The Effect of Atropine on the Gastro-Intestinal Canal and its Glands*

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WHEN the Editor asked for a review on Atropine and Belladonna, it seemed opportune to clarify certain conceptions which stand in the way of the intelligent use of atropine. The first of these is based on the typical experiment of the pharmacologist, who stimulates the vagus and perhaps the chorda tympani, and then gives a large dose of atropine; the heart rate increases and then stimulation of the vagus fails to produce its previous decrease in cardiac rate and that of the chorda no longer produces secretion of saliva. This is a legitimate pharmacological experiment, but not a therapeutic one, as the dose employed is many times larger than that used therapeutically; sufficient, in fact, to produce intoxication in man. But the student, and indeed the older text-book, retain the impression that a therapeutic dose will increase the cardiac rate. This misconception is unfortunate. A therapeutic dose, 1/150-1/75 gr. (2/5-4/5 mgm.), given per os or hypodermically will, as a rule, cause reduction of the pulse rate by a few beats at the end of half an hour; while a 1/50 gr. may increase it by a few beats, 1/30 gr. will increase it by some 20-30, and it will take 1/10 gr. to have as great an effect as in the pharmacologist's experiment. With a therapeutic dose the mouth is dry but some reflex saliva can still be obtained.

The second misconception is that after therapeutic or even massive doses of atropine the vagus innervation of the gut is abolished. This has been abundantly disproved by Cushny (1), Bayliss and Starling (2) and Henderson (3). Even small doses (0.2 mgm. to a dog) decrease gut tonus but vagus stimulation will cause an increase in contractility even after huge doses (30 mgm. to a dog). Similar results have been obtained for the cardiac sphincter and the colon (Langley and Anderson (4)).

The third misconception often repeated in text-books is that atropine stimulates the gut. This is due to the work of Magnus (5), who first employed the isolated gut in the water bath and found that in his experiments a concentration of 1:4000 was required to produce any effect and then an increase of movement was shown. Any modern experimenter who knows his technique, can see that Magnus, working before our knowledge of the importance of controlled hydrogen-ion concentration, had a bad bath fluid. Unger (6) in the next year produced a decrease in tonus and contractility with a concentration of 1:1,000,000 or less. But Cushny, who had not used the technique, preferred to believe the famous Magnus rather than the unknown Unger and recorded Magnus' results in his text-book; yet Unger has been abundantly confirmed by subsequent workers.

The fourth misconception arises from the fact that it is assumed that Tincture of Belladonna owes its activity to atropine and that the chemical assay of the pharmacopoeias indicates atropine content. In the British Pharmacopoeia a full dose of 30 mins. of Tincture of Belladonna contains alkaloids assayed as Hyoscyamine equal to 1/100 of a grain. It has been shown by Jendrassik and Will (7), van Lieuwen and Maal (8) and others that the pharmacological activity of preparations of Belladonna are greater than the alkaloidal content if this is considered to be atropine, and somewhat greater even if considered as l-hyoscyamine. Indeed, based on tests in our laboratory some 6-10 mins. Tincture of Belladonna seem to give an effect equal to that of 1/100 gr. Atropine in man. This is due probably to two factors. The chief alkaloid in Belladonna is laevo-hyoscyamine which is known to be at least twice as active as atropine, which is the racemic form; in addition, it seems probable that the other alkaloids present also increase the pharmacological activity.

The great step in knowledge initiated by Loewi (9) and Dale (10) and for which they got the Noble Prize, was that on stimulating any parasympathetic nerve fibre, acetylcholine was produced at or about its terminations. The acetylcholine then acted on the gland or muscle cells and led in turn to its activity. Further, it was shown that the sympathetic nerves to sweat glands led also to a production of acetylcholine and this is true of certain sympathetic fibres to vessels in muscles, in certain animals at least. Hence Dale suggested the term 'cholinergic' for those fibres, parasympathetic or sympathetic, which, on stimulation, liberated acetylcholine, and the old observation that pilocarpine led to the activity of sweat glands as well as all parasympathetically innervated glands or muscles, appeared in a new light. Pilocarpine activates all cholinergically innervated structures and atropine usually depresses them. The word 'usually' is used advisedly. A motor nerve to a skeletal muscle when stimulated, also liberates acetylcholine and the effect of stimulation cannot be

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abolished by atropine. This is true also of the preganglionic fibres, whether sympathetic or parasympathetic, which also liberate acetylcholine in the ganglion and which are uninhibited by atropine.

