded since the perfused loops were entirely isolated from the general circulation. In these experiments also, the possibility of any vasodilatation arising from tissue

asphyxia is remote since in many cases the diminution of the blood flow upon lowering the perfusion pressure was insufficient as to cause any anoxic effects.

In the interpretation of our experimental results, the question arises as to whether the observed blood flow changes consequent upon the pressure alterations might be explained merely on the basis of passive elasticity of the vascular walls. Thus, the initial increase of the blood flow upon sudden elevation of the arterial pressure can be attributed to passive distension of the blood vessels of the loop by virtue of their elasticity. The secondary decrease of the flow, however, can hardly be explained on the basis of elastic property of the vessels, since the maintenance of the elevated arterial pressure should lead to the maintenance of the distended condition. Furthermore, the facts that : (1) the initial augmented flow was maintained for about one minute (part A) before the secondary gradual diminution began, (2) this gradual diminution continued for a relatively long period (3 1/2 minutes in part A) before a steady low level of flow was attained, would exclude the possibility that such secondary decrease in flow was due merely to a passive reaction to an overdistended elastic vessel. We may be justified, therefore, in attributing the secondary decrease of blood flow, during the maintenance of the elevated arterial pressure, to an active constriction in the vascular bed induced locally by the sudden vascular distension. To illustrate

these reactions, the vascular caliber has been represented diagramatically in the figure by circles of different diameters. In A and B the caliber has been increased by elevation of the pressure, this distension constituting a stimulus to the vascular musculature which caused an active constriction resulting in gradual narrowing of the vascular caliber to below that obtaining before the elevation of pressure until a steady state is attained.

The interpretation of the changes in blood flow consequent upon sudden lowering of the arterial pressure to new steady levels, led to similar conclusions. Thus, the initial decrease in blood flow is attributed to a passive decrease of the vascular caliber while the secondary gradual increase is due to an active vasodilation. The occurrence of such a secondary increase in flow cannot be explained on the basis of a passive reaction in the vascular elasticity since such reaction would result in the maintenance of the initial decreased flow as long as the arterial pressure remains lowered.

In summary then, the experimental evidence presented above, justifies the conclusion that the intestinal blood vessels are capable of actively changing their tone in response to sudden alterations in the intravascular pressure. These vascular responses must be of local origin, and may be induced by the mechanical stimulation inherent in the alterations in the intra-vascular pressure.

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IV INFLUENCE OF PULSATILE PRESSURE ON INTESTINAL MOTILITY AND INTESTINAL BLOOD FLOW

Plain muscle is very responsive to mechanical stimuli; one may well suppose, therefore, that the mechanical stimulation inherent in the pulse pressure changes within the blood vessels might exert an exceedingly important influence on the smooth muscle of the intestine, and perhaps on the vascular wall itself. Surprisingly enough, an examination of the literature reveals no experimental data or information on this basic question.

The experiments presented below were undertaken to study the effect of pulsatile perfusion pressure on both the intestinal motility and the intestinal blood flow. For application of pulsations to the perfusion blood a simple valveless pump with modifiable rate and stroke was employed (see Methods).

For purpose of convenience, the experimental results are divided into (a) effect of pulsations on intestinal motility and (b) effect of pulsations on intestinal blood flow.

(a) Effect of pulsations on Intestinal Motility:

Shifting from constant to pulsatile perfusion pressure usually caused marked changes in the motor activity of the loop; typical results are shown in fig. 33. In part A of this figure, shifting from constant to pulsatile pressure caused, after a relatively long latent period (50 seconds),

an initial temporary rise of tonus followed by a sudden drop of tonus and a considerable decrease in the amplitude of the rhythmic contractions; the venous outflow diminished markedly throughout the period of pulsations (total 9 minutes). Shifting back to constant pressure (part A" of the figure) caused, after a latency of about 50 seconds, a reverse of

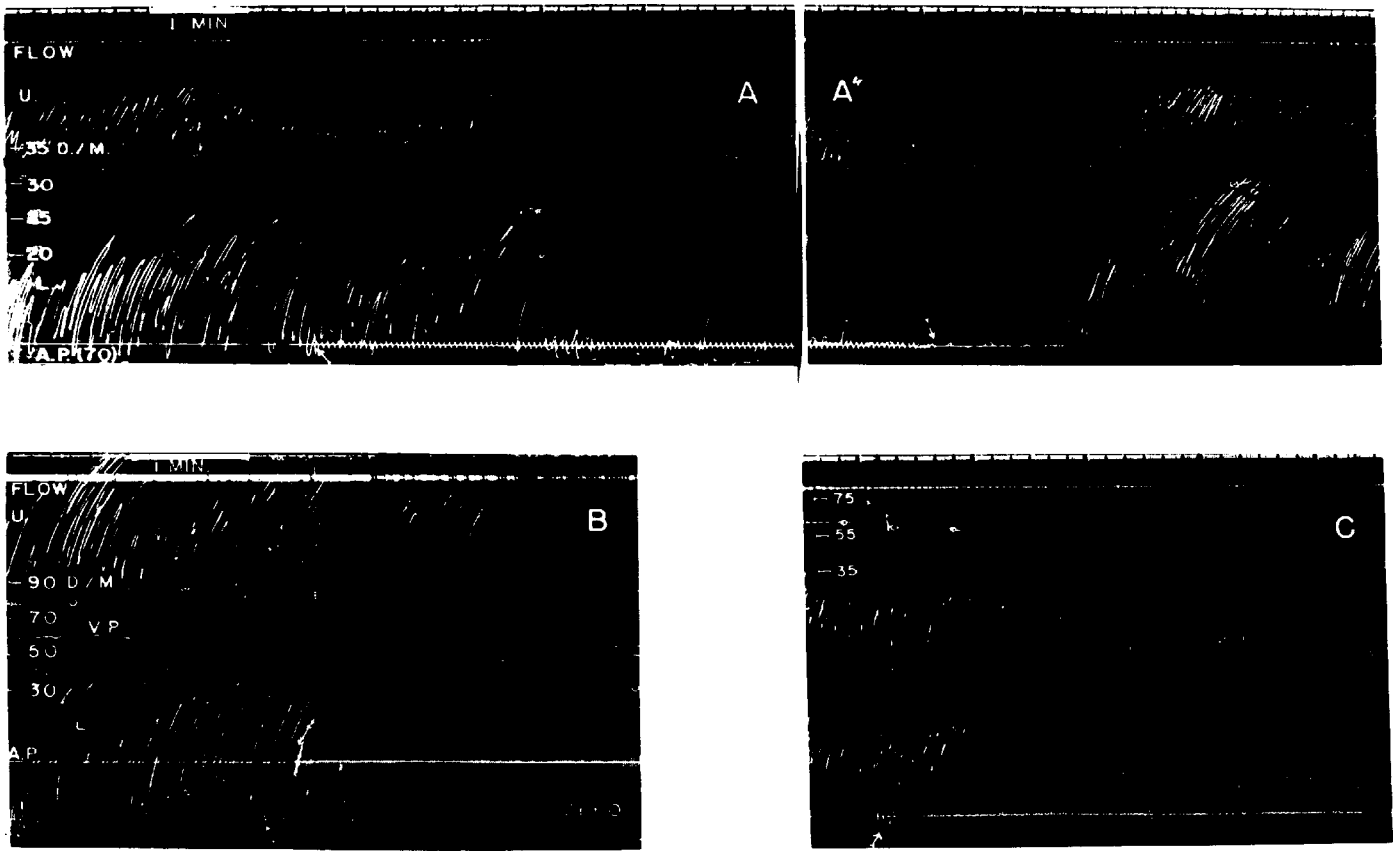


Figure 33. Illustrates influence of pulsatile pressure on intestinal motility. Tracings from above downward: time in minutes; venous outflow drops; U. intestinal contractions from upper end of loop; venous outflow plotted in drops per minute; V.P. venous pressure (in B); L. intestinal contractions from lower end of loop; A.P. arterial pressures, with arrows pointing to beginning and cessation of pulsations. Part A" is a continuation of A; 3 minutes of the recording between A and A" has been omitted for convenience of reproduction.

these changes in the gut motility as well as in the blood flow: the rhythmic contractions and tonus increased markedly then gradually decreased toward the pre-pulsation level; the blood flow returned gradually to the original level. Parts B and C of the figure, derived from two other experiments, show similar reactions upon shifting to pulsatile pressure, with the exception that the initial temporary rise of tonus, observed in A, was missing in part B.

The fact that, in this figure (33), both the blood flow and gut activity decreased during pulsations, suggests that these changes might be interdependent, i.e., pulsations caused primarily a decrease in the blood flow which, in turn, led to the reduction in the motor activity, or vice versa. However, the results shown in fig. 34 demonstrate that pulsations caused opposite changes in the gut activity and the blood flow. Here, as in fig. 33, the rhythmic activity of the loop was markedly depressed upon shifting to pulsatile pressure but the blood flow was definitely increased, and again, as in fig. 33 A and A", these changes were reversed by shifting back to constant perfusion pressure. It is evident, therefore, that in this case the reduction in gut activity under pulsatile pressure cannot be attributed to any decrease in the blood flow. Thus, we may be justified in attributing the reduction in the gut activity induced by pulsations as shown in this figure, and probably that in fig. 33, to an inhibitory influence of pulsations acting

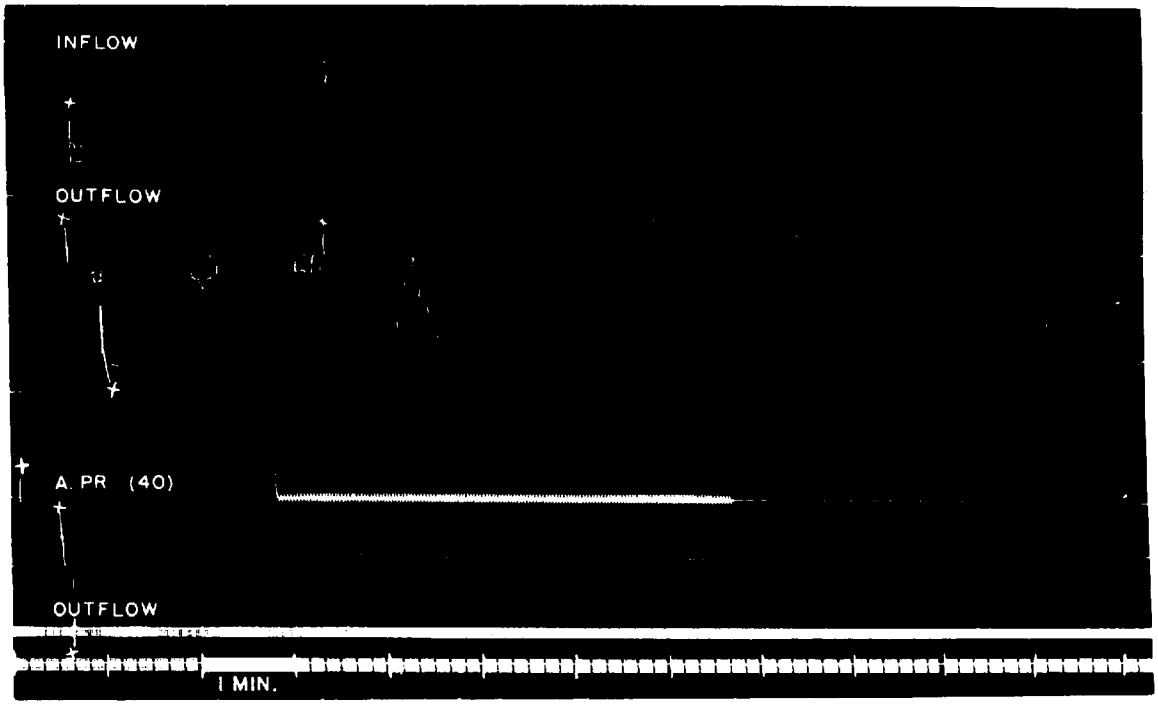


Figure 34. Illustrates influence of pulsatile pressure on intestinal motility. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; intestinal contractions from upper end of the loop; A.PR. arterial pressure (40 mm. Hg mean pressure, constant and pulsatile); intestinal contractions from lower end of loop; zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Mean arterial pressure is the same throughout the record.

directly on the intestinal smooth muscles, or through local reflexes mediated by the myenteric plexuses. The exact nature of this inhibitory influence is not known, but it may be speculated that the underlying factor is an inhibitory stimulus inherent either in the mechanical changes of the pulsations, or in some physico-chemical change in the blood consequent upon agitation, or alterations in diffusion properties.

(b) Effect of Pulsations on Intestinal Blood Flow:

Shifting from constant to pulsatile perfusion pressure caused, in many instances, definite changes in the blood flow independent of alterations in the motor activity or tonus of the gut. Thus, in fig. 35 A, pulsations caused

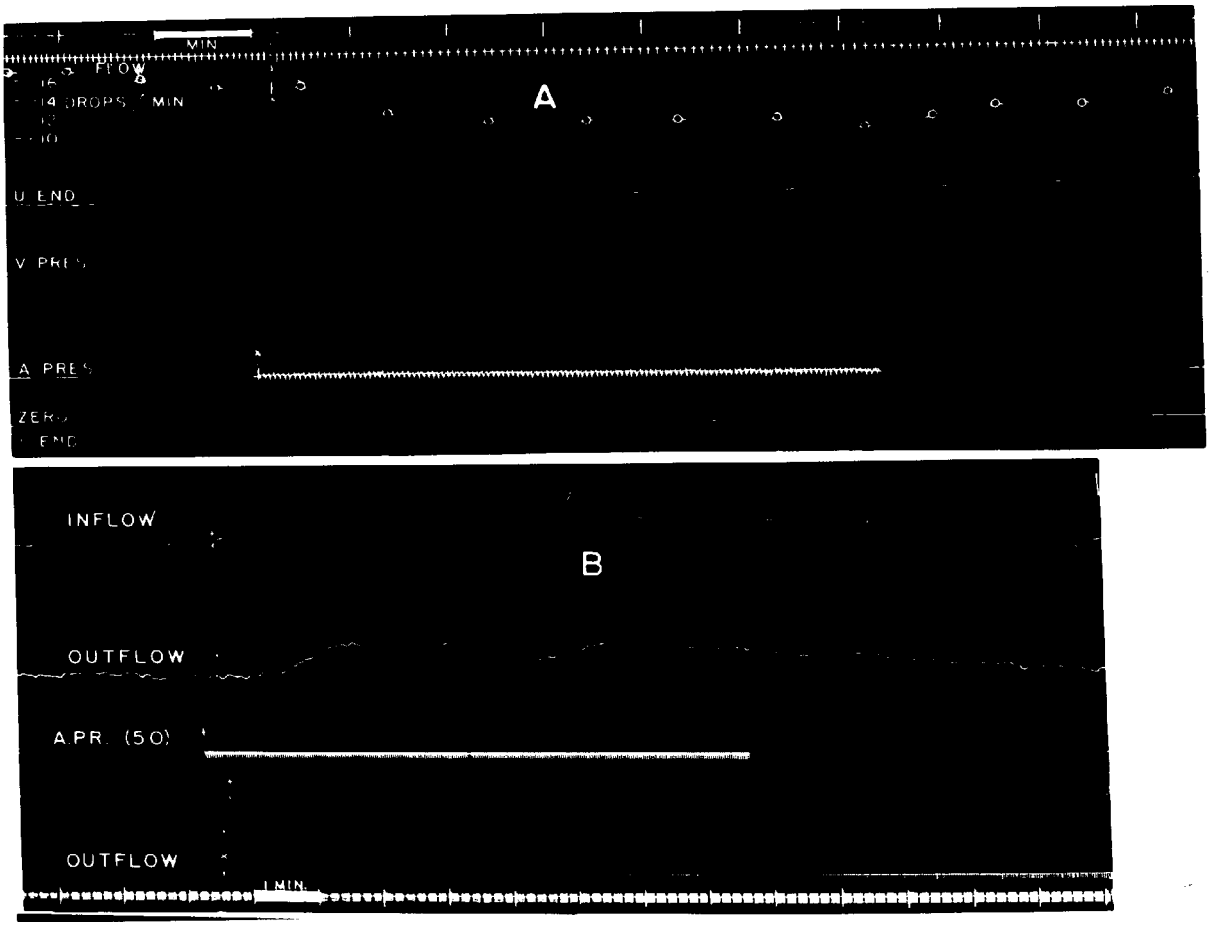


Figure 35. Illustrates influence of pulsatile pressure on intestinal blood flow. Tracings from above downward: part A: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; U.END intestinal contractions from upper end of loop; V.PRES. venous pressure; A.PRES. arterial pressure; zero line for arterial pressure; L.END intestinal contractions from lower end. Part B: arterial inflow and venous outflow recorded by thermopile; A.PR. arterial pressure; intestinal contractions; venous outflow drops; time in minutes. Simultaneous ordinates marked by X in both A and B. Beginning and end of pulsations indicated on arterial pressure tracing. Throughout each record mean arterial pressure was the same.

a predominant diminution of the blood flow, followed by a return to normal upon shifting back to constant pressure. Here, it is to be noted that the gut was quiescent throughout the record and consequently the blood flow changes must be attributed to alterations in the vascular tone itself. In contrast to the results in part A, pulsations, in part B of this figure, caused a predominant reversible increase in the blood flow (inflow and outflow) of about 30%. Here again, these changes must be ascribed solely to vascular reactions since the gut activity and tonus were unaltered throughout the record.

In many instances the vascular reaction to pulsatile pressure consisted of a combination of the two opposite effects just described in fig. 35 A and B. Thus, in fig. 36, application of pulsations caused an initial slight increase in both the inflow and outflow, followed shortly thereafter by a very pronounced and more prolonged decrease (of about 30%), which gave way gradually to a predominant increase about 40% above the pre-pulsation value. Shifting back to constant pressure led to gradual return of flow toward normal. In this figure, as in fig. 35 A and B, neither the gut activity nor tonus were significantly affected by application or cessation of pulsation, which observation indicates that the blood flow changes must again be ascribed to changes in the vascular tone itself.

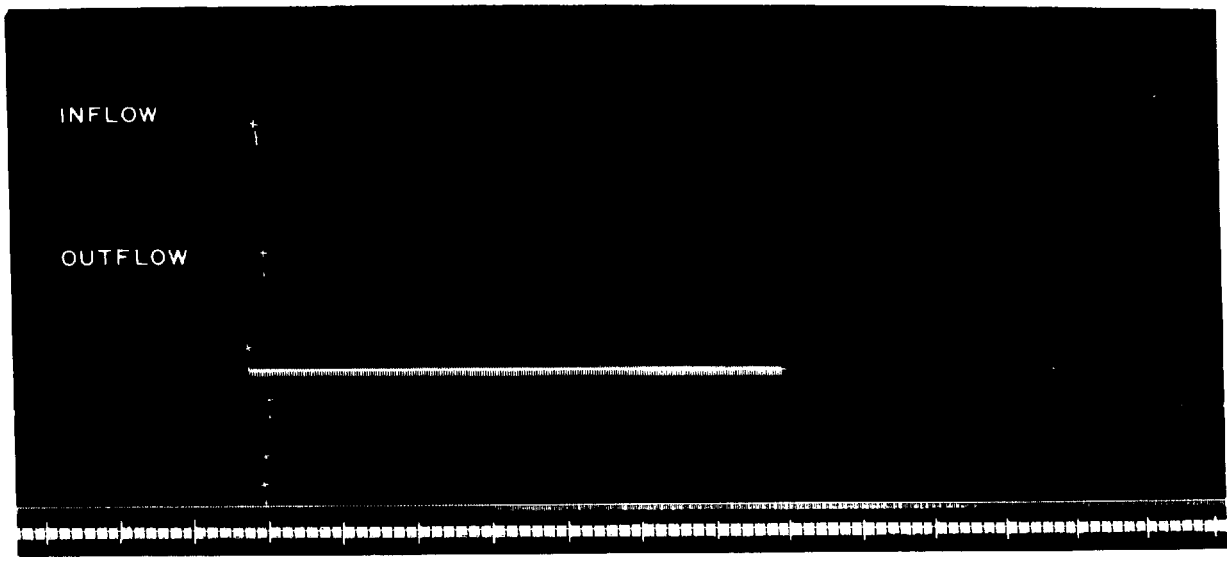


Figure 36. Illustrates influence of pulsations on intestinal blood flow. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; arterial pressure, intestinal contractions from one end of the loop; zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Beginning and end of pulsations indicated on arterial pressure tracing. Mean arterial pressure same for constant and pulsatile presure.

