THE METABOLIC GRADIENT UNDERLYING PERISTALSIS *

WALTER C. ALVAREZ, M.D.
SAN FRANCISCO

Why does food normally go in one direction down the intestine? Why sometimes does it go slowly and haltingly, giving rise to symptoms of indigestion? Why sometimes does it turn around and come back through the mouth? These questions are fundamental; and the future of gastro-enterology as an exact science depends on the fulness with which they are answered. Until we obtain such physiologic knowledge we must face the fact that in practice we are trying to repair a machine, the normal structure and workings of which are largely unknown to us. Naturally the results are often unsatisfactory, just as they would be if we were trying to repair broken-down adding machines or wireless telephones.

What could the heart specialist learn about the arrhythmias until Gaskell, McWilliam, His, Keith, Lewis and others showed him where the beat normally arises and how it is transmitted from sinus to ventricle? Given that information, the student of heart pathology became inspired and rejuvenated; his knowledge advanced by leaps and bounds; and his textbooks had to be rewritten and remodeled. We should take hope from this good fortune which has come to our confrères and should seize on the methods of study which have been so productive in their hands. With these I believe we can advance to similar triumphs over the baffling problems in our own chosen field. We should study the gastro-intestinal tract in embryos and in lower and simpler forms of life; we should look for structural and metabolic differences in the neuromuscular apparatus in different parts of the tract, and we should study minutely the reactions of the muscular coat—its rhythmicity, irritability, conductivity, reaction to drugs, etc.—in different regions. As clinicians, we must get over the habit of thinking in terms of plumbing and rigid tubes held in one position. We must think instead of a muscular tube which has to contract in a coordinated way if material within it is to be pushed for many feet in one direction or the other.

Six years ago I showed that there is a very definite gradient of rhythmicity in the muscle of the small intestine from duodenum to ileum[1]. It seemed to me then that this gradient of rhythmicity or perhaps some underlying gradient of tone might be the essential factor in determining the direction of peristalsis. This gradient might conceivedly be reversed by any distention, irritation or inflammation which would increase the tone and activity of the lower parts of the tract to a level above that maintained by the upper parts. In two papers[2] I reviewed much of the literature and showed how easily a great many clinical and roentgenologic observations can be explained on the basis of such a theory.

I cannot see now why there should be any great difficulty in accepting this idea of a gradient of forces as a working hypothesis in the study of peristalsis. Wherever we find movement in this world we find a gradation of forces. Thus, water flowing in a ditch follows a gradient of gravity, i. e., the pressure on any one drop is greater on the upstream than on the downstream side. Electricity in a wire follows a gradient of potential or voltage; in a battery it follows a gradient of chemical activity, flowing from regions in which oxidation predominates to regions in which reduction predominates. The impulse in the heart follows a gradient of rhythmicity; and according to Tashiro[3] the impulses in nerves follow gradients of oxidation. In the stomach and intestine the contents move from regions of high rhythmicity, high irritability and high tone to regions of low rhythmicity, low irritability and low tone.

During the last two years I have been able to show that there is a definite gradient of oxidation and carbon dioxid production in the intestinal wall, underlying and probably giving rise to the other gradients of rhythmicity, tone, etc.[4]. In other words, the chemical processes of life go on at a faster rate in the duodenum than in the ileum or colon. Theoretically, if we should speed up these processes in the duodenum we might steepen the gradient and cause the food to go faster through the bowel; if we should speed them up in the ileum so that they would be faster than those in the duodenum, we might reverse the gradient and stop the downward progress of food. Recent study has shown that the local life processes are greatly speeded up by inflammation[5], so it may be that the hypermotility actually seen in many cases of duodenal ulcer and cholecystitis and the hypomotility with appendicitis are due to changes in the metabolic gradient brought about by these lesions.

Galvanometric studies of bruised tissues suggest strongly that their metabolic rates are increased by the trauma[6]. If this be true in the intestine we can easily explain the fact that its contents cannot approach or pass through segments which have recently been pinched in hernial rings or maltreated at operations[7]. A local increase in the metabolic rate would make the gradient uphill in the section of bowel just orad to the lesion.

There is yet another and perhaps an even more important way in which the gradient may be reversed. Child[8] has shown repeatedly that tissues with a fast rate of oxidation are more susceptible to the effects of low concentrations of certain poisons, such as potassium cyanid, than are tissues with slow rates. If two lots of small planarian worms of different ages are put into a weak solution of potassium cyanid, the younger ones, with the faster metabolic rate, die first. Similarly, if children and old men were to be put into a room full of ether vapor, the children would probably all go to sleep first. Child showed that in some of the lower forms of life which have rows of swimming plates along their sides, the direction of the beat can be reversed by potassium cyanid because the pacemaking region suffers most from the effects of the drug. Using excised segments from different parts

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1. Alvarez, W. C.: Am. J. Physiol. **35**: 177 (Sept.) 1914; ibid. **37**: 267 (May) 1915.