The dilatation of the vessels of the salivary glands on chorda stimulation persists after atropine. This might be explained on the basis that the stimulation produced acetylcholine, as we know it does, and that the acetylcholine diffused to the vessels and dilated them. Dale seeks to explain the failure of atropine (again even in massive doses) to prevent the stimulation of the pelvic nerve causing contraction of the bladder by the failure of atropine to block the action of acetylcholine as it does elsewhere; and again this failure must apply to the gut, as was pointed out above. The acetylcholine hypothesis of nerve transmission is quite properly generally accepted, though there are some dissidents; but it is not to be followed too slavishly as yet.

Undoubtedly there is one thing which this work has taught us, namely, that injected acetylcholine will act on cells, gland or smooth muscle and put them into activity. Pilocarpine acts also on cells and atropine, acting upon certain cells, prevents acetylcholine from activating them.

SALIVARY GLANDS

Ivy (11) has well summed up the evidence leading to the conclusion that the salivary glands are entirely under nervous control. After atropine the effect of vagus stimulation is lost before that of chorda, although this, too, is greatly reduced; but Henderson (12) found great variability in the amount of atropine actually required by different dogs. In one case 0.1 mgm. atropine sulphate intravenously to a 10 kgm. dog decreased the effect of chorda stimulation from 15 to 10 drops of saliva; 0.2 mgm. decreased the effect of vagus stimulation; 0.5 abolished it, but chorda stimulation was not inhibited completely. There is abundant evidence that about 1.2 mgm. atropine to a man did not entirely release the heart from vagus control and that to do so 1/30 gr. or 2 mgm. is required. In man about 0.5 mgm. usually produces a dry mouth but some reflex saliva can still be obtained. As far as can be judged, man is somewhat more sensitive than the dog per body weight, the required dose being about 0.3 mgm./10 kg. for man and 0.5 mgm. for the dog.

GASTRIC GLANDS

When we turn to the gastric glands and the effect of atropine upon them, the same variability in sensitivity should be remembered and secondly, it should be realized that even an intravenous dose of atropine does not exert its full effect for some minutes, while the effect of a subcutaneous dose does not reach its maximum for some 30 minutes. Orally the latent period is nearly as long. These points have been overlooked by some workers.

The gastric glands are put into activity by the so-called psychic secretion which, in as far as it arises from sense endings in the mouth or nose, might more properly be called a reflex secretion. The efferent pathway is the vagus. Secondly there are other sources, mechanical distension, secretogogue substances which act reflexly or directly on the glands. Histamine may be one of these, and finally there is evidence of a hormone, usually termed gastrin (after Edkins), which has been most persistently sought for by Ivy. A good summary of the evidence may be obtained in his papers (13-22).

Direct evidence of gastric secretion produced by stimulation has been but rarely sought. Pawlow and Schumova (14) and Uschakow (15) however, have shown that direct stimulation of the vagus leads after a long latent period, to a secretion of gastric juice with high peptic activity, but low acidity, probably owing to the amount of mucus with which it is secreted. The administration of atropine abolished the effect of such stimulation. Further, it must be remembered that splanchnic stimulation also seems to produce secretion.

Hartzell (16) showed that cutting the vagi decreased gastric acidity for 5 months, but not after a longer period on the same animals (Van Zant (17)).

In animals there is evidence that atropine decreases the secretion after food has been given (Riegel (18), Keeton, Luckhardt and Koch (19)) and on the whole the acid secretion seems to be more depressed than the total amount. Lim, Ivy and McCarthy (20) found that the secretion obtained by distension was reduced by 1 mgm. atropine. The secretion produced by secretogogue substances, partly purified and given in various ways, was again abolished. Gray (21), who produced a constant secretion by repeated small injections of histamine in dogs, showed that 0.5 mgm. atropine subcutaneously decreased the acidity by 25%, 1 mgm. by 37% and 2 mgm. by 43%, but that if the histamine dosage were larger, such doses of atropine had much less effect, thus confirming Keeton, Luckhardt and Koch, and Ivy (22) who states that 1 mgm. of atropine to a dog will antagonize threshold doses of histamine, but not larger ones.