In an attempt to further eliminate the effects of gut motility on the blood flow in these experiments, a solution of atropine sulfate (0.08 mgm.) was injected by a hypodermic needle into the inflow tube near the arterial cannula. The results of such procedure are shown in parts A and B of fig. 37, which illustrate the responses of the gut and blood flow to pulsations before and after atropinization of the loop respectively. In part A, the loop exhibited periodic tonic activity under constant perfusion pressure accompanied by periodic changes in the blood flow. Application of

pulsations caused, after a latency of about 40 seconds, a temporary initial decrease of tonus and cessation of rhythmic contractions attended by a temporary sharp increase in the

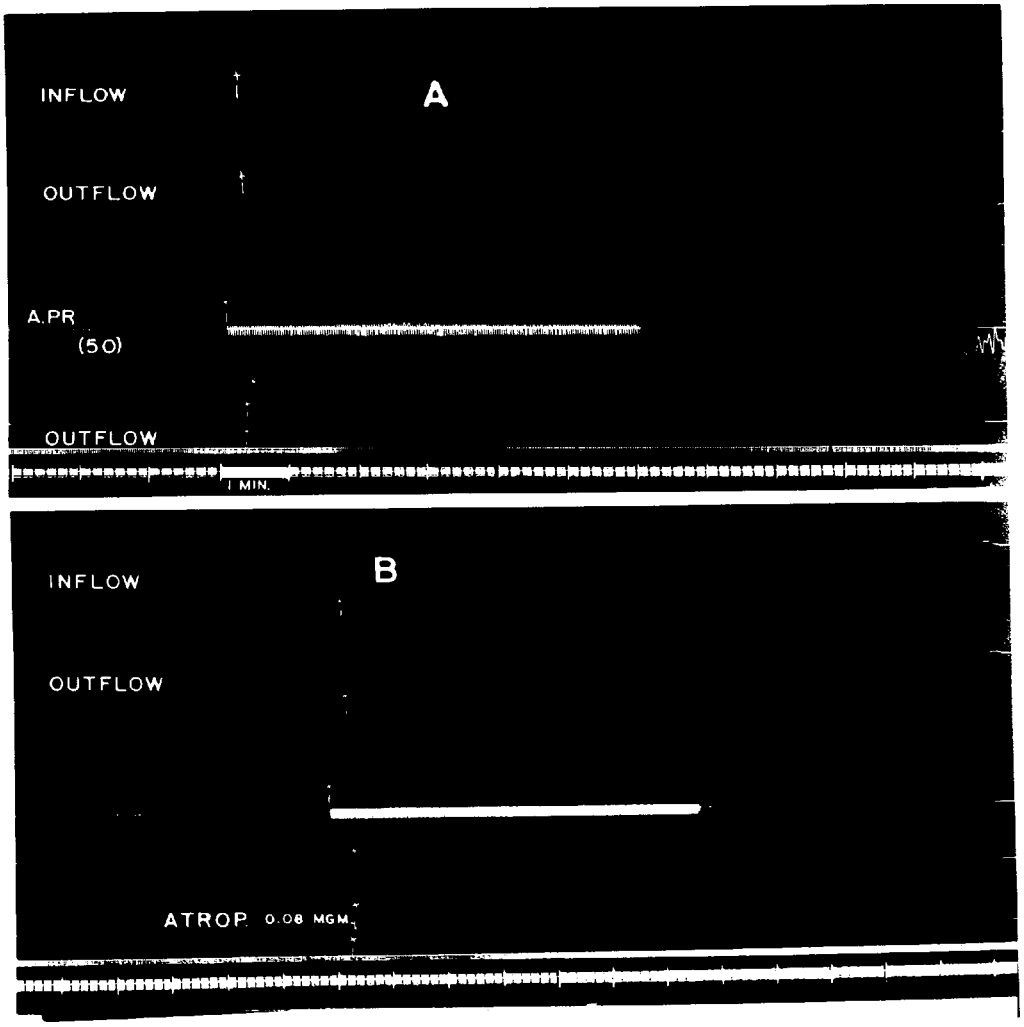


Figure 37. Illustrates influence of pulsations on intestinal blood flow before and after atropinization, A and B respectively. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; A.PR. arterial pressure; intestinal contractions; zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. In both A and B, same magnitude and rate of pulsations were used. In B atropine sulfate (0.08 mgm.) was administered intra-arterially.

blood flow. There then occurred a tonic contraction similar to those observed under constant pressure, followed by a drop of tonus and a slight decrease in the rhythmic contractions which was maintained for the remainder of the period of pulsations. Both the arterial and venous flows were profoundly decreased to much below the pre-pulsation value, and while the flow, then, gradually increased to a relatively steady level during the remainder of the pulsation period, normal levels were not attained until after the cessation of pulsations. The gut activity showed no recovery until some minutes after shifting to constant pressure. In this procedure, therefore, it is evident that the predominant effect of pulsation was to decrease the blood flow very appreciably. In part B of the figure, atropinization of the gut caused a brief and slight tonic stimulation accompanied by a slight temporary decrease of the blood flow; the gut remained completely quiescent throughout the rest of the record. After the establishment of a steady state of blood flow and gut quiescence by this atropinization, shifting from constant pressure to pulsatile pressure caused a much less pronounced initial depression in the blood flow but an enhanced late augmentation.

In comparing records A and B of figure 37 it is evident that whereas the predominant response to pulsatile pressure before atropinization was a profound depression of flow, the predominant response after atropinization was an augmentation

of flow. It is to be noted, however, that there are some points of similarity between these two parts A and B of this figure, namely an initial increase in blood flow under pulsations followed by a decrease, both of which changes are more pronounced in A than in B.

From these findings, it may be suggested that atropine had acted differentially on two antagonistic mechanisms involved in the response of the vessels to pulsations: (1) it paralyzed, at least in part, a vasoconstrictive mechanism, and (2) it left an augmentative or vasodilator mechanism unaffected. As a result of such differential action of atropine, pulsations, applied to the atropinized gut, caused a predominant increase in the flow. However, the persistence of some initial vasoconstriction after atropinization (fig. 37 B) indicates that the paralysis of the vasoconstrictive mechanism was not complete.

The results shown in fig. 38 illustrate further the vascular responses of another atropinized loop to pulsations. Here, as in fig. 37 B, pulsations caused an initial temporary but more pronounced decrease of the blood flow, followed by a gradual increase to above the pre-pulsations level. Cessation of pulsations led to a relatively prompt and gradual decrease in flow to a subnormal level followed by a slow return to normal. Throughout this entire procedure the gut remained relatively quiescent.

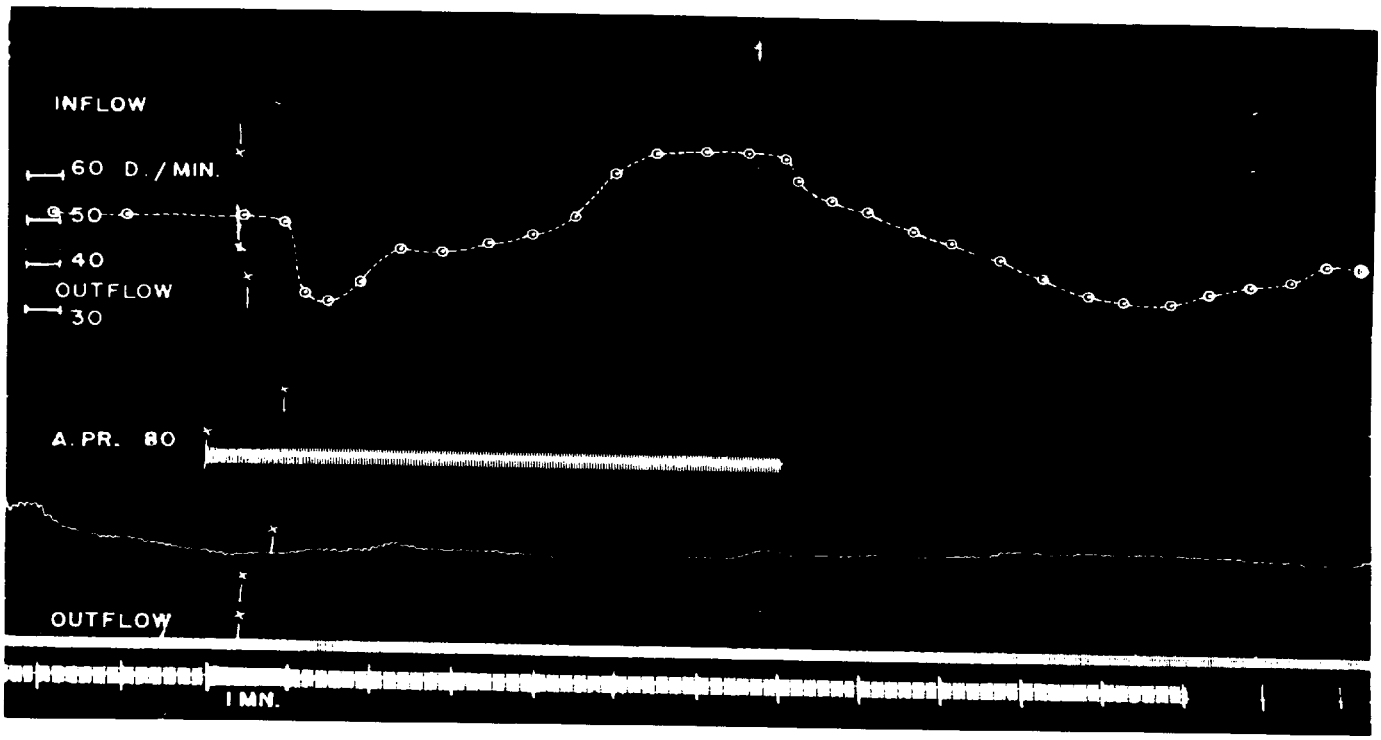


Figure 38. Illustrates influence of pulsations on blood flow of an atropinized intestinal loop. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops per minute, and recorded by thermopile; intestinal contractions from upper end of the loop; A.PR. arterial pressure (mean 80 mm. Hg throughout record); intestinal contractions from lower end of loop; zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Range of pressure change in pulsations was 12 mm. Hg.

In the experiments described above no attempt was made to determine quantitatively the effect of variations in the magnitude of the pulsatile pressure either on the blood flow or on the intestinal motility. It is of interest to note, however, that Hooker (1910), in his work on the blood flow and urine formation in the perfused kidney, observed that the rate of the blood flow varied directly with the

magnitude of the pulse pressure. Gesell (1913), on the other hand, working on the intact kidney found that the blood flow through this organ was not significantly altered by changing from constant to pulsatile pressure or by varying the magnitude of the pulse pressure, (the quality of urine was, however, appreciably affected thereby). Reingold (1928) stated that application of pulsation to the perfusion blood in the rabbit's ear usually caused an increase in the flow, which he attributed to an active vasodilator response of the arterial walls.

Conclusions:

The experimental data presented above justify the following conclusions:

(1) Shifting from constant to pulse pressure causes a definite inhibitory influence on the motor activity of the small intestine; not infrequently such inhibition is preceded by an initial stimulating action.

(2) This motor response to pulsations is not necessarily dependent on simultaneous changes in the blood flow, but is evidently induced by a direct action on the smooth muscles of the intestinal wall, or is mediated through the myenteric nerve plexuses.

(3) The experimental results indicate that while pulse pressure may markedly affect the motor activity of the small intestine, it is not essential for the maintenance of the motor activity.

(4) Shifting from constant to pulsatile pressure causes definite changes in the vascular tone in the small intestine. The most common vascular reaction is a combination of an initial vasoconstriction and a secondary vasodilatation (fig. 36); occasionally these reactions may appear separately, i.e. pure vasoconstriction (fig. 35 A) or a pure vasodilatation (fig. 35 B).

(5) These vascular reactions are independent of any changes in gut activity or tonus since they appear in the absence of such changes (figures 35 and 36) and after elimination of the gut activity by atropine (figures 37 B and 38); such vascular changes must be due to a local response to pulsations.

(6) Atropine influences these vascular responses (fig. 37); the experiments suggest a differential action of atropine in which a vasoconstrictive reaction to pulsations is, in part, paralyzed while an augmentative or vasodilator reaction is unaffected.

(7) The effectiveness of the pulse pressure in eliciting intestinal or vascular responses may be attributed to the mechanical stimulus inherent in the rhythmic variations of the pressure or to the physico-chemical variations in the blood consequent upon the agitation, or to alterations in diffusion properties.

V EFFECT OF ALTERATIONS IN THE INTRALUMENARY PRESSURE ON THE INTESTINAL BLOOD FLOW AND INTESTINAL MOTILITY

The significance of the intralumenary pressure in relation to the intestinal motor activity has long been recognized, and perhaps the best known phenomenon related to this subject is the "Law of the Intestine" (Balyiss and Starling, 1899). Although some question has been raised about the validity of this "Law" (Alvarez, 1928), the fact remains that the introduction of food in the lumen of the intestine induces characteristic motor reactions in this organ by virtue of the pressure exerted on its walls. The work of Crane and Henderson (1924) using the Trendelenburg technique on isolated pieces of the rabbits small intestine, has shown that a certain minimal pressure within the lumen is essential for activation of these intestinal pieces. Gruber and Denote (1935) found that increasing the intralumenary pressure (15 to 20 cm. of water) increased the amplitude of the peristalic waves, or evoked such waves when they were originally absent. However, with the exception of some anatomical studies by Noer (1943), the effect of variations in the intralumenary pressure on the blood flow through the small intestine has been overlooked.

The aim of the experiments described below, was to investigate the effects, if any, of alterations in the intralumenary pressure on the intestinal blood flow as well as on the intestinal motor activity. The experiments were performed on the isolated loops of the dog's small

intestine set up and perfused as previously described.

Results

The desired alterations in the intralumenary pressure were accomplished by raising or lowering the pressure bottle (fig. 3). In the preparatory procedures, the intestinal lumen was washed out with Tyrode's solution from the pressure bottle. It is of interest to mention that as a result of this procedure the gut became relatively quiescent, a reaction which may be attributed to a removal of some stimulating agent present in intestinal contents.

The characteristic effects of raising the intralumenary pressure are shown in fig. 39. In this figure, elevation of the pressure from 4 to 14 mm. Hg caused two outstanding and sudden changes:

(1) A sudden passive rise in the contraction curve, followed immediately by an authentic increase in the tonus of the loop upon which were superimposed strong rhythmic contractions that persisted throughout the period of the elevated intralumenary pressure.

(2) An immediate decline in the arterial inflow to a steady level which was maintained to the end of the period of increased intralumenary pressure. The venous outflow followed a parallel course except for an initial slight increase.

Returning the intralumenary pressure to the original lower level (4 mm. Hg), caused an immediate passive drop

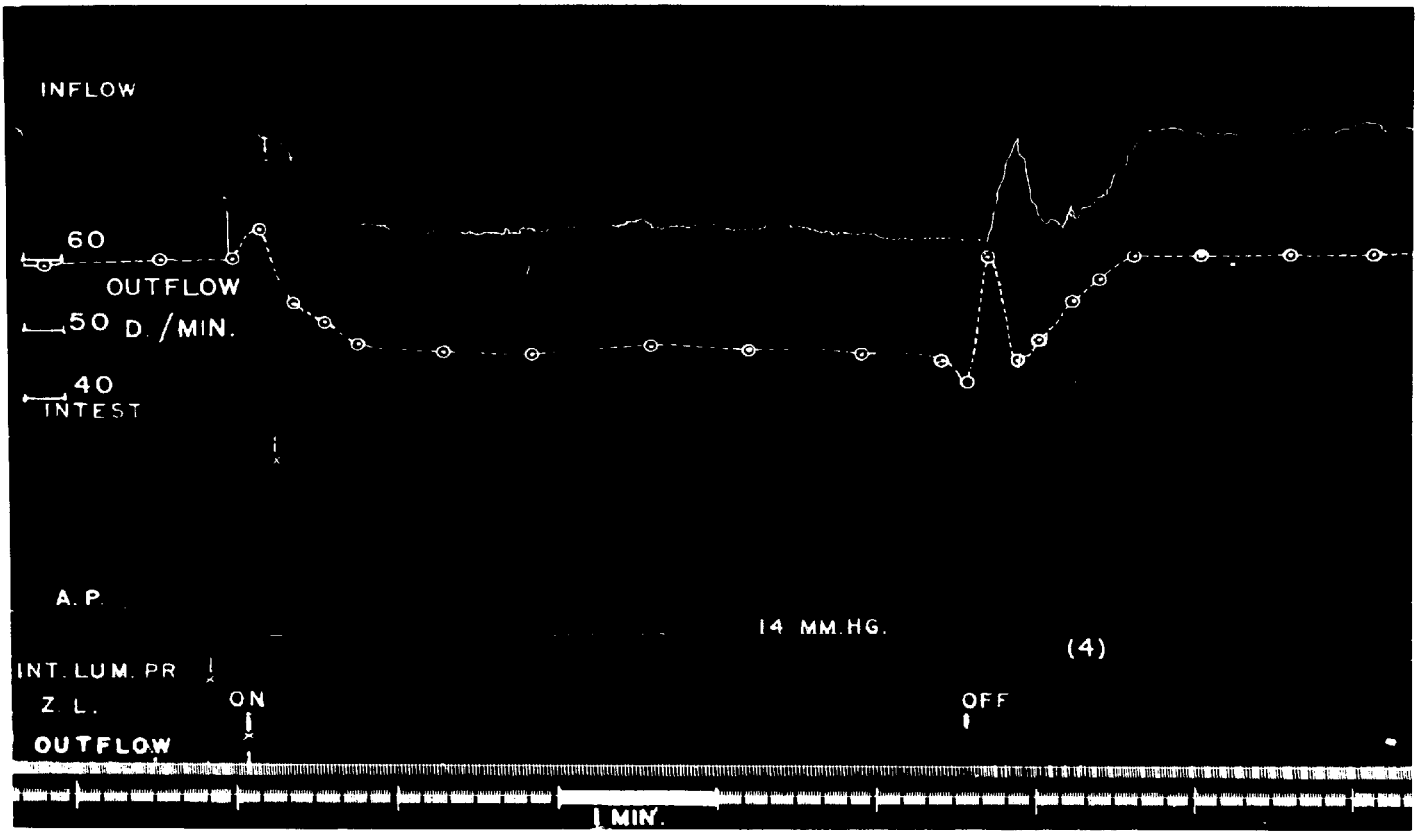


Figure 39. Illustrates effect of alterations in the intralumenary pressure on the intestinal motility and the intestinal blood flow. Tracings from above downward: arterial inflow recorded by thermopile; venous outflow plotted in drops per minute; INTEST. intestinal contractions from one end of the loop; A.P. arterial pressure; INT.LUM.PR. intralumenary pressure recorded at other end of the loop; Z.L. zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

of the contraction curve followed, after a brief latency of quiescence, by a temporary period of marked rhythmic contractions and subsequent complete quiescence similar to that obtaining before the pressure application. The arterial inflow increased promptly upon lowering the intralumenary pressure to almost the normal level, but then decreased temporarily to increase again to the pre-elevation value.

The outflow followed a parallel course except for an initial slight decrease. It is of interest to note that the brief period of decreased flow coincided with the period of increased rhythmic contractions induced by lowering the intralumenary pressure.