2. Alvarez, W. C.: The Motor Functions of the Intestine from a New Point of View, J. A. M. A. **65**: 388 (July 31) 1915; The Syndrome of Mild Reverse Peristalsis: ibid. **69**: 2018 (Dec. 15) 1917.

3. Tashiro, Shiro: A Chemical Sign of Life (Irritability), Chicago, University of Chicago Press, 1917.

4. Alvarez, W. C., and Starkweather, E.: Am. J. Physiol. **46**: 186 (June) 1918; ibid **47**: 60 (Sept.) 1918.

5. Segale, M.: J. Exper. M. **29**: 235 (March) 1919.

6. Hyman, L. H.: Science **48**: 518 (Nov. 22) 1918.

7. Cannon and Murphy: Am. J. M. Sc. **131**: 569, 1906; Alvarez: J. A. M. A. **65**: 392, 1915.

8. Child, C. M.: Am. J. Physiol. **43**: 87 (April) 1917; Senescence and Rejuvenescence, Chicago, 1915.

of the bowel, all beating rhythmically together in the same beaker of Locke's solution, I had no difficulty in showing that the duodenum is much more sensitive to potassium cyanid and to the lack of oxygen than is the ileum. Time and again while working in the laboratory I have been impressed by the great sensitiveness of the duodenum and of the pace-making region in the stomach to trauma of all kinds[9]. Compared with them, the ileum and the pyloric antrum are tough and hardy. I have also been impressed with the fact that the gradients of rhythmicity, latent period and metabolism are abnormal in sick animals. Just as we should expect, the duodenum and jejunum seem to suffer more from the effects of the toxins than do the ileum and colon. The distempered dogs and snuffling cats generally refused food. When it was put in their stomachs it remained there until it was vomited. Cannon has commented on the remarkable gastric stasis seen in distempered dogs. Similarly, food may remain for hours in the stomachs of people with tuberculosis and other intoxications. There I feel sure the stagnation is not always due to a failure in peristalsis; the waves may be seen traveling regularly over the stomach, but they do not force the contents through the pylorus. Something must be wrong with the gradient. I believe it has been altered by an unequal effect of the toxins on the muscle at the two ends of the organ. How simple this explanation is as compared with those which drag in a cumbersome and so far quite undemonstrated mechanism of nerves and internal secretions!

AN ILLUSTRATIVE SIMILE

Perhaps I can best express my ideas of what goes on in the intestine by means of the following simile: Let us imagine a game of push-ball played by a long line of men who have been graded according to their metabolic rates. At one end they are young, wide-awake and active; at the other end they are old and lethargic. These men represent the muscle fibers along the intestine. The ball is started by the first young man, who tries to force it past the second. The second resists but is soon overcome, owing to the greater activity and aggressiveness of number one. As soon as the ball passes number two, he joins with number one in trying to push it past three and four. Once past them, one and two rest while three and four push it past five and six, and so it goes. The men in the first third of the line (jejunum) play incessantly so long as the ball is near them, and they soon force it down among the old men. These play only occasionally, often letting the ball lie quiet while they sit down about it to rest. New balls are started down the line from time to time, and sometimes the old men will have three or four on their hands at once. Ordinarily they are roused to get rid of one or two of these when they see that a new one has started down (ileocolic reflex and defecation).

Usually the ball moves in one direction and there is small likelihood that the old men with their intermittent efforts will ever overcome the youths. But one day some of the old men get drunk, and under the influence of liquor they fight so fast and furiously that the others cannot push the ball anywhere near the lower goal. On another occasion some of the old men are injured and beg their comrades to relieve them for a while from the trouble of handling the ball. Again these old men are stimulated to fight back so desperately that some of the balls are even thrown out the way they entered. On still another occasion a cloud of poison gas is liberated over them. All are weakened and made ill, but the young men who breathe faster are more susceptible to the poison and suffer more from the lack of proper air than do the old men. Until they recover, the game is slower; the old men are more active than the young ones and the ball is sometimes sent back to the original starting place.

A change in the play might be brought about also by making the balls unpleasant or painful to handle. Let us suppose that they have been filled with pepper or stuffed full of sharp spikes. The first one or two to start down the line would probably be rushed through so that the players could get rid of them as rapidly as possible. The men would then be so irritated by this annoyance that they would probably throw back the next few balls that were offered them (diarrhea and vomiting).