Again Keeton, Luckhardt and Koch found that while 0.025 mgm. atropine reduced the secretion produced by a purified but still impure gastrin, 12 times this dose did not abolish it. Klein (23) found that when secretion from a completely denerved pouch was produced by hydrochloric acid, 1-1.5 mgm. per kg. dog abolished it, but not if the flow was larger. Ivy and Jarvois (24) showed that protein hydrolysates administered by stomach tube caused secretion in a denervated pouch and that 1 mgm. of atropine prevented it.

This brief summary of the striking evidence obtained from dogs where conditions can be closely controlled, makes it evident that experiments on man are not likely to furnish more than uncertain evidence, particularly when there is good evidence that psychic inhibition occurs readily, even in dogs.

The evidence of Adlor (25), Lockwood and Chamberlin (26), Rall (27) and Winkelstein (28), all using

test meals, may be summed up by saying that 0.5 mgm. (1 120 gr.) produces but slight reduction in gastric acidity, whether given per os or subcutaneously; 1 mgm. (1 65 gr.) produces more effect, and 1.2 mgm. (1 50 gr.) still more effect, but the individual variation is great.

Keefer and Bloomfield (29), using an alcohol test meal (50 cc. 7%) found that after atropine (2 mgm.) there was often a prompt initial secretion in the first 10 minutes and then a decrease from the normal. In other cases this decrease occurred earlier. The acidity also decreased.

Polland (30) using 0.2 mgm. 10 kgm., i.e. about 1.2 mgm. and a histamine stimulus, found a decrease in juice volume and pepsin content.

Crohn (31) found that 1 65 gr. might increase the acidity but in 2 cases where there was a continuous secretion; the dose stopped it.

It should be remembered also that changes in acidity, as a criterion of the amount of secretion, are full of possible fallacies.

A careful study on a gastric fistula case, using various stimuli, reflex, alcohol, histamine and hydrochloric acid, with measures of total secretion, acidity and ferments (and the effect of atropine), would be of value.

It does not seem improper to sum up the impressions derived from the literature by saying that 0.5 mgm. will decrease the psychic secretion more than that due to histamine or the hormone, but that the total effects will not be great, while a dose of 1.2 mgm. atropine will abolish a continuous secretion, but not that found in some cases of duodenal ulcer. The same dose will decrease, to some extent, the effect of histamine and alcohol and may have some effect if a meal is the stimulus (see also Ivy 13-22).

THE PANCREATIC SECRETION

Pancreatic secretion can be produced by vagus stimulation in dogs, but as is evident in the experiments of Modrakowski (32), the amounts are small. On the whole, he obtained more response by rhythmic mechanical stimulation of the sympathetic. The small amount of secretion may be explained by the work of Korovitsky (33), who showed that in the cat the vagus contained fibres which constricted the pancreatic ducts. Popielsky (34) claimed that pancreatic secretion was as prompt on stimulating the vagus in dogs as saliva on stimulating the chorda; however he speaks of choosing certain vagal fibres or fibres accompanying the vessels in the gland; but these might be sympathetic. Popielsky states that his results could be obtained even if the pylorus were tied. There is every evidence that the secretion may, in part, be psychic.

Some of the difficulties in interpretation of the earlier workers were resolved when Bayliss and Starling (35) suggested and produced evidence for the existence of a hormone, secretin, formed by the action of acid or other substances on the gut wall and carried by the blood stream to the pancreas. Any doubt about the existence of this hormone was cleared away by the work of Farrell and Ivy (36). Even prior to the work of Bayliss and Starling it was evident that in the dog the gastric secretion produced by taking food was reduced by atropine, for example Babkin and Sawitsch (37), Bylina (38) and Babkin (39). It is, however, clear that the effect of atropine on hormonal secretion is much less. Farrell and Ivy, for example, found that the secretion produced by giving hydrochloric acid was not reduced by 1.5 mgm. to a dog, and Bayliss and Starling could not reduce the secretion from the injection of their impure secretin by atropine; and as was found by Pawlow (40) and Gottlieb (41), the continuous pancreatic secretion in rabbits doubtless due to secretin, is not reduced.