Similar results of raising and lowering the intralumenary pressure (through 10 mm. Hg) are shown in fig. 40 except that, here, the brief period of increased gut activity, seen in

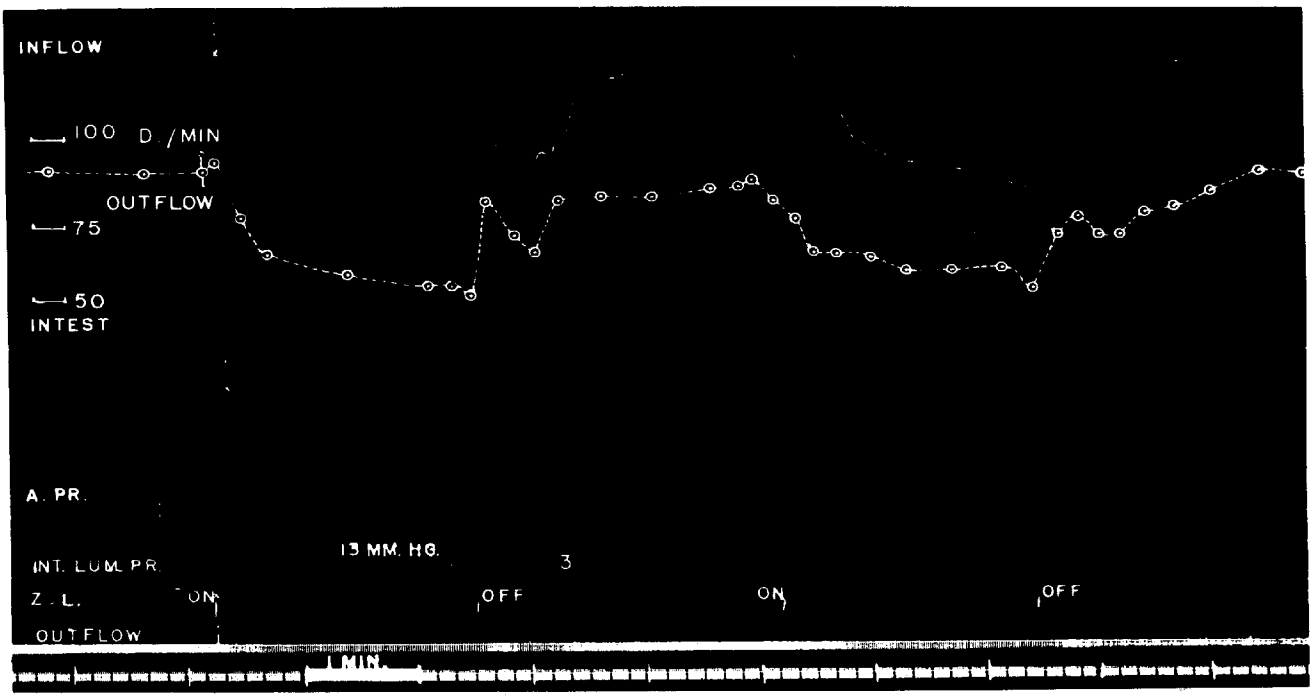


Figure 40. Illustrates effect of alterations in the intralumenary pressure on the intestinal motility and intestinal blood flow. Tracings from above downward: arterial inflow recorded by thermopile; venous outflow plotted in drops per minute; INTEST. intestinal contractions from one end of the loop; A.PR. arterial pressure; INT.LUM.PR. intralumenary pressure recorded at other end of loop; Z.L. zero line for arterial pressure; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

fig. 39, upon lowering the pressure was absent. In this case (fig. 40), the temporary decrease in flow which followed the sudden rise induced by the drop of the pressure may be due to: (1) and active vasoconstriction induced by the sudden distension of the vessels, or (2) a possible increase in gut tonus not registered on the record because of the open connection to the pressure bottle. That the latter possibility might be the case is supported by the observation that the lumenary contents were partially regurgitated into the pressure bottle after its lowering.

Discussion and Conclusions:

The predominant diminution in the blood flow under an increased intralumenary pressure is attributed to the passive compression of the vascular bed resulting from the stretching of the intestinal wall during its distension. That this is the case is supported by Noer's anatomical studies on the arrangement of the arterial supply to the small intestine of the dog. This author (1943) found that distending the lumen with inflated balloons caused a passive closure of small blood vessels in the intestinal wall.

As a result of a sudden elevation of the intralumenary pressure and consequent sudden vascular compression, there occurs an initial temporary increase in the outflow (figures 39 and 40) due to the expulsion of venous blood mainly from the submucosal venous plexuses. Similarly, with a sudden

drop of the intralumenary pressure and consequent sudden vascular decompression there occurs an initial brief decrease in the outflow during the period of filling of the vascular bed, followed immediately by an increase.

The alterations in the intralumenary pressure carried out in this study would certainly fall within the range of those which occur in the intact normal gut. One is justified, therefore, in concluding that, in the gut in situ, just as in the isolated loop, an increase in the intralumenary pressure causes an increase in tonus and rhythmic activity and a diminution in the blood flow. Such intestinal reactions are of local origin and are either entirely myogenic in nature or may also involve local myenteric reflexes.

SECTION III

EFFECT OF CARBON DIOXIDE, LOW OXYGEN AND ACETYLCHOLINE ON INTESTINAL BLOOD FLOW AND INTESTINAL MOTILITY

There is a considerable volume of information in the literature concerning the effects of CO_2, low O_2, acetylcholine and adrenalin on the blood flow and motility of the small intestine. Most of these earlier experimental studies were carried out either on the intact animal, where the effects of these substances involved reflex and central nervous influences as well as those of circulating humoral agents, or on strips of the intestine where these substances were administered in the bath fluid. In contrast to these studies, the experiments reported herein have been confined almost entirely to the study of the local effects of the above substances administered through the blood supply, on the motor activity and blood flow of the isolated perfused loops of the small intestine.

I EFFECT OF ALTERATIONS IN CO_2 CONTENT OF ARTERIAL BLOOD

In these experiments the perfusion blood was equilibrated with gas mixtures containing the desired concentration of

CO_2, extreme care being exercised to keep the concentration of oxygen at "normal" value (30%).

For purposes of convenience the experimental results concerning the effect of CO_2 on the intestinal blood flow will be presented separately from those concerning the effect on intestinal motility. However, in view of the intimate relationship which exists between the intestinal activity and the flow of blood, passing reference will be made to any such interaction.

(1) Effect of CO_2 on Intestinal Blood Flow

On the assumption that normal blood is in equilibrium with a gas mixture containing 4% CO_2, the effects of increasing this concentration (hypercapnia) and lowering it to zero (acapnia) were studied:

(a) Effect of hypercapnic blood: Five different concentrations of CO_2 (in the equilibrating gas mixture) in excess of the "normal" level (4%) were used: 6.7% - 8% - 10% - 12% and 15%, corresponding to tensions in the blood of 40.25-60-75-90 and 112.5 mm. Hg respectively in comparison to a "normal" tension of 30 mm. Hg.

The effect of a 6.7% concentration of CO_2 in the perfusion blood, is seen in fig. 41. In this figure, showing two successive CO_2 administrations in the same loop, the hypercapnic blood caused a marked but gradual increase of the blood outflow. In the first procedure (upper record),

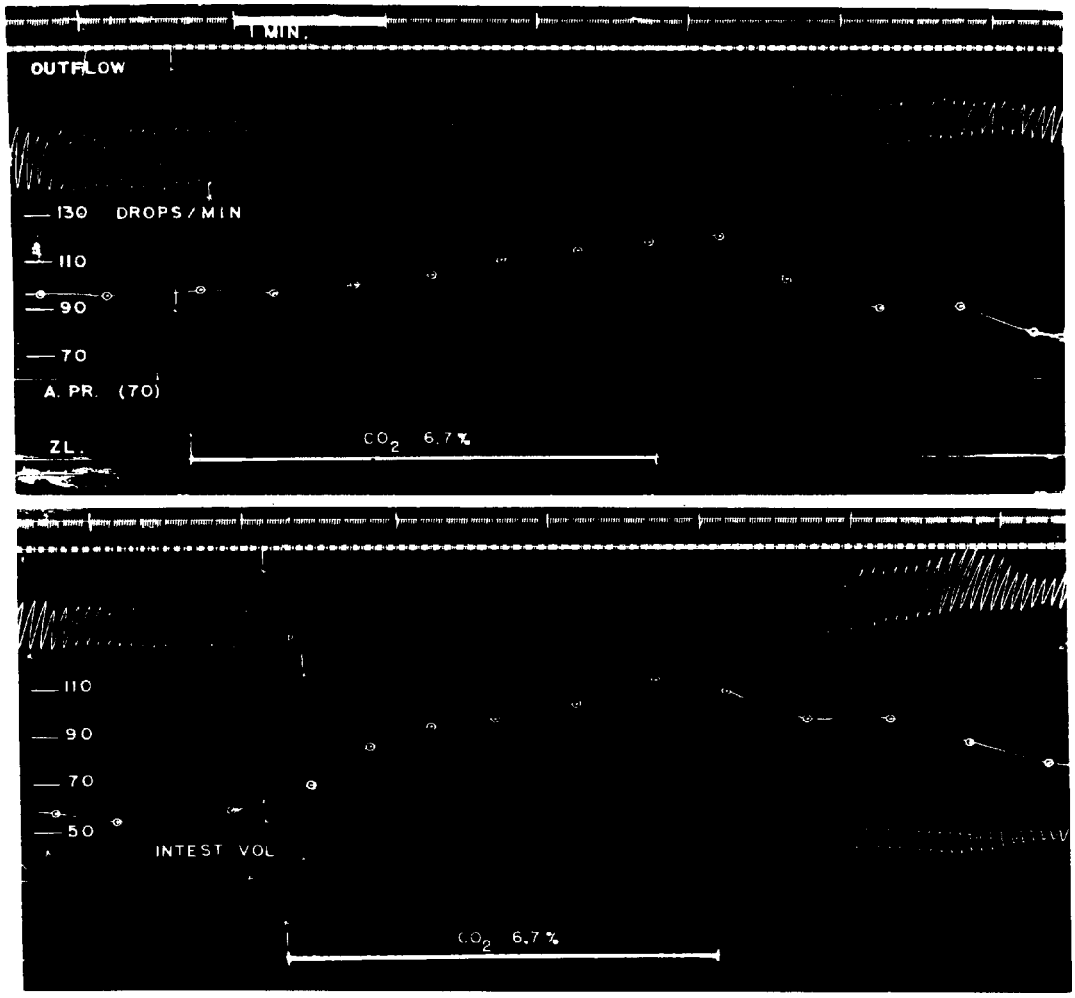


Figure 41. Illustrates effect of 6.7% CO_2 on intestinal blood flow. Tracings from above downward: time in minutes; venous outflow drops; intestinal contractions; venous outflow plotted in drops/minute; A.PR. arterial pressure; INTEST.VOL. changes in intestinal volume (not recorded in A); Z. L. zero line for arterial pressure. Simultaneous ordinates marked by X.

the blood flow was increased by about 30%. Neither the tonus nor the contractions of the gut was appreciably affected until toward the end of the hypercapnic period when the tonus rose slightly, whereas the increase in the flow had a very early

onset. This observation indicates that the increase in the flow represented an actual vasodilatation. Shifting back to "normal" blood caused a gradual diminuation of the blood outflow to a subnormal level and a marked rise in the gut tonus. The decrease in the blood flow to a sub-normal level was probably due to the rise of gut tonus. The second administration of CO_2 to this tissue (lower record) resulted in a more pronounced increase (100%) in the blood flow. In this record the intestinal tonus was slightly decreased initially. Changing to "normal" blood caused a gradual decrease of the blood flow to normal and simultaneously a gradual rise of the gut tonus similar to that shown in the upper record.

It is of interest to note in this figure (41) that although the magnitude of vasodilatation was evidently greater in the second CO_2 administration, the actual maximum value of the flow in both instances was nearly the same: 120 drops/minute in first procedure and 115 drops/minute in the second. This observation suggests that the magnitude of hypercapnic vasodilatation was, in part at least, conditioned by the vascular tone obtaining before the CO_2 was administered. Thus, in the first procedure it may be that the vascular tone was originally lower, and consequently the magnitude of vasodilatation under hypercapnia was less, than in the second procedure.

onset. This observation indicates that the increase in the flow represented an actual vasodilatation. Shifting back to "normal" blood caused a gradual diminuation of the blood outflow to a subnormal level and a marked rise in the gut tonus. The decrease in the blood flow to a sub-normal level was probably due to the rise of gut tonus. The second administration of CO_2 to this tissue (lower record) resulted in a more pronounced increase (100%) in the blood flow. In this record the intestinal tonus was slightly decreased initially. Changing to "normal" blood caused a gradual decrease of the blood flow to normal and simultaneously a gradual rise of the gut tonus similar to that shown in the upper record.

It is of interest to note in this figure (41) that although the magnitude of vasodilatation was evidently greater in the second CO_2 administration, the actual maximum value of the flow in both instances was nearly the same: 120 drops/minute in first procedure and 115 drops/minute in the second. This observation suggests that the magnitude of hypercapnic vasodilatation was, in part at least, conditioned by the vascular tone obtaining before the CO_2 was administered. Thus, in the first procedure it may be that the vascular tone was originally lower, and consequently the magnitude of vasodilatation under hypercapnia was less, than in the second procedure.

Higher concentrations of CO_2 caused greater vasodilatation. Thus, in fig. 42, a 10% CO_2 caused a marked reversible increase in the blood flow of about 100%, without

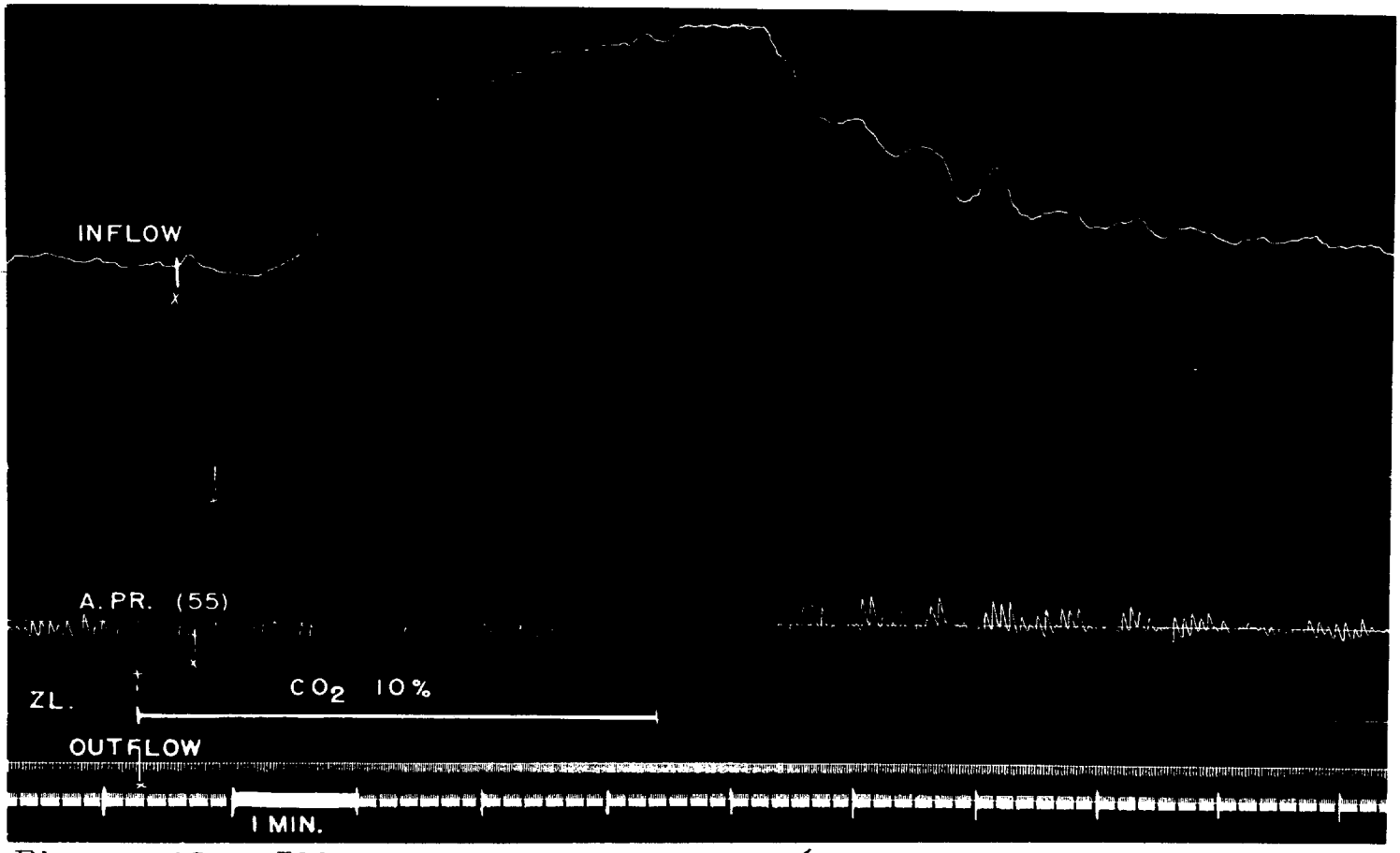


Figure 42. Illustrates effect of 10% CO_2 on intestinal blood flow. Tracings from above downward: arterial inflow recorded by thermopile; intestinal contractions from upper end of the loop; A.PR. arterial pressure; intestinal contractions from lower end of the loop; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

causing any significant change in the gut activity except for a very slight drop in tonus. It is of interest, however, that here, CO_2 had a distinct after-effect on the gut activity which consisted of a distinct increase in the rhythmic contractions and a slight rise in tonus. This increase in blood

flow under hypercapnia must obviously be due to a vasodilator action of CO_2.

The results shown in fig. 43 demonstrate a reversible vasodilator action of 15% CO_2. Here, again the gut activity or tonus was not significantly affected.

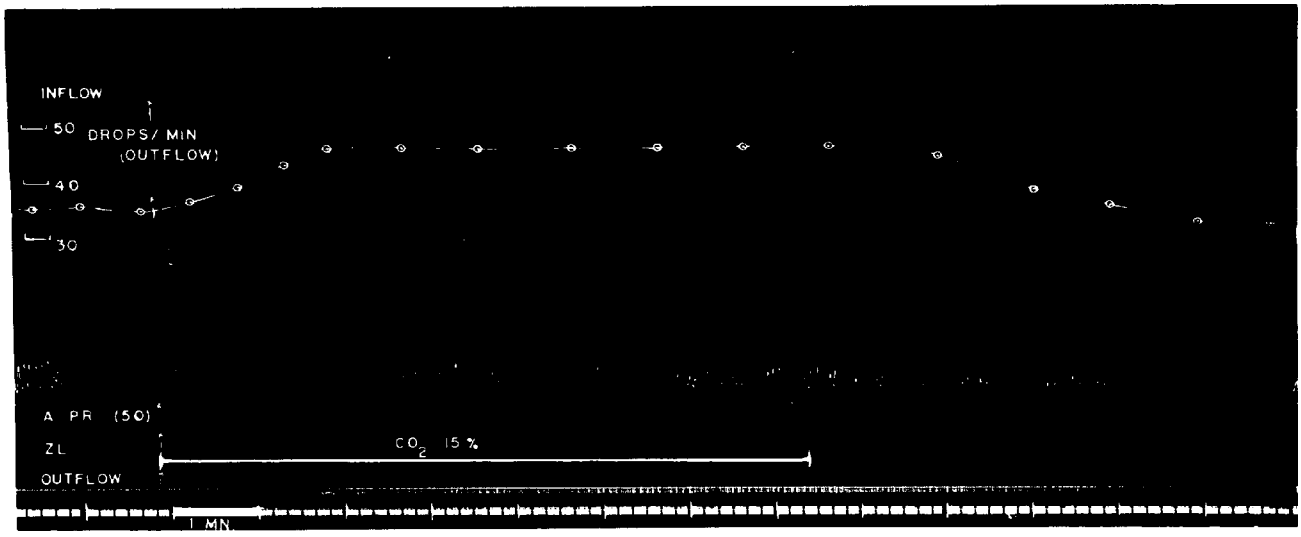


Figure 43. Illustrates effect of 15% CO_2 on intestinal blood flow. Tracings from above downward: arterial inflow recorded by thermopile; venous outflow plotted in drops per minute; intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; ZL. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

A typical vasodilator effect of CO_2 (15%) is also shown in fig. 44 A, but in this case, the well marked and sustained increase in the blood flow (for four minutes) was followed by a secondary diminution to below the pre-hypercapnic level. This secondary decrease may be interpreted as due to a secondary vasoconstriction. In part B of the figure, representing another 15% CO_2 administration

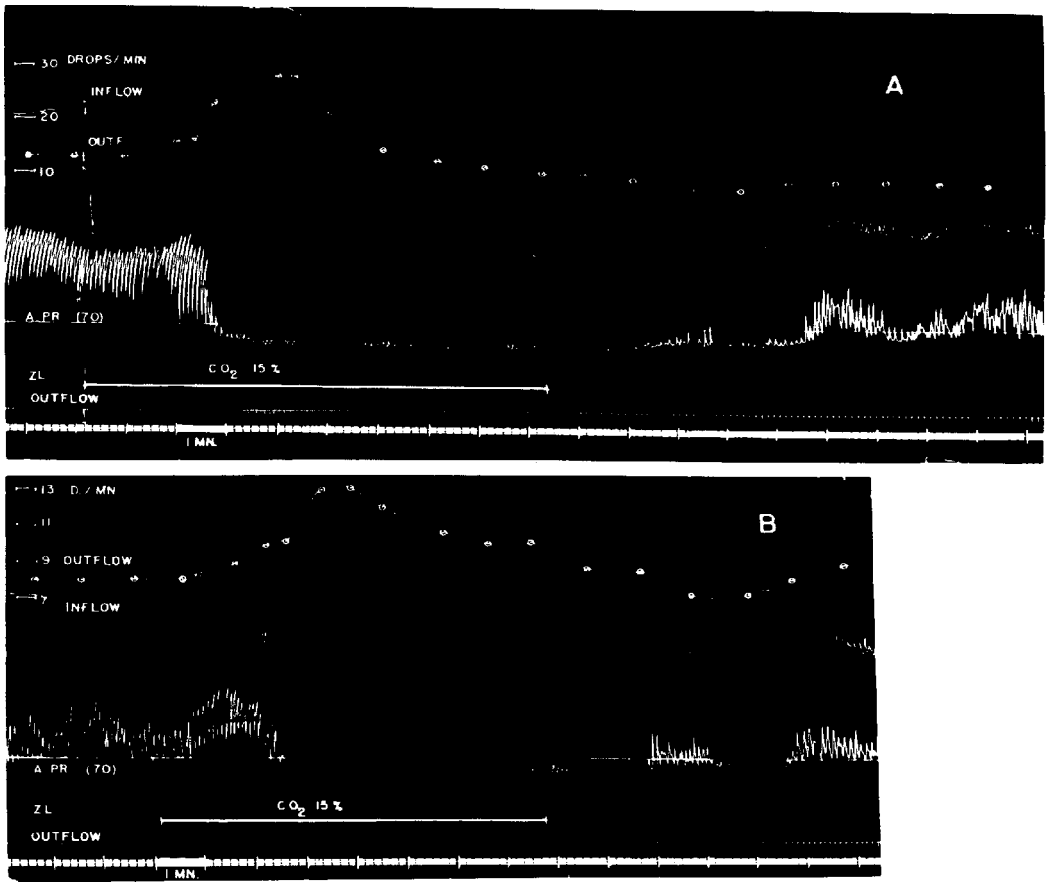


Figure 44. Illustrates effect of 15% CO_2 on intestinal blood flow. Tracings from above downward: in A: arterial inflow recorded by thermopile, venous outflow plotted in drops per minute; in B: venous outflow curve is plotted above arterial thermopile tracing; intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X in A. Both A and B on same tissue.

to the same tissue, a similar vascular reaction was observed, but in this instance the secondary vasoconstriction was not strong enough to cause a subnormal flow so that the secondary decrease may simply represent an adaptation of the tissue to the increased CO_2 rather than an active vasoconstrictive

response. In both parts of the figure, the gut underwent a remarkable drop in tonus accompanied by great depression of rhythmic contractions.