If the game was being played on the side of a hill it would not make much difference whether the young men were above or below the old. The position of the line would not be the important thing. The essential factor determining the movements of the ball would be the gradient of activity in the line of players. If the men were to play in a lane between two board fences, a slowing of the progress of the ball would not mean necessarily that the lane had been narrowed or closed. As likely as not some of the players might be fighting back too hard, or those above might not be pushing down as they should.

I think most of my readers will recognize the bearings of this simile on the problems of gastro-enterology. Some may be surprised at the idea of one part of the bowel resisting the propulsive efforts of another part above, so I will say that I have watched this conflict take place so often, particularly in the rabbit's bowel, that I feel sure that it is a big factor in the regulation of diastalsis.[10] It is well known that it is this type of bowel action that keeps the food from pouring out of the stomach after pyloroplasties and gastrojejunostomies[11].

CONCLUSION

I wish to point out briefly some of the ways in which these studies may throw light on the pharmacology of the heart and on the functional disturbances of that organ seen in asthenic states and during convalescence from acute infections. Since the heart beat follows a gradient of rhythmicity and almost undoubtedly one of metabolism, we should expect to find certain drugs and disease toxins reversing it just as they reverse other metabolic gradients. A review of the literature shows considerable evidence in favor of such a view. Thus chloroform will paralyze the auricle in concentrations which will only slightly inhibit the ventricle[12]; digitalis has a similar tendency, and I believe we must begin to ask ourselves whether this action may not flatten or reverse the gradient. Such changes might account for some of the retarding in conduction and also for the tendency to heart block and a reversal of the beat. Similar

9. Alvarez, W. C.: Am. J. Physiol. **35**: 178, 179 (Sept.) 1914; ibid. **42**: 426, 430, 445 (Feb.) 1917; ibid. **45**: 346, 348 (March) 1918; ibid. **46**: 189 (June) 1918; **47**: 65 (Sept.) 1918.

10. Alvarez, W. C.: Am. J. Physiol. **37**: 279 (May) 1915.

11. Cannon and Blake: Ann. Surg. **41**: 708, 1905. Dagaew, W. F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**: 179, 1913. Marbaix: La cellue **14**: 283, 1898. Van Gehuchten: La cellule **6**: 277, 1890.

12. Rasche, A.: Ztschr. f. Biol. **55**: 469, 1911.

upsets, with palpitation, nodal rhythm and even transitory blocks may arise through the activity of disease toxins. The disordered heart action and the digestive disturbances seen side by side in people recovering from infections such as influenza may easily be due to the flattening effect of the one poison on the two gradients. I feel hopeful, therefore, that further study of the digestive gradients and of their modification in disease will not only bring rich rewards to those of us interested in gastro-enterology, but will also enable us to repay the heart physiologists and biologists with interest for the loan of their methods and working hypotheses.

ABSTRACT OF DISCUSSION

DR. FRANKLIN W. WHITE, Boston: We are under great obligation to Dr. Alvarez and to other physiologists who develop these new ideas which are likely to be of so much service later. Alvarez has compared the gastro-intestinal canal to a railroad under the control of a "block system," where delay low down the line regularly holds up the passage of material for several blocks above. My clinical and roentgen-ray observations have shown that delay in emptying the stomach is the exception, not the rule, in lesions of the lower bowel, and that a strong stimulus is needed from the lower bowel to slow the stomach. We made a few simple experiments a year or two ago to test the correctness of this theory. We irritated the cecum in cats with a few drops of mustard oil, injected through a rectal catheter, and we found that one of several things happened: moderate irritation had no effect on the emptying of the stomach; marked irritation caused either (*a*) delay in emptying the stomach up to about twice the normal time or (*b*) hyperperistalsis and rapid emptying of the stomach and whole digestive tract. Intense irritation caused prompt reverse peristalsis in the stomach with vomiting of its whole contents. Similar experiments were made in human beings by giving them a large enema and allowing them to retain it as long as it could be conveniently done, for twenty minutes or one half hour, and watching to see if that would slow the down hill progress of things, that is, the emptying of the stomach. We found, as a matter of fact, that their stomachs continued to empty. We could see the pylorus passing things on at very much the normal rate. Obviously, the effect of this gradient, which is undoubtedly present is not a perfectly simple affair. Its results depend largely on the grade of irritation at the lower end of the canal, and the action of the mechanism is complicated by the contrary results of spasm and hyperperistalsis.