If, then, we turn to observations in man, Holsti (42) showed clearly that the prompt secretion (in one minute) on taking food and the decrease in secretion on injection of 1 mgm. of atropine one hour after taking food, reached its maximum in about 20 minutes and lasted about one hour.

Comfort, Osterberg and Priestley (43) found that 1 75 gr. (0.8 mgm.) taken at the beginning of a meal and repeated at the end of the first and second hours, caused a decrease in secretion, especially in that of the second and sixth hours. This may, in part, have been due to an effect on gastric movements. McCaughan, Sinner and Sullivan (44) found that 1 100 gr. (0.6 mgm.) caused a slight decrease in a continuous secretion, as did Snyder and Lium (45) after food.

The doses employed therapeutically in man are small and it is hardly to be expected that much effect would be produced, especially when the secretion is hormonal.

GASTRIC MOVEMENT

A careful study of the literature, well summarized by Barclay (46) and Alvarez (47) and illustrated by unpublished experiments in gastric movements and by several studies of intestinal movements from this laboratory (48, 49), leads to the following condensed pictures of the movements of the stomach. Perhaps the most important change is in that of the tonus, which produces variable but not marked changes in internal pressure and to changes in form and position owing to the peculiar distribution of the longitudinal and particularly of the oblique fibres. Secondly, there are the so-called peristaltic waves, which like those of the intestine as Cannon (50) has shown, are produced by stretching, but which according to the evidence of Thomas and Kuntz (51) do not require the participation of the plexus as do those of the intestine. These waves frequently begin in the area of the incisura, but may occur in the cardia. Usually not deep at first, as they progress towards the pylorus, they become deeper and may in extreme cases cut the content in two. When a wave has progressed to within 2-3 centimeters of the pylorus, there is often a sudden contraction of this area (called a systole). Superimposed on these waves are smaller more frequent waves (wavelets of Alvarez and Zimmerman (52)). These are possibly not progressive and more or less resemble the

rhythmic waves of the intestine. Just before a peristaltic wave, they are more marked and may be superimposed on it. Apparently there are also waves of a slower character than either of these; the waves of tonus change. The musculature of the pylorus is continuous with that of the pyloric antrum, but somewhat thicker. Functionally it seems to act as a continuation of the stomach but the tonus of this region is highly variable. In some cases it is almost patulous and content passes easily, very slight peristaltic waves being enough to forward the content, but on the other hand the tonus may be high and even deep waves force little or nothing, as though the contraction of the pyloric sphincter had occurred so promptly that it prevented the passage of content. The careful work of Quigley and Read (53) indicates that most of the ejected stomach content passes before the sphincter contracts, but that some passes in the early phase of sphincter contraction.

The stomach is supplied with both vagus and sympathetic nerves. *The vagus:* there is clear evidence that vagus impulses reflexly produced by the act of swallowing cause a relaxation of the cardiac sphincter and of the cardia. The work of May (54) and Cannon and Lieb (55) shows this clearly in animals and also that vagus stimulation may produce the same effect, often followed by a rise in tonus of the sphincter. It is not known how far these inhibitory fibres spread over the cardia. On the other hand, there is abundant evidence that stimulation of the vagi may produce increase of tonus and of peristalic waves (McSwiney and Wadge (56), McCrea and McSwiney (57)). Hence it is not astonishing that varying results have been obtained by all students of the question, but the evidence may be summed up by saying that if the tonus is high and/or movements marked, vagus stimulation produces a more or less marked inhibitory effect, at all events for a short period, while if tonus is low and/or movements slight, vagus stimulation is augmentor. As the action of pilocarpine varies similarly, it seems that both types of fibres are cholinergic. The effect of atropine might also be expected to be indefinite. In McSwiney and Robson's (58) work with isolated gastric muscle strips from the cat, vagus stimulation which produced contraction changed to relaxation after atropine, as though augmentor actions were more readily depressed by this drug.