(b) Effect of acapnic blood: In the experiments performed to demonstrate the effect of acapnia on the intestinal blood flow, the acapnic blood was prepared by equilibration with 30% O_2 and 70% N_2 and no CO_2. The vascular effect of such acapnic blood is demonstrated in fig. 45. In the upper part

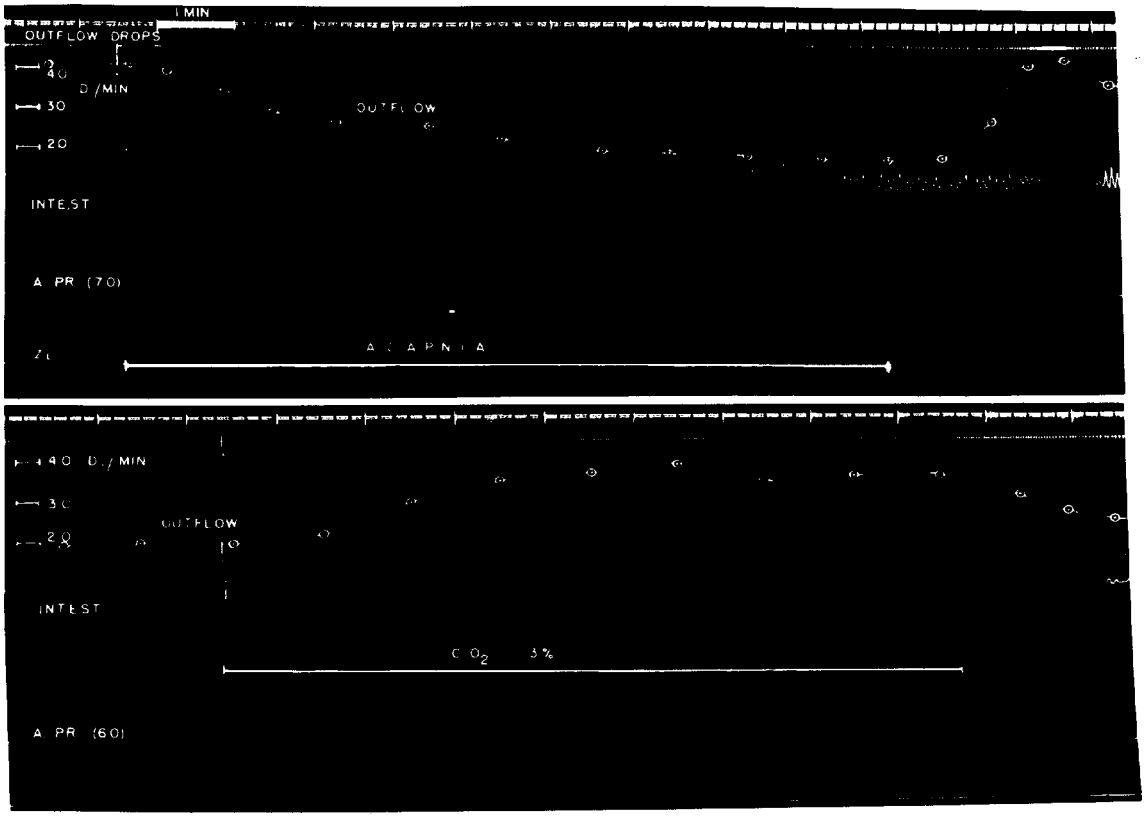


Figure 45. Illustrates effect of acapnic blood on intestinal blood flow. Tracing from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; INTEST. intestinal contractions; A.PR. arterial pressure; ZL. zero line for arterial pressure. Simultaneous ordinates marked by X. In lower record perfusion was shifted from acapnic blood to one containing 3% CO_2, then returned to acapnic blood.

of this figure, a shift from "normal" to the acapnic blood caused a marked decrease of the blood flow to about half the normal value; this reaction was reversed upon reperfusion with "normal" blood. The lower part of the figure represents the effects of shifting from an acapnic blood to blood containing 3% CO_2; this caused about 100% increase in the blood flow, and readministration of acapnic blood reversed the picture and decreased the blood flow to the original pre-CO_2-administration level. In both procedures shown in this figure (45), it is evident that the decrease of blood flow under acapnia was not due to any change in the gut activity or tonus since these remained unaltered during each of the entire procedures; this diminution of the flow must, therefore, represent an active vasoconstrictor effect of acapnia.

To supplement the experimental study of the local effects of CO_2 on the blood flow through the isolated loop of small intestine, some experiments were carried out to determine what influence this gas, acting centrally and reflexly, might have on this vascular bed. In these experiments, the loop with its nervous connections to the C.N.S. intact, was perfused 'in situ'. The trachea of the anesthetized animal was connected to a spirometer and respiratory tanks which permitted rapid shift of the animals breathing from normal to the desired CO_2 and O_2 gas mixtures, the intestinal loop being perfused with "normal" blood under a

constant pressure throughout the procedure.

The results of shifting from "normal" to a 10% CO_2 in breathing gas mixture, with the animal breathing spontaneously, are shown in fig. 46 B. Here, after a relatively long latent period of about 2 minutes, there occurred a gradual decrease in the blood flow of about 20%. The fact that the gut remained relatively quiescent throughout the CO_2 administration excludes the possibility that the diminished flow might have

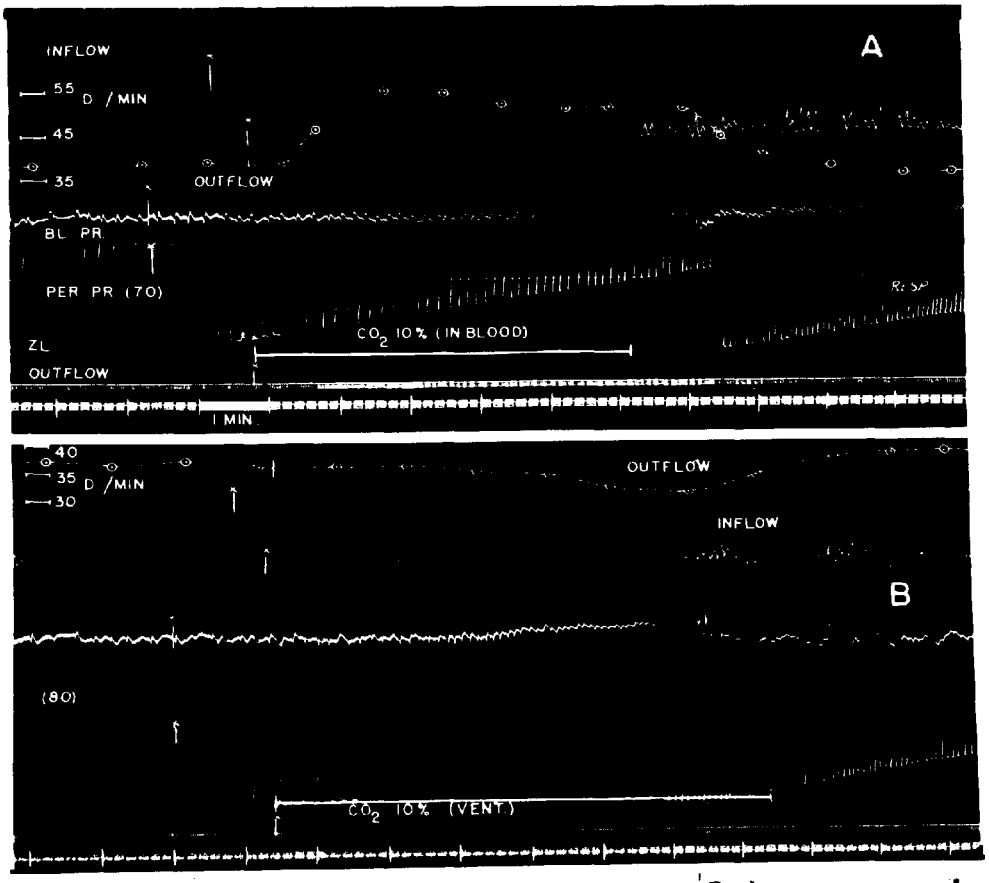


Figure 46. A: Illustrates influence of hypercapnic perfusion blood (10% CO_2) on blood flow through loop completely isolated except for its nervous connections to C.N.S. B: Illustrates influence of administration of 10% CO_2 in respiratory gas mixture on blood flow through same loop, perfused with "normal" blood. Tracings from above downward: A: arterial inflow recorded by thermopile; venous outflow plotted in drops per minute; intestinal contractions; BL.PR. animals blood pressure; RESP. respiration; PER.PR. perfusion pressure; ZL. zero line for animals arterial and perfusion pressures; venous outflow drops; time in minutes. B: venous outflow plotted in drops per minute; arterial inflow; intestinal contractions; other tracings as in A. Simultaneous ordinates marked by X.

been due to change in the motor activity or tonus; this diminution must, therefore, be attributed to an active vasoconstriction. The usual effects of hypercapnic ventilation, hypernea and rise of general blood pressure, can also be seen in this figure. Readministration of normal gas mixture led to a gradual recovery (increase) of the blood flow to a slightly supra-normal level, and the general blood pressure returned to normal.

The decrease of the blood flow during hypercapnic ventilation, coupled with the rise of the general blood pressure, indicate that such effects are due to vasoconstriction, at least in the intestinal vascular area; such vasoconstriction must be of a central origin induced by excess CO_2 acting directly on vasomotor centers in the brain and reflexly on the chemoceptors in the carotid and aortic bodies.

For purposes of comparison, the same loop in situ with nerves intact, was subjected to the direct action of 10% CO_2 administered locally to the tissue in the perfusion blood. The results of such procedure are shown in part A of figure 46 where it is seen that the hypercapnic blood produced a local vasodilatation typical of that shown in the isolated loops.

Discussion:

The importance of the CO_2 content of blood as an effective factor for the regulation of peripheral circulation

has been recognized by most workers. However, in spite of the fact that extensive experimental investigation has been carried out in this connection, there is still disagreement about the direct effect of CO_2 on the vascular tone and about the exact nature of such effect. Thus, while the majority of authors: Bayliss (1901), Hooker (1912), Dale and Evans (1922), Fleisch (1932) and others, believe that excess CO_2 in the blood of the intact animal causes vasodilatation by a local action on the peripheral blood vessels and that a decrease of CO_2 causes direct vasoconstriction, some workers: Bernthal (1937), Mercker (1943), and others have obtained opposite results, i.e. local vasoconstriction with excess CO_2 and vasodilatation with decreased CO_2. As for the central and reflex effect of CO_2 on the blood vessels, there is general agreement that an excess CO_2, acting on the vasomotor center and the chemoreceptors of the carotid and aortic bodies, leads to central and reflex peripheral vasoconstriction.

Bayliss (1901) observed an increased flow in the hind legs of frog perfused with Ringer's solution saturated with CO_2 above "normal". Hooker (1912) found that an excess CO_2 caused a loss of tone of venous and arterial strips with recovery under O_2. Dale and Evans (1922) concluded that the fall of arterial pressure subsequent to washing out of CO_2 by overventilation of the intact animal, was due to depression of the normal activity of the vasomotor centers in the medulla and spinal cord. Destruction of these centers caused reversal

of the effect of overventilation, i.e. increase of arterial pressure, which they attributed to a direct vasoconstrictor action of loss of CO_2 (hypocapnia) on the peripheral vessels. McDowall (1930) attributed the fall of arterial pressure during overventilation to a central vasodilator action of low CO_2 overbalancing its direct or peripheral vasoconstrictive action. He stated, "Just as the capillaries are dilated by the CO_2 and the center is stimulated, so the opposite may occur if CO_2 is washed out." This view was also supported by experiments of Collier and Dudham and Wells (1927). Fleisch and Ponomarev (1932) carried out perfusion experiments on the innervated and denervated hind limbs of cats, and found that excess CO_2 in the blood caused, in most instances, a combination of primary constriction and secondary stronger dilatation; occasionally there occurred pure vasodilatation but rarely pure vasoconstriction. These authors emphasized that for a vasodilator action of excess CO_2 to occur, the blood vessels should still retain their tonus; they also specified that the vasodilator action is not due to any specific ation of CO_2 but is attributed to the increased acidity produced by excess CO_2. Krogh (1922), by microscopic observations on the blood vessels of frog's tongue, found that bubbling a gas mixture containing at least 10% CO_2 in the fluid bathing the tissue produced a vasodilator effect.

In contrast to the above findings, the work of Bernthal and Shoemaker (1937) and Mercker (1943) led them to conclude

that excess CO_2 has a local vasoconstrictive action. Bernthal's work (1937) on the perfused dog's foreleg showed that in most cases excess CO_2 concentration in blood decreased the blood flow, whereas in only a few cases it caused an increase. The experimental results of Mercker and co-workers (1943), obtained on perfused hing limbs of cats, conformed largely with those of Bernthal. These workers also emphasized that the vascular reactions were dependent on the presence of a vascular tone; absence of the vascular tone, as occurred immediately following denervation, led to opposite reactions (increase in flow) which they regarded as passive to the changes in the general blood pressure consequent upon the general hypercapnia.

With regard to the effect of CO_2 on the vascular bed of the splanchnic area, particularly that of the small intestine, the work of Mathison (1911) and that of Bernthal (1930) shows the variability of the experimental results. Mathison found that when an animal breathed an air mixture containing 10% CO_2, with an adequate percentage of oxygen, the arterial blood pressure rose immediately and the intestinal volume (plethysmographically recorded) fell. He attributed this fall of the intestinal volume and the rise of arterial pressure to a general vasoconstriction induced centrally by hypercapnia. Bernthal, on the other hand, observed an increase of blood flow through the superior mesenteric artery during CO_2 breathing, and that this reaction was not altered

by denervation of the splanchnic area. The same author obtained variable results when he measured the blood flow through the abdominal aorta after tying off the main arteries of the lower extremity; accordingly he did not draw any definite conclusions from his observations on the superior mesenteric arterial flow. In the light of our experimental evidence presented above, concerning the intimate relationship between the motility of the small intestine and its blood flow, the variability of Bernthal's results may be attributed to changes in the motor activity of the gastro-intestinal tract.

The intimate nature of the action of CO_2 has been a subject of debate for many years. According to the widely accepted view, CO_2 is believed to act through its acid properties. However, some authors believe that CO_2 acts in specific manner independent of any associated changes in the hydrogen ion concentration.

So far as the local effects of CO_2 on the intestinal vascular bed are concerned, our experimental results unequivocally support the view that excess CO_2 causes local vasodilatation in the intestinal vascular bed, whereas lack of CO_2 causes local vasoconstriction. Our findings also demonstrated that excess CO_2, acting centrally or through reflexes e.g. carotid and aortic chemoreceptors, causes constriction of the intestinal blood vessels. The results of these experiments and the conclusions derived therefrom may be

summarized as follows:

a) In almost all instances, perfusion of the loop with hypercapnic blood, in equilibrium with gas mixtures containing from 6.7% to 15% CO_2 ("normal" CO_2 4%), caused a well pronounced reversible increase of the blood flow; the magnitude of such increase varied from a low of 30% to a high of 400%.

b) The fact that the intestinal loop was completely isolated from the animal excludes any possibility that these effects on flow and contraction might have been due to influences of central or reflex origin, or of circulating humoral agents; they must therefore be attributed to the local action of CO_2.

c) Lack of CO_2 (acapnia) in the perfusion blood caused definite decrease in the blood flow.

d) Administration of high CO_2 tensions in the respiratory gas mixtures to the intact animal caused a definite diminution in the blood flow through the loop in situ but with the nerve supply intact. Since the loop was entirely isolated from the general circulation and attached only by its extrinsic nerves, the diminution of the blood flow must be attributed to a vasoconstriction induced centrally or reflexly by hypercapnia in the general blood circulation.

(2) Effect of CO_2 on Intestinal Motility

In the majority of cases, variations in the CO_2 content in the perfusion blood led to definite reactions in the

movements of the intestinal loop. Thus, as is shown in fig. 44, 15% CO_2 in the perfused blood caused a precipitous drop of tonus and an almost complete stoppage of rhythmic contractions; readministration of normal blood led to gradual and slow recovery of movements and tonus.

Similar reactions of the intestinal motility were also observed upon perfusion with blood containing 10% and 12% CO_2, as shown in figures 47 and 48 respectively. In these figures, the motor response of the loop to hypercapnia consisted of a marked decrease in the amplitude of the rhythmic

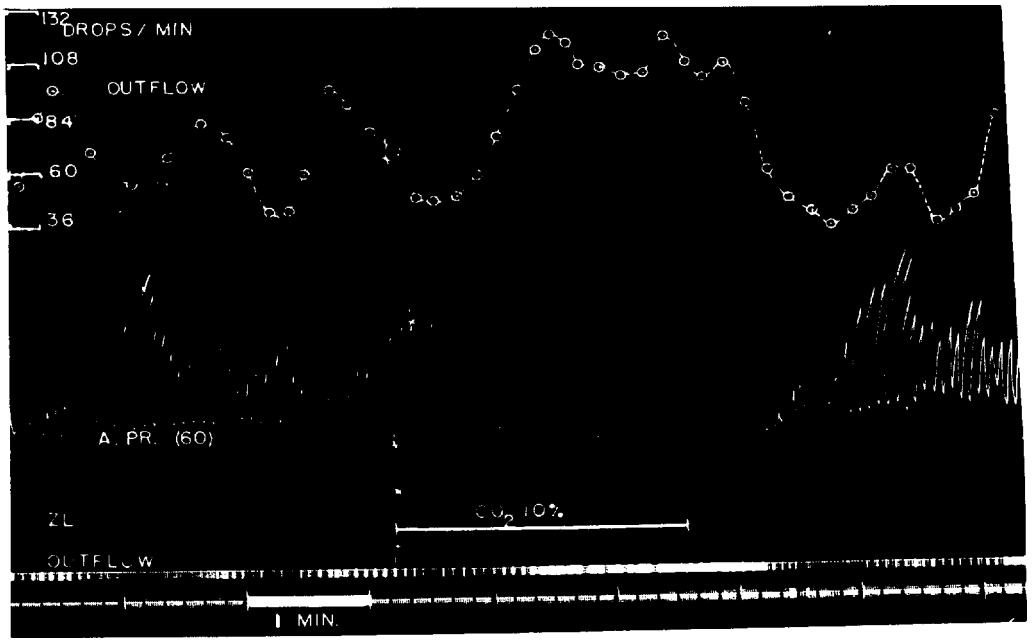


Figure 47. Illustrates effect of 10% CO_2 on intestinal motility and blood flow. Tracings from above downward: venous outflow plotted in drops per minute; intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

contractions and a definite drop of tonus; the figures also show typical reversible vasodilator action of CO_2. Complete recovery of the intestinal activity and blood flow was observed upon shifting back to "normal" blood.