DR. JAMES T. CASE, Battle Creek, Mich.: I am very pleased to hear the interesting and instructive theory advanced by the author of this paper. To the support of this theory I can bring a large series of clinical observations which I have made during the last ten years, especially regarding the point to which an ingested meal will penetrate in the alimentary tract in cases of intestinal obstruction. In the early days of the roentgen-ray examination, when I studied cases of colonic obstruction by means of the barium meal, I found that in my estimate of the exact site of the obstruction I was usually off a foot or more too far up the canal, for I judged the point of obstruction by the farthermost point to which, as far as I could observe, the ingested barium progressed. I did not realize at that time that there is a state of peristaltic unrest in these cases so that the ingesta may at one hour be advanced or withdrawn alternately.

Checking up these estimations by means of the opaque enema soon showed us exactly the point of obstruction. These phenomena could be explained very easily by the theory of peristaltic gradient to which we have just listened. About ten years ago, I called attention to the fact that in colonic obstruction, for instance, the barium ingested by mouth would after entering the colon be found, as a rule, not just proximal to the obstruction, but on the contrary as far away from the obstruction as it was possible to get it. In other words, in obstruction of the sigmoid we would usually find the collection of barium to occur in the cecum, only rarely in the distal colon. I have even known of cases of gangrene of the cecum in sigmoidal carcinomas. We have observed the same thing in the small intestine. The administration of the opaque meal is a valuable means of determining the fact of obstruction, but the farthermost point attained by the barium is usually some feet short of the actual point of obstruction in the bowel. While the essayist's theory seems abundantly confirmed by our barium meal studies, it does not seem to be true regarding gas accumulations occurring throughout the bowel for these are apparently just as marked immediately proximal to the obstruction as in more remote segments of the bowel.

DR. NATHAN ROSEWATER, Cleveland: Rectal fissures produce a tendency toward constipation, sometimes alternating with diarrhea, because nature finally asserts itself and a forced movement takes place. I found that by giving individuals inclined to seasickness (antiperistalsis) a cathartic, and continuing it for two or three days before embarking, antiperistalsis would not occur. Patients who before that were so inclined to seasickness that they could not stand being on the water could be on it in spite of the greatest storm, while others were sick, even the sailors. By giving them something which would overcome antiperistalsis by hyperperistalsis, if the gradient is sufficiently strong outward or downward, you have no tendency toward antiperistalsis. We have all tried it in numerous ways, with cathartics in cases of nausea, but the treatment must be guided by that principle of overcoming antiperistalsis. Twenty years ago I maintained that headaches, colds, etc., are often due to fecal obstruction, the effect of such stasis on the vasomotor mechanism, demanding greater heart action to overcome the narrowed caliber of the vessels from stasis and drag; it is forced to greater effort and pressure than the vessels of the upper tracts are adapted for, therefore, some headaches are relieved by enemas or cathartics long before the bowels are emptied. After feces have passed downward enough so that the place of obstruction is relieved, together with the resultant vascular pressure, which causes the headache, the headache disappears. These headaches cannot be toxic; relief is too quick. They are obstructional. At that time I stated that enlarged thyroid glands or any vascular engorgement or enlargement in the thoracic or cranial cavities may be from cardiac overaction. In these locations there is too much blood sent to the upper tract relative to the quantity sent into the abdomen. If the greatest amount of blood reaches the thyroid, it slowly enlarges and begins to overfunctionate in quantity and quality; the tonsils enlarge the same way. So much free space in the oral cavity causes a greater tendency for engorgement there, also in the nose and throat, the wedgeshaped nasal spaces are engorged the soonest and occluded with oozing of serous fluid or mucus. Obstruction of the narrow nasal passages is the logical result; coughs, colds, congestions and inflammations of the nasopharyngeal and respiratory apparatus soon follow.

DR. WALTER C. ALVAREZ, San Francisco: As I remember Dr. White's paper, when he stimulated the lower bowel mildly, he was unable to see any change; but when he stimulated it powerfully, he could see stasis above and signs of reversal. This is what we should expect. I believe, however, that mild stimuli will produce disturbances which a man can feel but which we cannot demonstrate in an animal. For instance, an enema, particularly one made irritating by the addition of much salt and soap, will produce nausea. This, I believe, is a sign of mild reversed peristalsis. Similarly, a constipated man will stop regurgitating his food the minute the rectal plug is removed. With such mild stimuli I do not believe we could see any changes in an animal's peristalsis. What I would emphasize is that the gradient is there in normal animals; there is no difficulty in demonstrating it; moreover, it is found reversed or flattened in diseased animals. These things must have some significance and it is up to us to face the problem and carry it to a solution.