THE SYMPATHETIC

Similar results have been obtained by stimulation of the sympathetic, but when tonus is high or movements marked, inhibition is produced and when low the reverse. The work of Brown and McSwiney (59) should be noted, as they found that the frequency and strength of the stimulus produced different effects. In the dog, for example, in the antrum only occasionally did low frequency produce augmentation, but usually all strengths and rates caused inhibition, while in the body of the stomach 1 per second or weak stimuli might produce increased rate of movement and some increase of tonus while more frequently a stronger stimulation produced inhibition of tonus and movement. A careful study with modern methods of condenser discharges on the two nerves might be of value.

EXPERIMENTS WITH ATROPINE IN MAN

Here again we find a varying result obtained, and even more than in the experimental animal it is difficult to select the best technique (see the discussion of this problem by Neidhardt (60). The balloon technique, so often used, gives information which may or may not be adequate. In the pyloric region a small well-filled balloon should record both tonus changes and peristaltic waves, but the smaller waves are not seen unless they fuse. In the body of the stomach, unless the balloon lies in apposition with the walls, i.e. is large, tonus changes may not be recorded and if the balloon is large and not distended fully (when it will act as a source of stimulation as it has been frequently shown that distension of the stomach does) then a small peristaltic wave may not be recorded. Unfortunately, most observers have not furnished adequate details of the method used. Use of the X-ray, when continuously watched, has a large subjective error and when plates are taken they show only the state at their particular time.

Lasch (61), using the X-ray technique, reports that in normal stomachs if gastric tonus was high or normal, tonus was decreased by atropine 1-1.5 mgm. intravenously, if low there was little change. Marked peristaltic waves were decreased or abolished.

Titelbaum (62), using a pyloric balloon, reports that 0.5 mgm. intravenously decreases the balloon pressure (tonus) and also the large waves, but not in all cases in which higher doses were required. He brings forward the following observations which seem to be important. After recording for 20 minutes, 0.3 mgm. atropine intravenously was given, the waves ceased: then 100 cc. of gruel was given; the peristaltic waves reappeared, as one might expect from the additional stretching produced. These were recorded for 15 minutes and 0.5 mgm. of atropine was given intravenously with no effect, nor did a repetition of this dose produce any effect. However, 1 mgm. did lead to a decrease. This suggests that the effect of atropine depends on the conditions present in the stomach. This work might well be repeated.

Veach (63), using a balloon method, used a preliminary injection of morphine (7.5 mgm., ⅛ gr.). This usually produced an increase in tonus and movements (probably on account of a central vagus action), though in cases with low tonus the morphine might produce inhibition. Atropine, 0.3 mgm. intravenously, decreased the movements and lowered tonus. Frequency of the recorded waves was not much changed.

Quigley, Johnson and Solomon (64) in normal men recording with a triple balloon method and using an insulin hypoglycemia stimulus (which is also probably vagal), injected 1 mgm. atropine subcutaneously and the movements were decreased. Their results parallel

those of Wilder and Schlutz (65) in the dog with insulin stimulation. Quigley (66) in another paper contrasting the effects of atropine and novatropine, found that in his cases the increase of movements produced by insulin was completely inhibited by 0.65 mgm. atropine subcutaneously in about 8 minutes, the effect lasting 45 ± 15 minutes. It required 1.5 mgm. of novatropine to produce the same effect.

The work of Anderson and Morris (67), who were careful to estimate the sensitivity of their patients by recording the effect of atropine on cardiac rate, again showed in fasting men varying effects, 0.05-0.3 mgm. intravenously might increase the hunger movements, 0.4-1.0 caused cessation. Subcutaneously 1.2 mgm. would seem to be required to produce an equal effect. They found, however, that 0.1 mgm. intravenously and repeated in 30 minutes, produced an effect equal to a single dose of 0.6 mgm. Neidhardt (60) and Otvos (68) report similar varying results.

It seems obvious that the results of atropine administration on the peristaltic waves and tonus will depend on the dose and an effective one may be estimated at 0.6 mgm. intravenously or 1-1.2 mgm subcutaneously. The effect of such doses will, however, in part, depend on the causation of the movements, for example the fullness of the stomach, and on the existing tonus and degree of the movements. Further, it is probable that under certain conditions of tonus smaller doses will produce some effect on the movements and on gastric emptying time.