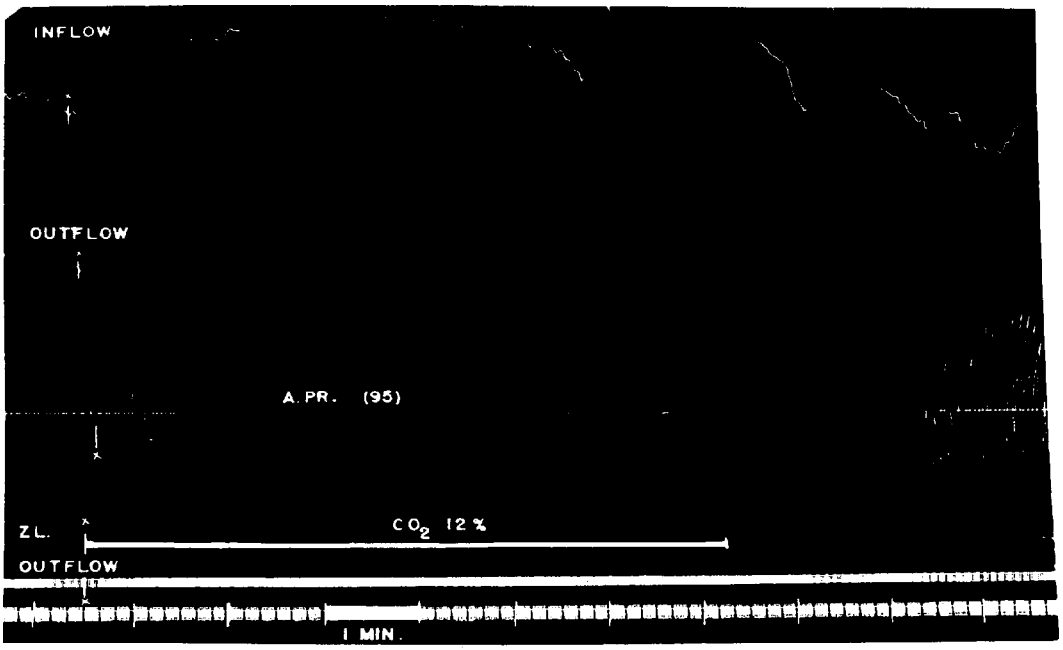


Figure 48. Illustrates effect of 12% CO_2 on intestinal motility. Tracings from above downward: arterial inflow and venous outflow recorded by thermopile; A.PR. arterial pressure; intestinal contractions; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

However, while the above figures represent the typical and most frequent motor reactions during hypercapnia, another type of response occasionally elicited is shown in fig. 49. Here, a 10% CO_2 caused an initial temporary stimulation of both tonus and rhythmic activity of the loop followed by almost complete quiescence which lasted for the remainder of the hypercapnic period. Readministration of normal blood led to gradual increase in the amplitude of the rhythmic

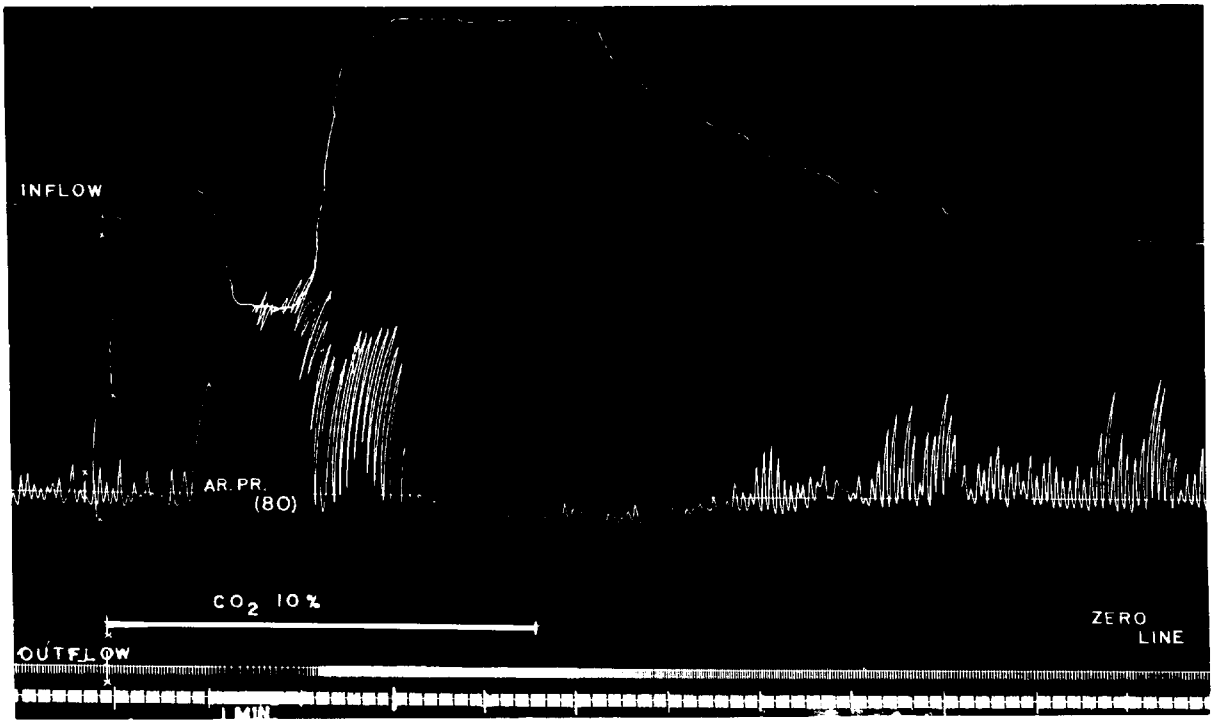


Figure 49. Illustrates effect of 10% CO_2 on intestinal motility. Tracings from above downward: arterial inflow recorded by thermopile; intestinal contractions from upper and lower ends of the loop; A.PR. arterial pressure; zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

contractions to a level higher than that obtaining before hypercapnia. Three other features worthy of special note are shown in this figure: (1) the increase in blood flow induced by CO_2 occurred before the motor response of increased tonus, (2) the sharp rise of the gut tonus temporarily decreased the blood flow to well below normal, and (3) the flow rose abruptly far above normal with the decrease of tonus and temporary augmentation of the rhythmic contractions, and remained high after the gut had become quiescent. Gradual return of flow to normal occurred after cessation of the

CO_2 administration. The sharp decrease in blood flow induced by the tonic contraction, notwithstanding the vasodilator action of CO_2, is of particular interest since it may explain some of the variable results obtained, and commented upon, by various investigators in their measurement of intestinal blood flow in the intact animal subjected to high CO_2 (Bernthal, 1930).

Still another less frequent type of intestinal motor reaction to hypercapnia is shown in fig. 50. In this figure,

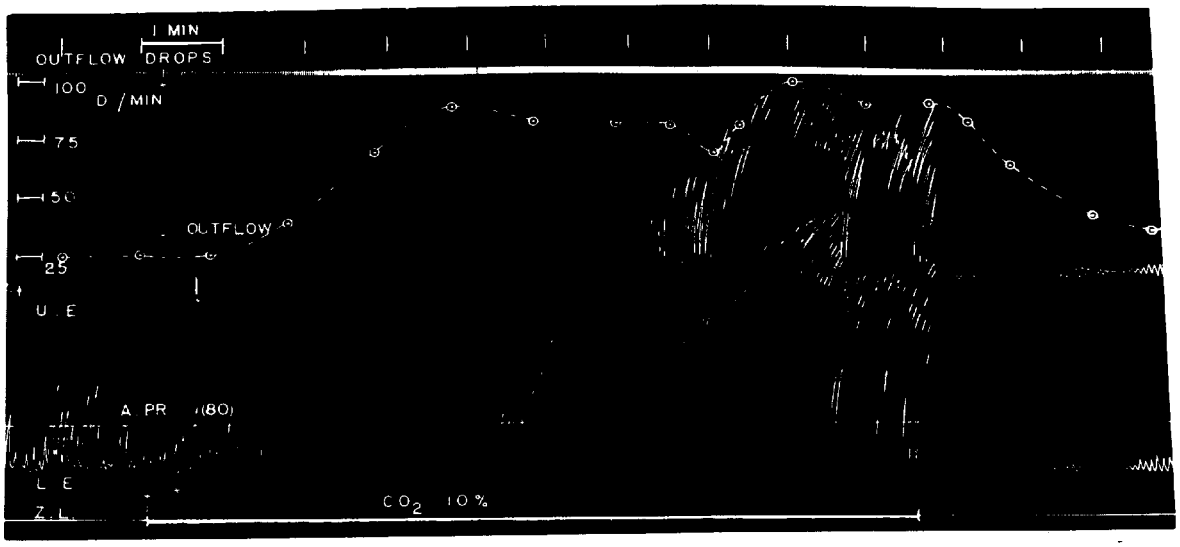


Figure 50. Illustrates effect of 10% CO_2 on intestinal motility. Tracings from above downward: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; U.E. intestinal contractions from upper end of the loop; A.PR. arterial pressure; L.E. intestinal contractions from lower end of the loop; Z. L. zero line. Simultaneous ordinates marked by X.

a 10% CO_2 caused an initial slight drop of tonus and cessation of the rhythmic movements, followed by a sharp increase in tonus and contractions. This state of increased gut activity was maintained for a relatively long period, but eventually came to an abrupt end with a drop of tonus and complete quiescence of the gut just before cessation of CO_2 administration. In spite of the marked rise in tonus, the CO_2 caused a considerable increase in the blood flow of about 400%. The fact that such high tonus did not significantly interfere with the flow (as it did in fig. 49) may be due to a less generalized tonic contraction, i.e. limited to only a part of the loop, while the rest of the tissue was relaxed, thus allowing a free flow of blood. Shifting to "normal" blood led to gradual restoration of pre-hypercapnic conditions.

Discussion:

The experimental results, described above indicate that the CO_2 content of arterial blood influences appreciably the motor activity of the small intestine. This has been recognized since the early work of Van Braam Hoockgeest (1872) who observed a peculiarly violent form of peristalsis in rabbits killed by asphyxia. It was Bokai (1885) who first studied the direct effect of CO_2 on intestinal movements; he found that violent peristalsis could be set up by injecting CO_2 in the intestinal lumen. Bottazzi (1897) also observed the direct action of CO_2 and stated that the action

of this gas caused a contraction of the longitudinal muscles of the frog's esophagus which continued as long as the tissue was exposed to the action of the gas. More recently Hooker (1912) studied the effects of CO_2 on strips of intestinal wall of cold and warm-blooded animals. He found that bubbling a gas mixture containing excess CO_2 (5%) in the bath fluid caused a dual action: quiescent preparations were activated to contract, whereas rhythmically active strips were inhibited and their tone depressed. Gunn and Underhill (1914) also obtained results similar to those of Hooker, i.e. excess CO_2 had a dual action. Young (1914), however, failed to observe any local stimulatory action of CO_2 on isolated strips of cats' small intestine; he found that under CO_2 the segmental movements were inhibited and the tone was reduced. He also found that recovery occurred after removal of CO_2, provided the period of exposure was not too long; long exposures (15 minutes) caused permanent damages to the tissue with no recovery. Fraser (1925) carried out experiments in which he studied the effect of CO_2 and acids on isolated small intestine (rabbit) and found that, in the presence of CO_2, the rhythmic contractions were nearly always suppressed at a pH of 6.4, whereas in absence of CO_2 much greater acidity (pH 5.4 or less) was required to produce a similar effect. He also observed that recovery from CO_2, as indicated by the height, rate and form of the rhythmic contractions, was complete while recovery from acidity not due to CO_2 was

much less complete. From this he concluded that CO_2 acts on the intestinal tissue in a specific manner due to a faster rate of penetration through the cell membranes than the hydrogen ions.

Our experimental results indicate that excess CO_2 in the perfusion blood has a predominantly inhibitory action on the intestinal movements and tonus. It has also been observed that, not infrequently, this inhibitory action was preceded by a transient stimulation of both rhythmic contractions and tonus. As to whether CO_2 has a dual action (Hooker, Gunn and Underhill) our observations do not permit any definite conclusions since it was only in a few cases that excess CO_2 activated an almost quiescent gut (fig. 50); furthermore, in these cases a conspicuous initial temporary inhibition was observed.

In the present study, the recovery of the tissue after cessation of hypercapnic perfusion was in the majority of instances complete. The absence of evidence of permanent injury of the tissue may have been due to the relatively short periods (3-7 minutes) of exposure to excess CO_2. The rate of recovery varied from tissue to tissue and also from procedure to another on the same tissue.

The manner in which CO_2 exerts its effect on the intestinal tissue is, as already pointed out in relation to the vascular effects, still a matter of debate. Here again, the CO_2 is believed to act through the change in the

hydrogen ion concentration; however it may possess a specific action independent of such acidity changes.

II EFFECT OF LOW OXYGEN TENSIONS IN ARTERIAL BLOOD

In the experiments carried out to determine the effects of low O_2, the same methods were employed as those already described for CO_2, the perfusion blood being equilibrated with a gas mixture of the desired composition. Low O_2, in concentrations of 7%, 10% and 12% in the equilibrating gas mixture was employed, in comparison to "normal" concentration of 30% (CO_2 concentration kept at 4%).

Effect of Low Oxygen on Intestinal Blood Flow:

Typical effects of shifting from "normal" to hypo-oxic blood (10% O_2) are shown in fig. 51. In both parts A and B of the record, the hypo-oxic blood caused an increase in the blood flow of about 25% and 30% above the normal level respectively; this effect was reversed by a return to normal blood. In these procedures, A and B, performed in two different experiments, the gut activity and tonus were not significantly altered by the low O_2 except for a slight drop of tonus in part B. The resultant increase of blood flow must, therefore, be attributed to an active vasodilatation induced by the low O_2.

The effect on blood flow of a more severe hypo-oxic blood is shown in fig. 52. In this figure, perfusion with 7% O_2 caused a well pronounced and reversible increase

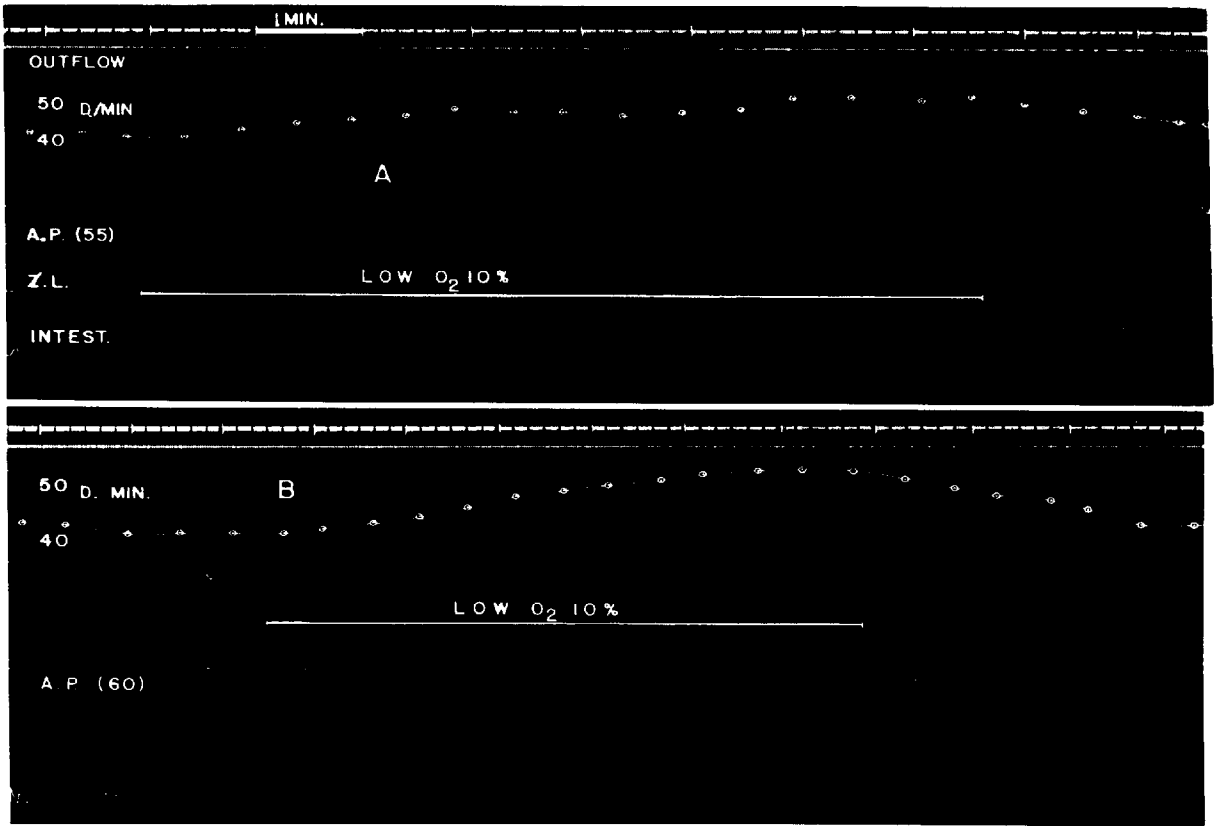


Figure 51. Illustrates effect of low O_2 (10%) on intestinal blood flow. Tracings from above downward: A: time in minutes; venous outflow drops; venous outflow plotted in drops per minute; intestinal contractions from upper end of loop; A. P. arterial pressure; Z.L. zero line showing period of low O_2 administration (heavy line); INTEST. intestinal contractions from lower end of loop. B: time in minutes, venous outflow drops; signal line; venous outflow plotted in drops per minute; arterial inflow by thermopile; heavy line indicating period of low O_2 administration; intestinal contractions; A.P. arterial pressure.

(about 110%) in the blood flow. Here, as in fig. 51, hypo-oxia did not alter the motor activity or tonus of the gut, which observation indicates again that the increased flow under hypo-oxia represents an actual vasodilatation.

Since the above results were obtained on the isolated loop, the well pronounced vasodilatation can only be due

to a local action of low O_2. Such a local vasodilator action was also obtained during perfusion of a loop which was completely isolated except for its nervous connections.

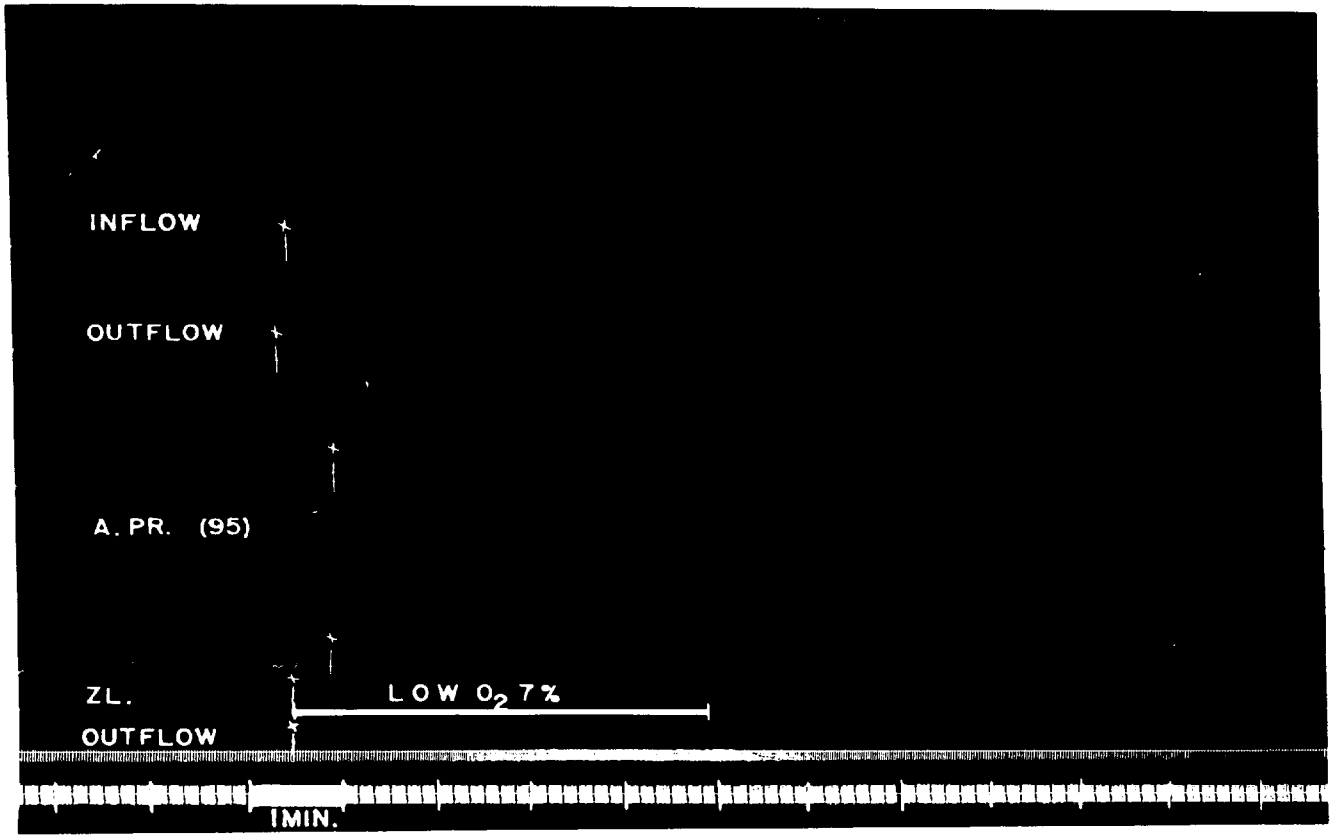


Figure 52. Illustrates influence of 7% O_2 on intestinal blood flow. Tracings from above downward: arterial inflow and venous outflow recorded by the thermopile; intestinal contractions from upper end of the loop; A.PR. arterial pressure; intestinal contractions from lower end of the loop; Z.L. zero line; venous outflow drops, time in minutes. Simultaneous ordinates marked by X.

Thus, in fig. 53, perfusion of the loop 'in situ' with 7% O_2 caused a sharp reversible increase in both the inflow and outflow of blood without any significant changes in the gut activity or tonus.

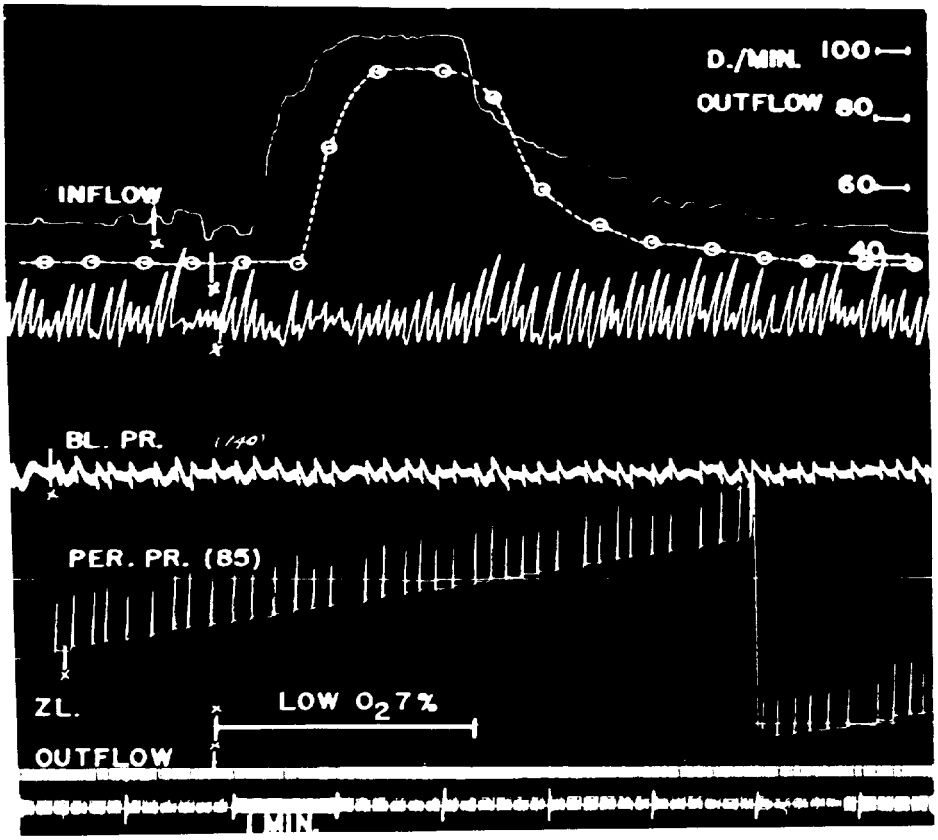


Figure 53. Illustrates effect of low O_2 in perfusion blood on blood flow in a completely isolated loop except for its nerve connections to the C.N.S.; animal breathing room air. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops/min.; intestinal contractions; BL.PR. animal's blood pressure (140 mm. Hg); PER.PR. perfusion pressure; respirations; Z.L. zero line for both BL.PR. and PER.PR.; venous outflow drops; time in minutes. Simultaneous ordinates marked by X.

The fact that the vascular response in fig. 53 was similar to that obtained in the completely isolated loop (figures 51 and 52), indicates that the local vasodilator effect of low O_2 predominates and masks any vasoconstrictive reflexes which, under these experimental conditions might be elicited from the loop.

In order to determine the central and reflex vascular effects of low oxygen, mediated through the extrinsic nerves

to the loop, the following experiment was performed. The loop, with its nervous connections intact, was perfused 'in situ' with "normal" blood and the central and reflex stimulation was provided by mechanical asphyxiation of the animal (by closure of trachea). The results of such procedure are shown in fig. 54. In both parts A and B of this figure, mechanical asphyxiation for a period of two minutes

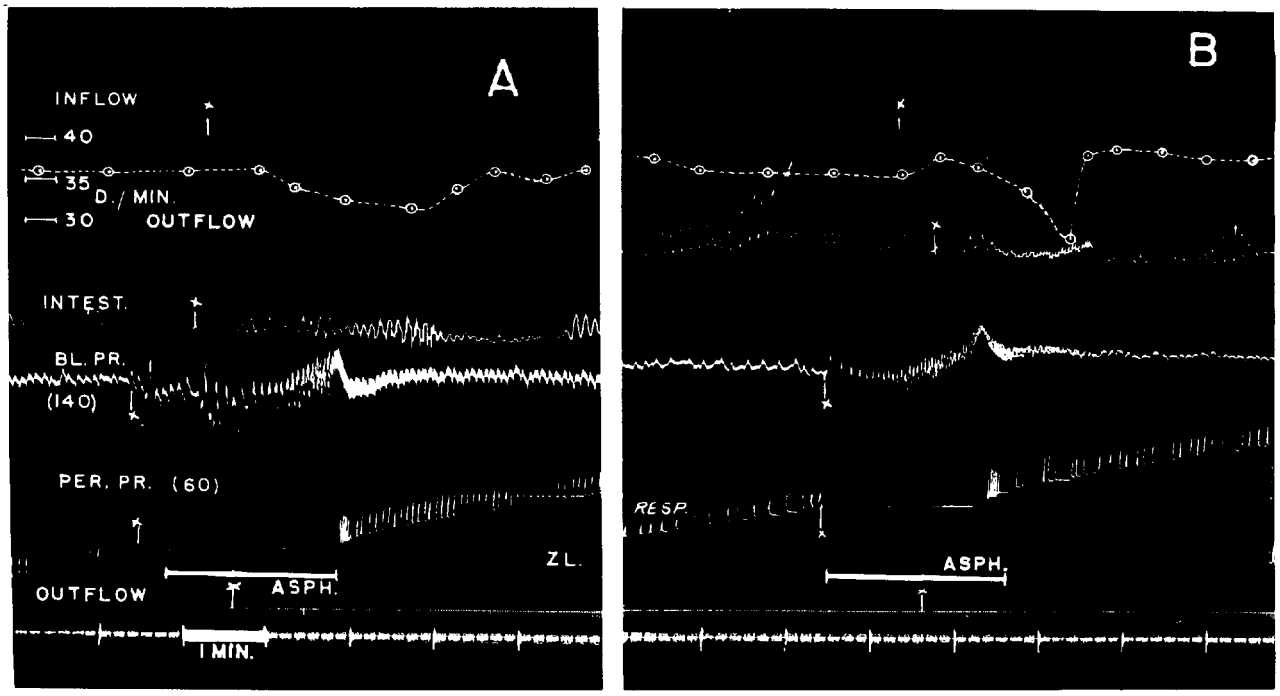


Figure 54. Illustrates influence of mechanical asphyxia on blood flow in intestinal loop perfused "in situ" with normal blood. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops/min.; INTEST. intestinal contractions; BL.PR. animal's blood pressure; PER.PR. perfusion pressure; RESP. respirations; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Periods of mechanical asphyxiation (ASPH.) shown on zero line.

caused a well pronounced decrease in the blood flow through the loop; in B this diminution of the flow was preceded by a slight increase. During asphyxia the animal's general blood pressure showed an initial slight decrease then gradually rose to above normal; the gut activity and tonus, however, were not significantly affected. With the termination of asphyxia the blood flow through the loop returned promptly to normal without any significant after-effects, and the animal's blood pressure decreased to about the pre-asphyxial level.

It is evident from this figure that these changes in the intestinal blood flow cannot be ascribed to changes in the intestinal activity or tonus, nor can they be attributed to a direct effect of the changes either in the animal's blood pressure or in general circulation. They must, therefore, be of central or reflex origin and mediated through the extrinsic nerves to the loop. The predominant decrease in the blood flow in the loop, as well as the rise of the general blood pressure during asphyxia, are attributed to a generalized vasoconstriction resulting from stimulation of the vasomotor center and probably by reflex stimulation of the chemoreceptors of the carotid and aortic bodies. The initial slight increase in the flow seen in fig. 54 B, together with the concomitant initial small drop in the general blood pressure, suggest the occurence of an initial active vasodilatation of central or reflex origin.

While the major contributing factor to the occurrence of these asphyxial effects is due primarily to reduction in the arterial oxygen tension, the participation of other agents, e.g. excess CO_2, is not denied.

The experimental results presented thus far indicate that reduction in the arterial O_2 tension (anoxic anoxia) has a dual action on the intestinal vascular bed: (1) a local vasodilator effect, (2) a central or reflex vasoconstrictor effect.

In an attempt to determine the influence of histotoxic anoxia, i.e., poisoning of the oxidative processes in the tissue, on the intestinal blood flow a cyanide solution was administered to the loop by injecting the cyanide into the arterial inflow tube with a hypodermic needle. The effects of injecting 0.3 cc. of a 1% solution of KCN are shown in fig. 55. In this figure, the cyanide caused a sharp increase (about 300%) in the blood flow without any significant change in the gut activity or tonus. The augmented flow then gave way to a gradual decrease until the normal level was attained. This distinct local vasodilator action of histotoxic anoxia resembled greatly that induced by hypo-oxic blood already described. To further illustrate the similarity between the two effects, the same tissue to which cyanide was administered (fig. 55 A) was subjected to the local action of hypo-oxic blood of 7% O_2; the results are shown in part B of the figure. A comparison of the blood flow curves in

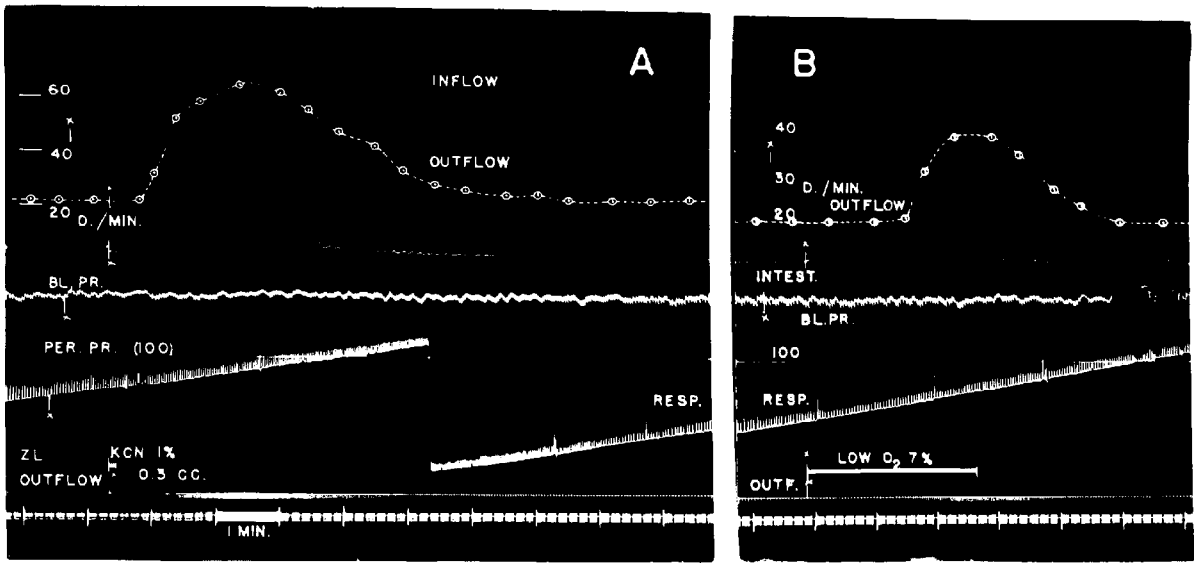


Figure 55. Illustrates influence of KCN (A) and 7% O_2 (B) on blood flow through perfused loop completely isolated except for nerve connection. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops per minute; intestinal contractions; BL.PR. animal's blood pressure; PER.PR. perfusion pressure; RESP. respirations; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Temporary drop in arterial inflow tracing upon cyanide administration is due to injection artefact.

both parts A and B shows the marked similarity between these curves with the exceptions of the greater area of those in A. This difference in the magnitude of the vasodilatation may be attributed to a stronger and more prolonged effect of the histotoxic anoxia.

Further, anoxia induced by arterial occlusion as already described, also has a vasodilator effect as indicated by the post-occlusion supra-normal flow (fig. 26).

Discussion:

The effects of low arterial oxygen tensions on the

peripheral blood vessels have been investigated by many workers. According to the generally accepted view, low O_2 has a dual effect: (1) a local vasodilator effect and (2) a central and reflex vasoconstrictor effect. Thus, Fleisch and co-workers (1932) obtained a local dilator action of low arterial oxygen on the vascular bed in perfused hind extremities of cats. These workers stated that reduction of O_2 concentration in the equilibrating gas mixtures to values above 6% were without effect, but reduction to lower concentrations caused definite vasodilatation. Our findings on the perfused intestinal loops, however, indicate that perfusion with hypo-oxic blood in concentrations as high as 10% caused distinct vasodilatation (fig. 51). Hilton and Eichholtz (1925) found that a fall of oxygen saturation of hemoglobin below 20% produced a maximum dilatation of the blood vessels, whereby the blood flow increased about five fold.

Bernthal (1930) measured the blood flow in the superior mesenteric artery (in dogs) and found that this flow decreased during hypo-oxic ventilation; denervation of the area supplied by the artery caused reversal of the effect on the blood flow. He attributed the decrease in flow in the innervated area to a central vasoconstrictor action of low O_2, and the increase after denervation to a predominant local vasodilation. Mathison (1910) had previously obtained similar results in his plethysmographic determinations of the intestinal volume. In his experiments, ventilation of the

animal with pure nitrogen caused a marked rise in the blood pressure with an attendant decrease in the volume of the intestine which he interpreted as indicative of generalized vasoconstriction of central origin. Both authors, however, did not take into consideration the humoral influences involved in such experiments, or the effects of the motor activity of the small intestine on the blood flow through the tissue.

With regard to the manner in which the local vascular action of low O_2 is brought about, several explanations have been advanced. According to the common belief, such local vasodilatation is attributed primarily to the anoxia of the tissue itself which leads to the disturbance of the normal aerobic oxidative processes and subsequent formation of anaerobic metabolic products of acid properties (other than carbonic acid), e.g. lactic acid; such acid substances would then cause vasodilatation. On the basis of this explanation the local vasodilator effect of anoxia induced by arterial occlusion may also be attributed to the impaired normal oxidation in the tissue resulting in the formation of vasodilator metabolites. Further, in histotoxic anoxia (by cyanide) the poisoning of the respiratory enzymes may account for the disturbed oxidative metabolism and consequent vasedilatation.

Another interpretation of the local vasodilator action of low O_2 is that ascribing such action primarily to a direct

effect of anoxia on the walls of the bigger arteries themselves. Thus, Fleisch et al (1932) found that the venous blood from tissues subjected to anoxic blood, did not turn acid as it would be expected to if there were actual accumulation of acid products of incomplete oxidation, e.g. lactic acid; on the contrary, the blood reaction even turned to the alkaline side. Hilton and Eichholz (1925) are also supporters of this view since they observed that the local vasodilator effect of low O_2 was much stronger than that produced by big doses of lactic acid or CO_2; they further stated that anoxic vasodilatation could not be due to accumulation of products of incomplete oxidation since the oxygen usage was normal during the anoxemia.

Effect of Low O_2 on Intestinal Motility

While hypo-oxic blood of 10% O_2 definitely decreased the tone of the intestinal blood vessels, this degree of hypo-oxia was apparently insufficient to induce significant changes in the motor activity or tonus of the gut as described above (fig. 51). More severe degrees of hypo-oxic, however, led commonly, but not invariably, to well pronounced changes not only in the blood flow but also in the rhythmic movements and tonus of the intestine. Thus, the effects of administration of 7% O_2 are shown in fig. 56. In the upper record of this figure, low O_2 caused a well pronounced depression of the gut movements and tonus. Here, it may be

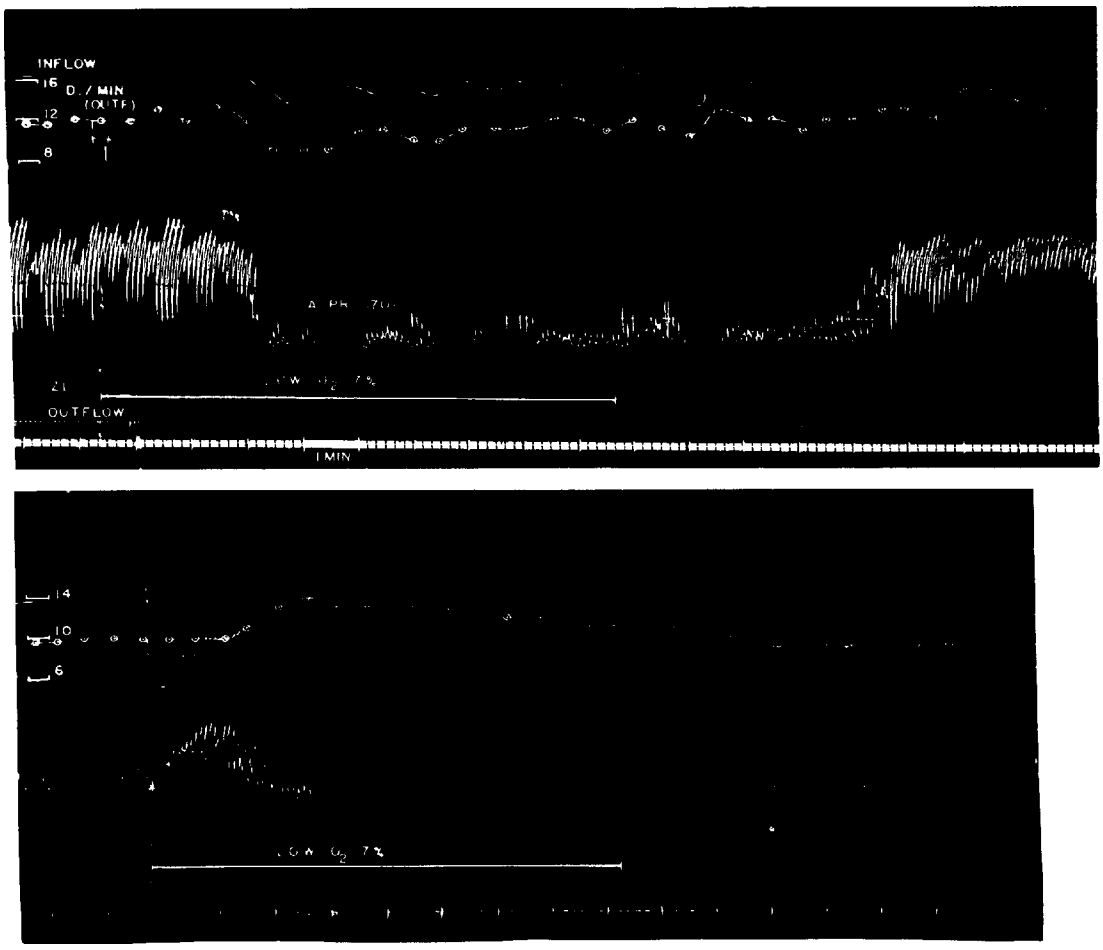


Figure 56. Illustrates influence of 7% O_2 on intestinal motility. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops per minute; intestinal contractions from both ends of the loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. Both procedures shown were performed on same loop.

noted that the typical vasodilator effect of anoxia was missing and instead there occurred an initial small but transient decrease of the blood flow followed by return to normal. This relatively small decrease of blood flow under anoxia represents the only exception in our experiments to

the consistent local vasodilator effect of anoxia. Readministration of "normal" blood led to complete recovery of both the rhythmic motility and tonus, but the blood flow showed little or no change. In the lower record of this figure (representing another procedure on the same loop), anoxia of 7% O_2 affected the gut activity in a manner similar to that shown in the upper record, except for an initial temporary stimulation of rhythmic movements and tonus. The blood flow, however, was increased by about 50% and this is to be attributed to active vasodilatation.