GASTRIC EMPTYING TIME

As might be expected from the foregoing, the studies of the effect of atropine on emptying time have given highly variable results, ranging from Folley and Abbott (69) in five carefully controlled cases, who conclude that 0.4-0.8 mgm. before a meal produce no essential change, to such a study as Herrin's (70) of thirteen normal cases in whom atropine about 1-1.2 mgm., given subcutaneously increased the initial emptying time in 9 out of 13 cases, and the time to final emptying in all 13 cases; the tonus was always lowered, peristaltic waves were of less depth and of the same frequency. He points out, however, that if a large meal was given, the delay was less. Lasch, too, found with doses of 1-1.5 mgm. intravenously, the emptying time was greater, but not in all cases; in atonic cases the delay was greater than with normal ones and greatest in hypertonic cases. Lowy and Tezner (71), giving 1 mgm. subcutaneously to children, report delay in 78% of the cases and with larger doses delay in all. Van Liere and Northup (72) found that in young and old the results of atropine were essentially the same.

When there is pyloric spasm in infants, atropine in very small doses, 0.065 mgm., preceding a feeding, may lead to a relief of the symptoms. Eumydrine may prove even better (Svensgaard (73), MacKay (74)). As so often happens with drugs, it is easier to reduce a hypertonic state than a normal one. The tonus of the pyloric sphincter is probably reduced in these cases more than that of the rest of the stomach or its movements.

ON THE SMALL INTESTINE

The evidence from animals and what little we have of value from man is much more consistent. The small gut shows tonus changes, peristaltic waves which certainly partake of the nature of local reflexes through Auerbach's plexus and are elicited by stretching (Trendelenburg (75)). There is little spreading of the stretch stimulus in the plexus (Henderson 48)). The third movement is the rhythmic waves or pendular movements and these often show an increase in activity before a peristaltic wave. The peristaltic wave is not proceeded aborally by a fall of tonus or decrease of the rhythmic waves. These various changes in activity may give rise to various patterns of activity when judged by a balloon method. Atropine even in low concentrations (Unger and many others), decreases the tonus and in the intact dog 0.01 mgm. per kg. definitely decreases the tonus of the small intestine, but the effect of vagus stimulation on the rhythmic movements is unaffected. Quigley, Highstone and Ivy (76) showed that atropine decreased greatly the rate of passage of a bolus through Thiery-Vella loops of the jejunum. Gruber, Green, Drayer and Crawford (77), using Thiery-Vella loops of the ileum, found that 0.5 mgm. of atropine intravenously reduced the tonus but the rhythmic movements appeared to be increased in some cases; this increase may be due simply to the lower tonus and may be seen with low concentrations of atropine in the isolated gut, if tonus is high.

Kendall and Drossner (78) in five patients, using a balloon of large size containing 40 cc. under a pressure of 10-12 cm. of water, which in itself would be likely to cause activity, found that in the duodenum the high tonus and frequent peristaltic waves were reduced by 0.4-0.6 mgm. of atropine subcutaneously. The peristalsis often appeared more pronounced but this may also be observed in the Trendelenburg gut because the internal content is greater when the tonus falls slightly. Similar effects were found in the jejunum and ileum. The effect on tonus lasted longer than that on movements. If a barium meal was also present, the rhythmic movements and the peristalsis persisted, and if the tonus were initially high the waves became larger as the tonus fell. Using a barium meal alone in the duodenum, atropine greatly decreased the rate of passage. This too, would be expected, as a fall of tonus in the gut has the effect that it must be stretched more before a peristaltic wave arises (Trendelenburg) and this wave often fades out sooner (personal).

LARGE INTESTINE

A study of the large intestinal movements has been less often undertaken. The irregular changes in the caecum and ascending colon, as seen by X-ray examination, are probably due to rhythmic haustral movements. Peristaltic movements occur infrequently and especially under the action of purgatives, or dis-

tension, or the defecation reflex, run for long distances. Tonus in the empty bowel appears to be high as a rule.