It is of interest that the effects of low O_2 represented in the above figure (56) are strikingly similar to those of hypercapnia (15% CO_2) on the same tissue (fig. 45). In both cases, hypo-oxia and hypercapnia induced a depression of rhythmic movements and a precipitous drop of tonus with complete recovery under normal blood.

A frequent motor response of the gut to anoxia is seen in fig. 57. In this figure, low O_2 (7%) caused an initial temporary but sharp rise of tonus and an increase in the amplitude of the rhythmic contractions; this was followed by a sudden depression of tonus and rhythmic motility to about normal. The initial increase of intestinal tonus was of such magnitude as to cause a distinct decrease of the already augmented blood flow to almost the normal level, in spite of the anoxic vasodilatation the onset of which preceded the temporary motor reaction.

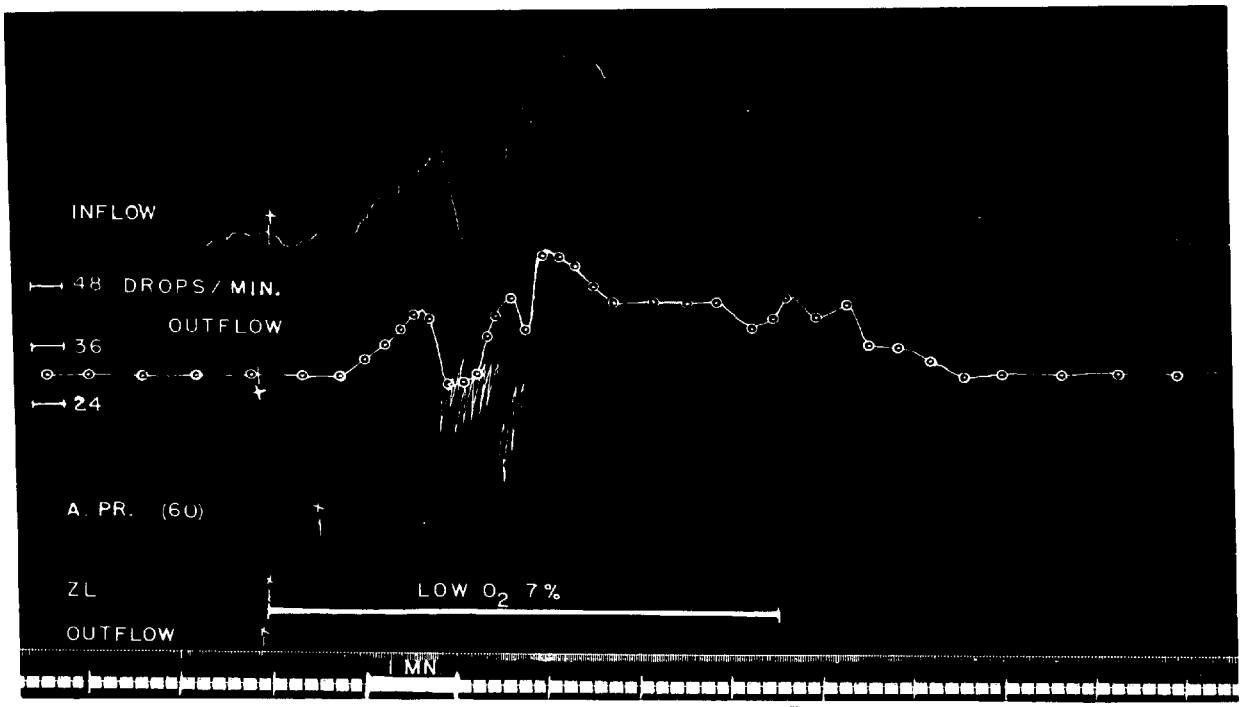


Figure 57. Illustrates influence of 7% O_2 on intestinal motility. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops per minute; A.PR. arterial pressure; intestinal contractions; ZL. zero line; venous outflow drop; time in minutes. Simultaneous ordinates marked by X.

With the termination of this tonic contraction the flow resumed its rise abruptly to about double the normal value. Shifting to normal blood caused a very slight but temporary increase of tonus and subsequent return to normal; and the blood flow decreased gradually to the pre-anoxic level.

In addition to the above experiments which demonstrate the influence of anoxia on the intestinal motility by administrating hypo-oxic blood (i.e. anoxic anoxia), the effect of anoxia resulting from arterial occlusion and from diminution of the blood supply consequent upon lowering the arterial

pressure were also investigated in this study, as already mentioned in Section II of this thesis (see figures 26 and 22). In all these anoxic states, as can be seen in the respective figures, there occurred a marked inhibition of the rhythmic contractions to almost quiescence, and a drop of tonus.

Discussion:

The literature contains a large volume of information concerning the influence of anoxia on the motility of the gastro-intestinal tract. The methods of study employed by the different workers are numerous, but, to our knowledge, no work has been done on isolated perfused loops. One of the most common methods is that in which small strips of the intestine are suspended in a bath through which oxygen, or the desired gas mixture, is bubbled. Schnohr (1934) employed another method in which he inserted a cellophane window in the abdominal wall through which he could observe the intestinal movements. He found that anoxia caused an immediate cessation of all intestinal motility. Peterson, Smith and Hale (1938) studied the effects of carbon monoxide anoxia on the gastro intestinal motility and found that saturation of the blood by 70 to 80% CO (inhalation) inhibited peristalsis by 33% and delayed the "egestion" time (time required for first appearance of fecal pellets following test meal) by 22%. Van Liere et al (1943) carried out extensive investigation on the study of the effects of anoxia

on the gastro-intestinal motility using mostly Macht's technique, i.e., the direct measurement in the small intestine of the progress of a pigment-mucilage mixture. They reported that an effective degree of anoxia (10% O_2 in respired air mixture) was capable of decreasing hunger contractions, gastric motility and contractions of the large intestine. On the other hand severe degrees of anoxic anoxia (as low as 45 mm. Hg pressure) had no effect on the motility of the small intestine of dog and only slight inhibition in mice. Frank and Grandpierre (1944) recorded the movements of the small intestine in the intact animal (by balloons) during inhalation of gas mixtures of low O_2 (3%), and found that under such conditions there occurred an immediate depression of motor activity of small intestine which they attributed to: (1) direct effect of oxygen deficiency on smooth muscles, (2) indirect effect through adrenalin discharge, (3) central inhibitory mechanism conveyed by sympathetic efferent roots. Gross and Clark (1923), using isolated intestinal strips, found that bubbling of nitrogen in the bath fluid led to a decrease of the intestinal tonus.

Our experimental results on the isolated perfused loop demonstrate that anoxia resulting from lowered arterial oxygen tension as well as from arterial occlusion and lowering of the arterial pressure, cause a predominant inhibition of the gut movements and a drop of its tonus; occasionally

such predominant inhibition was preceded by an initial transient stimulation. It is of interest that the motor reactions of the loop under these types of anoxia were strikingly similar, which observation may be indicative of a common causal factor operating under these conditions. It is evident that these responses to anoxia arise from a local action of the ultimate causal agent, whatever it may be, on the intrinsic nerve plexuses (myenteric), nerve endings, or the effector cells themselves.

III EFFECT OF ACETYLCHOLINE ON INTESTINAL MOTILITY AND INTESTINAL BLOOD FLOW

The physiological importance of acetylcholine in relation to the motility of the gastro-intestinal tract and to the tone of the peripheral blood vessels is well recognized. In the light of our experimental results concerning the intimate relationship between the motor activity of the small intestine and the blood flow through this organ, it was of interest to investigate what influences this substance might have on such interrelationship. This investigation was also called for in view of the inconsistency of the experimental data found in the literature pertaining to the direct effect of this drug on the intestinal blood vessels.

Results:

The effects of different concentrations of acetylcholine

hydrochloride (in saline), varying from 3:100,000,000 to 1:10,000, were studied in our experiments. Administration of the drug, previously warmed to the bath temperature, was accomplished by injection into the perfusion blood with the aid of a needle introduced into the inflow tube. In order to insure the arrival of the whole dose of acetylcholine to the loop, and to avoid its destruction by the blood, the drug was introduced as near to the tissue as possible; control injections of equal volumes of saline were carried out.

Typical effects of acetylcholine are shown in fig. 58. Here, injection of 0.4 cc. of a 1:10,000 solution of the durg over a period of 100 secs., caused a sharp increase in the blood flow and shortly thereafter a marked motor response in the loop. By careful examination of the record, it is seen that this motor response consisted of an increase in the amplitude of the rhythmic movements superimposed on three main tonic contractions. As would be expected, these tonic contractions led to a distinct interference with the augmentation of the flow induced by the drug so that, during each tonic contraction, the blood flow was markedly decreased then rose at the end of the contraction. In this figure, it is also noteworthy that the vascular reaction outlasted the motor response which came to an abrupt end while the flow diminished gradually toward normal. Control injection of an equal volume of saline over the same period of time,

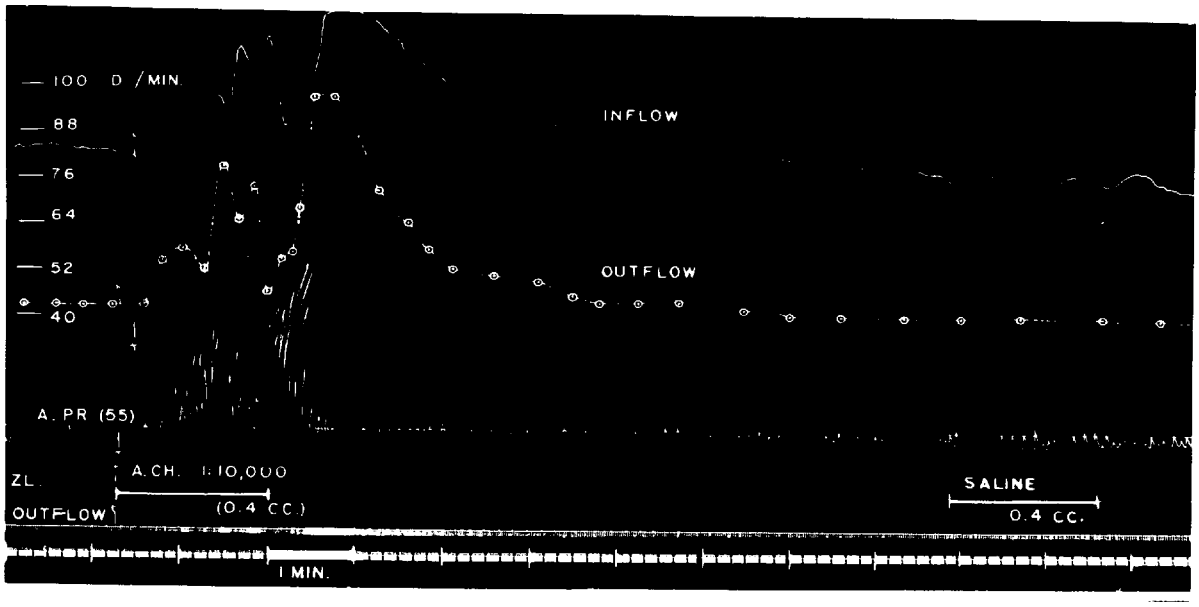


Figure 58. Illustrates effect of acetylcholine on intestinal motility and intestinal blood flow. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops/min.; intestinal contractions from upper end of loop; A.PR. arterial pressure; intestinal contractions from lower end of loop; Z.L. zero line; venous outflow drops, time in minutes. Simultaneous ordinates marked by X. 0.4 cc. of 1:10,000 solution of acetylcholine hydrochloride in saline injected over a period of 100 secs. Control is by 0.4 cc. saline injected over same period.

did not cause any significant change in the blood flow or the motor activity of the gut, which finding indicates that the increase in blood flow induced by acetylcholine represents as active vasodilatation.

From the above figure (58), it is evident that the motor reaction of the gut to acetylcholine tends temporarily to decrease the vasodilatation induced by the drug, by virtue of the passive vascular compression during the high tonus. In some cases, as in fig. 59, such motor response was so

strong as, not only to mask the vasodilatation, but also to cause a marked transient diminution of the flow to well below normal. Here, however, evidence indicating the occurrence of vascular dilatation by the drug can still be seen. Thus,

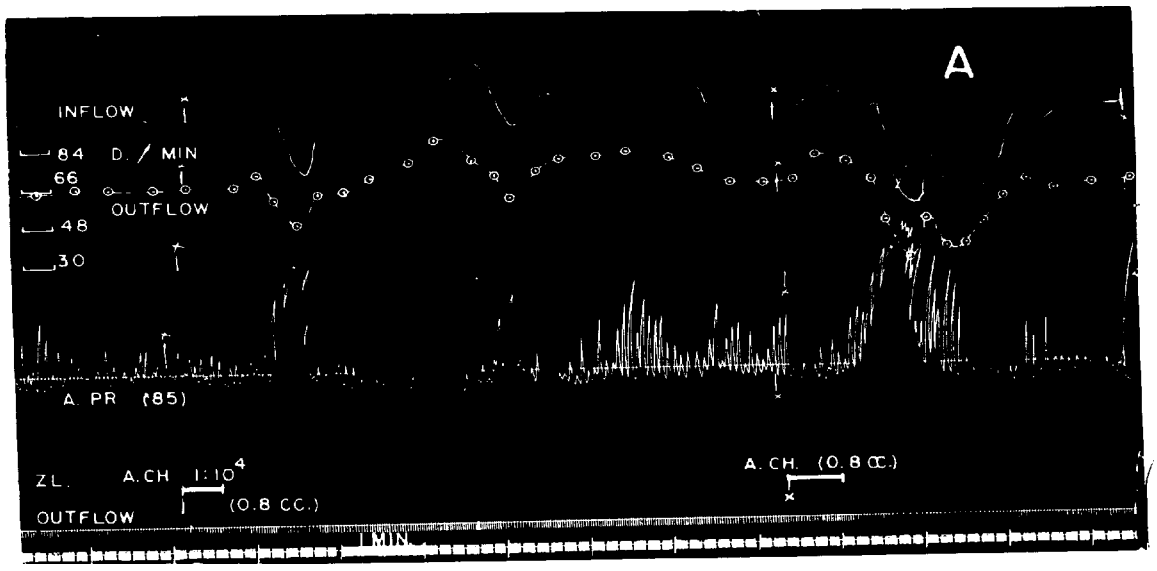


Figure 59. Illustrates effect of acetylcholine on intestinal motility and intestinal blood flow. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops/min.; intestinal contractions from both ends of loop; A.PR. arterial pressure; ZL. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. 0.8 cc. of 1:10,000 solution of acetylcholine hydrochloride injected twice over a period of 30 seconds each time.

in both administrations of acetylcholine in this figure (59) (0.8 cc. of 1:10,000 solution), there occurred a definite increase in the blood flow before the appearance of the motor response. This augmented flow was then decreased by the tonic contractions evoked by the drug to below the normal level. But, as can be seen in the first acetylcholine

administration, the flow increased again to above normal at the termination of the relatively short tonic contraction. In the second administration the motor response consisted of two partly separated tonic contractions and was not followed by an increase in the flow probably because of the disappearance of the temporary vasodilator action of the drug. However, the temporary brief rise of flow seen at the sudden drop of the first tonic contraction suggests that the predominant decrease in flow was due to a mechanical vascular compression rather than to an active vasoconstriction, since the latter should have resulted in continued diminution of the flow.

In further support of the vasodilator action of acetylcholine, are the results shown in fig. 60. In this figure, acetylcholine, in doses of 0.2 cc., 0.1 cc. and 0.05 cc. of a $1:10^4$ solution (in parts A, B and C respectively), caused a predominant increase in the blood flow; the gut activity on the other hand, was not significantly affected except for a slight initial inhibition, followed by a slight tonic rise in A to which is ascribed the simultaneous temporary small drop in the augmented flow. It is noteworthy that the vasodilator action of acetylcholine was proportional to the dose of the drug administered, as can be seen in the figure. (Control injection of saline did not cause any significant change in the blood flow, indicating that the increase in the blood flow, induced by acetylcholine, was due to an active vasodilation.)

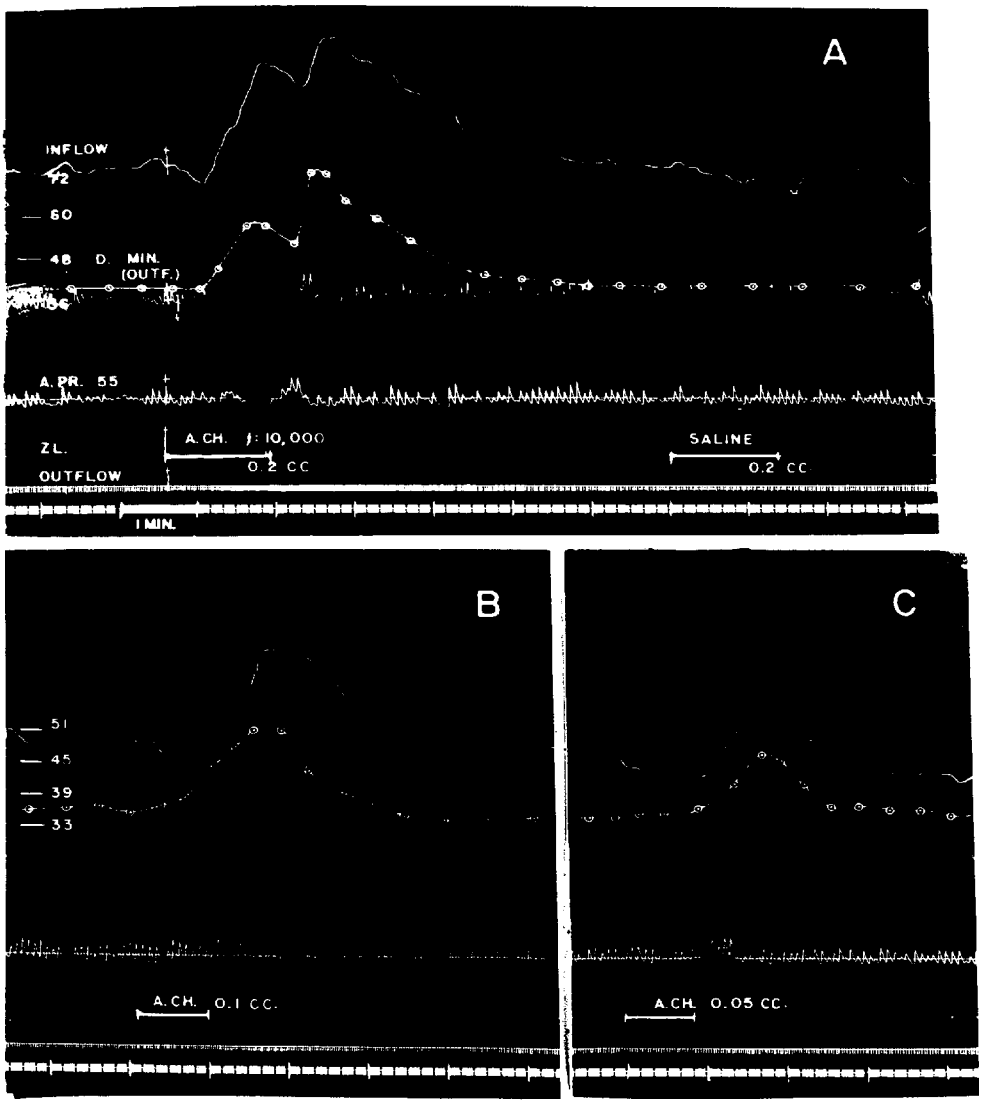


Figure 60. Illustrates effect of acetylcholine on intestinal blood flow. Tracings from above downward: arterial inflow by thermopile; venous outflow plotted in drops per minute; intestinal contractions from both ends of loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X in A. A, B and C are from same experiment; in A, 0.2 cc. of 1:10,000 solution of acetylcholine hydrochloride injected (and control injection of 0.2 cc. saline); in B, 0.1 cc. of same solution, and in C, 0.05 cc.