Combinations of these changes occur and give rise to various patterns well described by Templeton and Lawson (79) and by Adler and Ivy (80) in dogs and by Adler, Atkinson and Ivy (81) in man.

As shown by Adler and Ivy, 0.028 and 0.052 mgm. per kg. subcutaneously in dogs produces a decrease in tonus and in movements, the distal colon being more affected than the proximal. The increased tonus produced by small doses of morphine could be reduced by atropine, but that produced by larger doses was resistant.

The activity of the large gut in man was decreased by 1 mgm. of atropine in the experiments of Ganter and Stattmüller (82) and Katsch (83).

Jackman and Bargen (84), using a balloon and water manometer technique in man, have shown that 0.6 mgm. of atropine caused a fall of tonus and decrease of movements in the colon and Lium (85) has shown the same for the rectum.

Atkinson, Adler and Ivy (86) using a two-balloon method in a series of experiments on colostomized dogs and patients, found that for at least half of the time there is motor activity in the colon; of this, approximately 10% is propulsive. In the patients, 0.8 mgm. atropine depressed the spontaneous motility and larger doses decreased both propulsive and non-propulsive motility. Atropine was found to antagonize the hypertonicity produced by morphine; 0.7 mgm. atropine was given with 8 mgm. morphine sulphate and propulsive motility was abolished for 2 hours. Non-propulsive action and tonus were decreased.

Very little of the work outlined in this review is clear cut; there is real need for the clarification of the whole picture of the movements of the gut and their response to drugs.

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Newer Concepts in the Treatment of Diabetes Mellitus with Protamine Insulin

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OUR experience with protamine insulin in the treatment of diabetes has led us to the adoption of certain concepts, which deviated strikingly from the long established fundamentals of diabetic therapy. These were that the urine be free from sugar and that the blood sugar approach the normal level. When we attempted to treat our diabetic patients with protamine insulin, using such criteria for satisfactory control, we encountered difficulties which on further experimental and clinical study led us to other conclusions. It is the purpose of this paper to present the evidence for our newly adopted point of view.

Our guiding principles in the treatment of diabetes mellitus when using protamine insulin are:

1. Maintenance of weight.
2. Freedom from all symptoms of diabetes—thirst, polyuria, frequency of urination, hunger, weakness, fatigue, polyphagia, pruritus of the genitals, (chiefly in females), and visual disturbances.
3. Absence of ketone bodies in the urine—acetone and diacetic acid.
4. *Glycosuria*, we felt was desirable as its presence afforded protection from reactions.

On the first three there is general agreement. The last, namely the glycosuria and its unavoidable concomitant hyperglycemia, have been extensively criticized (9).

Our observations began in 1936 when we commenced using protamine insulin in our diabetic clinic at the New York Hospital. We selected a group of our ambulatory patients and explained to them that we had a new insulin which we wished them to use. These patients were intelligent and cooperative. Since we knew nothing of the technique for the use of protamine insulin we followed Hagedorn's recommendation, that is, the use of regular insulin in the morning, and protamine insulin at night. The logic for this technique was sound, as it is well established that the moderately severe and severe diabetics have a rising blood sugar during the night even if no food is taken (18).

A slowly acting preparation appeared ideal, therefore, as it tended to counteract this nocturnal hyperglycemia. At that stage of our therapy, we made every effort to adhere to the dicta of a sugar free urine and a normal blood sugar. Those were the established and conventional criteria. All agreed. However, when we found that with one daily dose of protamine insulin our patients revealed a glycosuria, we began to supplement the protamine insulin with regular insulin hoping in this fashion to eliminate the post prandial glucose loss. We also found ourselves juggling the diets so that our patients instead of receiving their daily dietary intake in the three equal divisions, were given an unequal distribution of the calories, as recommended by some workers in the field (17, 28). In addition we advised the withholding at breakfast of foods containing immediately available sugar, such as fruit juices (29). The results of all this maneuvering were that our patients were not free from sugar at all times, and when we attempted to obtain and maintain a urine free from sugar our patients developed most alarming and prolonged hypoglycemic reactions which were extremely subtle in onset. Thus the patients were receiving multiple injections of insulin, they were burdened with additional dietary instructions and they

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