In an attempt to further isolate the motor reactions of the gut to acetylcholine from the vascular reactions, and to ascertain whether atropine abolishes the vasodilator action of acetylcholine, as has been maintained by some investigators, the loop was atropinized to render the gut quiescent. (Atropine sulfate was administered in the same manner as described for acetylcholine). The results of administration of different concentrations of acetylcholine after such atropinization (by 0.2 mgm. atropine) are shown in fig. 61. Here, all acetylcholine injections were made instantaneously, and consequently the injection artefacts on the inflow recording (temporary sharp drop) were accentuated due to interference with normal flow through the thermopile vessel; as would be expected these artefacts were not registered by the venous outflow thermopile. In part A, the first injection was a 'control', in which 0.3 cc. saline was used; the next three injections and a fourth in part B were of increasing concentrations of the drug: 0.3 cc. of $1:10^7$, $1:10^6$, $1:10^5$ and $1:10^4$ respectively. The first administration of acetylcholine ($1:10^7$) caused a slight but definite increase of both outflow and inflow, followed by a gradual decrease to a subnormal level; with the second administration ($1:10^6$) both these changes were accentuated. The third administration ($1:10^5$) caused a marked increase in the flow, which subsequently diminished very gradually to below the pre-administration level. These first three concentrations of the drug did

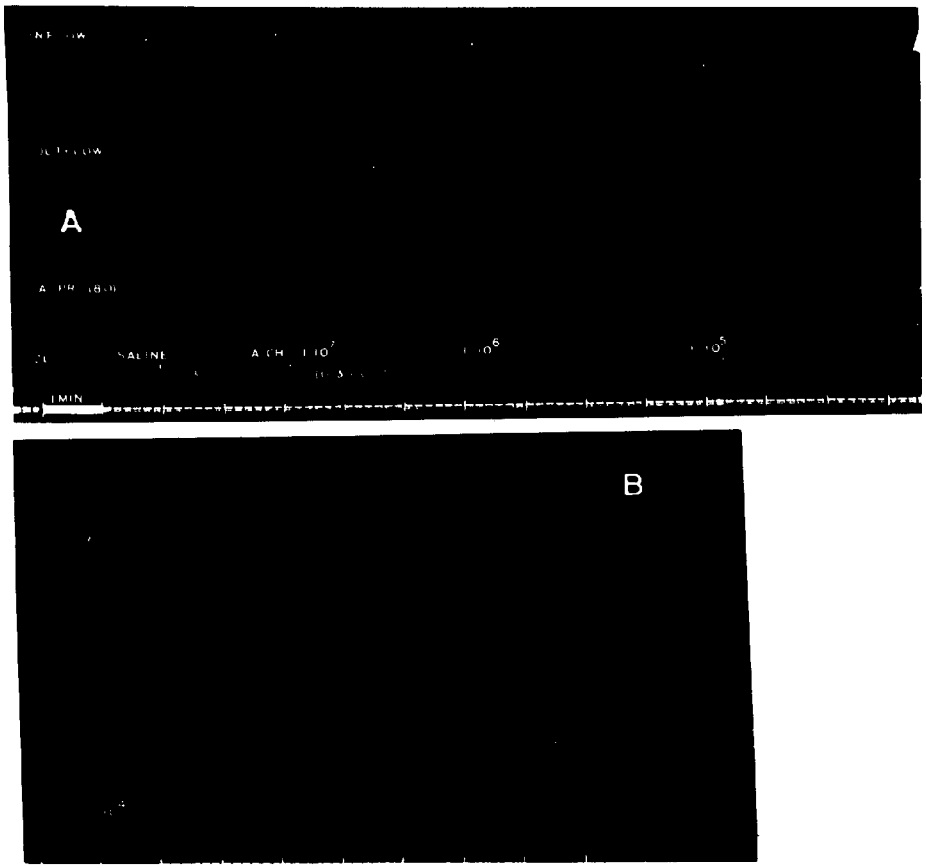


Figure 61. Illustrates effect of acetylcholine on atropinized loop. Tracings from above downward: arterial inflow and venous outflow by thermopile; A.PR. arterial pressure; intestinal contractions; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X in A. A and B from same atropinized tissue (by 0.2 mgm. atropine sulfate); in A, the following injections were made: 0.3 cc. saline (control), 0.3 cc. of $1:10^7$, 1.10^6 and $1:10^5$ solutions of acetylcholine in saline; in B, 0.3 cc. of $1:10^4$ solution of acetylcholine. Arrows on arterial inflow curve point to time of injections. Sharp temporary drop in inflow curve is an artefact due to instantaneous injection and consequent interference with 'normal' flow through inflow thermopile vessel.

not evoke any motor reaction in the loop, as can be seen in the figure. The highest concentration used ($1:10^4$), in

part B, caused the greatest increase of flow which was maintained above the pre-injection level for about 6 minutes, with a gradual diminution to below the pre-injection level. This concentration, unlike the others, did evoke a brief but well-pronounced tonic increase (in spite of atropinization), followed by quiescence; towards the end of the record the gut showed a rise in tonus and appearance of rhythmic contractions, probably a sign of recovery from the atropine effects.

The results described above in the atropinized loop constitute, therefore, further evidence that acetylcholine, in the doses mentioned, has a predominant local dilator action on the intestinal blood vessels. It is also evident that the vascular reactions to this drug were not eliminated by the action of atropine. The tendency of the blood flow to decrease with successive doses of acetylcholine (compare flow level at the beginning of A and at the end of B) suggests the possibility of some secondary vasoconstrictive effect of acetylcholine. There may, however, be other factors involved e.g. changes in blood viscosity or spontaneous changes in the vascular tone.

Since it is generally recognized that the different anticholinesterases, e.g. physostygmine, acids, CO_2, potentiate the action of acetylcholine in the various tissues (especially the nervous system), it was deemed of interest to determine the influence of CO_2 which is considered as a physiological anticholinesterase, (Gesell, 1942) on the

motor response of the intestine to acetylcholine. For this purpose identical doses of the drug (0.4 cc. of $1:10^4$ solution) were administered during "normal" as well as during hypercapnic (10% CO_2) perfusion. The results of such procedure are shown in fig. 62, where it is seen that during hypercapnia the gut response to acetylcholine was markedly augmented. This would indicate that CO_2 has acted as an anticholinesterase.

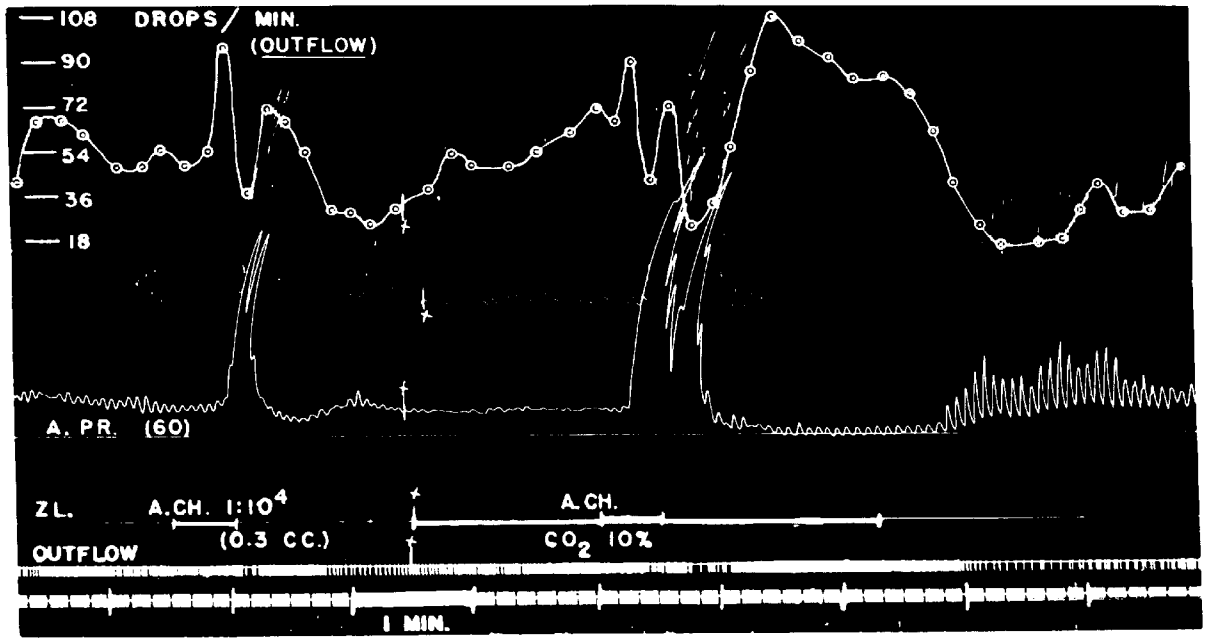


Figure 62. Illustrates potentiating influence of CO_2 on intestinal motor response to acetylcholine. Tracings from above downward; venous outflow plotted in drops per minute; intestinal contractions from both ends of loop; A.PR. arterial pressure; Z.L. zero line; venous outflow drops; time in minutes. Simultaneous ordinates marked by X. 0.3 cc. of 1:10,000 solution of acetylcholine injected during "normal", and during hypercapnic (10% CO_2) perfusion.

Discussion:

The experimental data reported in the literature concerning the action of acetylcholine on the intestinal blood vessels, and on the vascular bed of the gastro-intestinal tract in general, are distinctly inconsistent and even contradictory. Thus, following the discovery by Hunt and Taveau (1906) of the intense hypotensive action of this drug on the general blood pressure, Dale (1914), using a plethysmograph, found that acetylcholine caused an increase in the intestinal volume (cat) which he interpreted as due to vasodilatation. Hunt (1917) carried out similar plethysmographic experiments on the rabbits' small intestine and also determined the venous outflow from this organ (in cats) but declined to draw any final conclusion concerning the vascular effect of acetylcholine since he questioned whether his results were not complicated by contractions of the intestine and by changes in the general blood pressure. (He did state, however, that acetylcholine "...seems also to dilate the vessels of the intestine and liver.") Fleisch and coworkers (1931) found a vasoconstriction in the vena colica and vena mesenterica superioris (of cats and dogs) with a big dose of acetylcholine, and a vasodilatation with small doses. Hirose (1932) observed that big doses of the drug caused a decrease in the venous outflow from the portal vein together with a rise in the blood pressure. Necheles et al (1936) stated that acetylcholine in doses up to 1:2,000,000 caused constriction in the

vessels of the perfused (with Ringer's solution) stomach of rats; doses of greater dilution were without effect.

It should be emphasized here that none of the above authors carried out simultaneous recording of the intestinal contractions during the drug administration, a fact which might have great bearing in their interpretation of their findings. Thus, it has been shown in our results that the motor response of the gut was occasionally capable of masking the vasodilator action of acetylcholine or even causing a subnormal flow in the face of an existing vasodilation induced by the drug, especially with large doses (fig. 59). Therefore, it may be suggested that, what some of these authors (Fleisch, Hirose, and Necheles et al) interpreted as an active vasoconstrictive action of acetylcholine, was in fact due to a passive compression of the vascular bed during a simultaneous rise in gut tonus. In further support of this interpretation is the fact that these workers had used relatively big doses of acetylcholine which might have evoked considerable motor reactions; Fleisch mentioned that he obtained vasoconstriction with big doses of the drug and vasodilatation with small doses.

Our experimental results indicate conclusively, then, that acetylcholine, in concentrations of from 1:10,000 to 3:10,000,000 has a predominant local vasodilator action, the magnitude of which is apparently proportional to the dosage of the drug (figures 60 and 61). It has also been shown

that this vascular response usually appeared before and outlasted the motor response of the gut when such occurred, and with smaller doses of acetylcholine only the vascular response appeared (fig. 60). This apparent difference between the vascular and motor reactions may be attributed to a partial destruction of the drug during its passage from the blood vessels to the intestinal tissue, so that the latter would be subjected to a relatively smaller dose than the vascular walls.

The question as to whether acetylcholine dilates the intestinal blood vessels by stimulating some vasodilator nerve endings in the vascular walls or by a direct action on the smooth muscles of these walls, cannot be answered by our experiments. However, assuming that atropine "paralyzes" any vasodilator nerve endings (as maintained by many authors), our experiments on the atropinized loop (fig. 61), in which acetylcholine still caused vasodilatation, may indicate that this drug is capable of acting directly on the vascular walls.

The enhancement of the motor response of the gut to acetylcholine under hypercapnia (fig. 62), points strongly to a potentiating influence of CO_2. Such a potentiation would not be unexpected in view of the anticholinesterase action of CO_2, probably induced through its acid properties, as it is the case in other tissues, e.g. nervous system (Gesell, 1942).

SUMMARY OF RESULTS:

(1) In this study, isolated loops, about 5 inches long, of dogs small intestine were perfused with heparinized dog's blood; in some experiments the loops were perfused 'in situ' with their nervous connections to the C.N.S. intact. In these experiments the venous outflow, arterial inflow, intestinal contractions, arterial and venous pressures were continuously recorded.

(2) The rhythmic activity of the small intestine caused intermittence in its intrinsic blood flow. During each contractile phase the venous outflow was increased while the arterial inflow was decreased; this relationship was reversed during each relaxation phase.

(3) The increase in the outflow during each contractile phase is caused by the expulsion of venous blood contained in the capacious vascular bed of the intestinal wall. Such rhythmical expulsion during rhythmic contractions of the gut constitutes a propulsive force acting as a pump which facilitates the onward movement of venous blood.

(4) Tonic contractions of the small intestine caused a predominant decrease in both the arterial inflow and venous outflow which persisted throughout the period of high tonus; the decrease in the outflow was occasionally preceded by an initial temporary increase particularly in rapidly developing tonic contractions. Such initial decrease in the outflow is attributed to the sudden expulsion of venous blood upon

the onset of the tonic state.

(5) Strong and relatively sustained tonic contractions were followed by a pronounced after-effect which consisted of a temporary supranormal blood flow. This after-effect may be attributed to the action of vasodilator substances released from the tissue during the period of high tonus.

(6) Increased motor activity of the small intestine caused an augmentation in its intrinsic mean blood flow by virtue of increased formation of vasodilator metabolites and by increased propulsive power of the rhythmic contractions on the blood flow.

(7) Sudden elevation or lowering of the arterial pressure caused characteristic transient motor responses in the gut. Evidence was given that such responses are induced by the mechanical stimulation inherent in the pressure change per se. In the elicitation of these motor reactions the rate and the magnitude of the pressure change are important determining factors.

(8) Elevation of the arterial pressure and its maintenance at the high level caused a predominant enhancement in the motor activity of the gut, whereas lowering of the arterial pressure and its maintenance at the low level led to predominant depression after the initial stimulation. These changes in the intestinal motor activity are ascribed chiefly to the attendant increase or decrease of the volume flow of blood respectively, although here the changes in the

intravascular pressures per se may also be contributing factors.

(9) Alterations in the venous pressure caused motor responses similar to those induced by arterial pressure changes. Here again, the rate and the magnitude of the venous pressure change are important determining factors.

(10) Maintenance of a supranormal venous pressure caused a striking increase in the amplitude of the intestinal rhythmic contractions. This phenomenon is of extreme significance in the intact animal since such increase in the amplitude of rhythmic motility would lead to an increased propulsive power on the blood flow thus furnishing a means to aid the movement of venous blood from the small intestine to the liver against unduly high pressures in the portal vein.

(11) Occlusion of the arterial inflow to the tissue caused a predominant depression of the gut movements and a drop of the arterial pressure to zero. Such depression of activity is due chiefly to the stoppage of the arterial supply and probably also to the decreased intravascular pressure per se. De-occlusion of the inflow caused an initial temporary supranormal motor activity and blood flow, followed by a return to normal. The temporary supranormal flow is best explained as due to anoxic vasodilatation during the period of occlusion; the initial motor response is most probably due to the sudden rise of arterial pressure per se.

(12) Combined arterial and venous occlusion and de-occlusion caused reactions similar to those induced by simple arterial occlusion and de-occlusion.

(13) Venous occlusion caused predominant increase in the intestinal motor activity which is ascribed to the attendant rise in the venous pressure. The enhanced rhythmic activity led to an increased propulsive power on the blood flow which resulted in a further rise in the venous pressure to levels far in excess of the arterial pressure.

(14) Sudden elevation of the arterial pressure caused vasoconstriction while sudden lowering of the pressure caused vasodilatation in the isolated intestinal loop. These vascular reactions are attributed to the sudden increase or decrease of the intravascular tension respectively.

(15) Shifting from constant to pulsatile perfusion pressure caused a predominant depression in the motility of the isolated intestinal loop independent of any changes in the blood flow; occasionally this depression was preceded by an initial temporary rise in tonus.

(16) Shifting from constant to pulsatile perfusion pressure caused definite changes in the tone of the denervated intestinal blood vessels. In most cases the vascular reaction to pulsations consisted of an initial temporary decrease followed by a more prolonged increase in the blood flow. Occastionally pulsations caused pure vasodilatation or pure vasoconstriction. The suggestion was made that there

are two antagonistic mechanisms involved in the vascular reaction to pulsations, namely a vasoconstrictor and an augmentative or vasodilator mechanisms, and that atropine may act differentially on these mechanisms by paralyzing the vasoconstrictor reaction only.

(17) Raising the intestinal intralumenary pressure to levels within the range of those occurring in the intact animal, caused a predominant decrease in the blood flow and an increase in both the tonus and rhythmic activity of the isolated loop. The decrease in the blood flow is attributed to passive vascular compression.

(18) Hypercapnia (CO_2 concentrations equivalent to 6.7%, 10%, 12% and 15% in comparison to "normal" of 4% in equilibrating gas mixture) caused a predominant local dilatation and a central and reflex constriction in the intestinal blood vessels, both innervated and denervated. Acapnia caused a predominant local vasoconstriction.

(19) Hypercapnia (same CO_2 concentrations as above) caused a predominant depression of the gut movements which was occasionally preceded by an initial temporary increase in the rhythmic activity and tonus. Such initial rise in the gut tonus occasionally caused a decrease in the blood flow to subnormal levels in spite of the existing vasodilatation (induced by hypercapnia).

(20) Reduction in the arterial oxygen tension (to values equivalent to 10% and 7% in the equilibrating gas mixture,

in comparison to "normal" of 30%) caused a predominant local dilatation in both the innervated and denervated intestinal blood vessels. Asphyxia caused a predominant central and reflex vasoconstriction in the intestinal loop completely isolated except for its nervous connections to the C.N.S.

(21) Administration of cyanide into the perfused loop caused a predominant local vasodilatation.

(22) Anoxia resulting from low arterial O_2 tensions (equivalent to 7% in equilibrating gas mixture), or from arterial occlusion or lowering of the arterial blood pressure caused a predominant depression in the motor activity and tonus of the perfused isolated loop. This depression was occasionally preceded by an initial temporary stimulation.

(23) Acetylcholine in doses of from 3:10,000,000 to 1:10,000 caused a predominant local vasodilatation, and with the stronger doses there occurred strong stimulation of gut motility and tonus. This increase in tonus was occasionally capable of masking the vasodilator action of the drug, or even decreasing the blood flow to subnormal levels.

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