THE PANCREATIC SIDE-EFFECTS OF MORPHINE

BY

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Prior to the publication of Lagerlöf's studies (1945, 1947), information regarding the influence of morphine on the pancreas was very fragmentary. In 1907 Bickel and Pincussohn observed in two dogs with pancreatic fistulae that it first decreased and later increased the output of the external secretion. Cohnheim and Modrakowski (1911), using dogs each with a duodenal and an ileal fistula, found that morphine depressed the natural response to food. Babkin (1928) also noted a diminution in the duodenal content after its administration to animals. A more remote effect, which has been reported in rabbits, is an increase in the diastatic index of the urine (Sato, 1940).

The first recorded studies in humans are by Lagerlöf. Primarily interested in the fat-splitting enzymes in the blood, particularly those elaborated by the pancreas, he conceived that morphine might serve as a safe means of deranging the function of the gland. He compared the effect produced by the intravenous administration of purified secretin on the content of digestive ferments in the blood and duodenum with the effect of secretin given along with morphine. For the recovery of the duodenal juice he made use of the gastro-duodenal tube, thus minimizing the amount of gastric juice entering the duodenum. Secretin alone produced an abundant flow of pancreatic juice of high bicarbonate content unassociated with any appreciable change in the lipase levels in the blood. When it was given along with morphine there resulted a reduction in the volume of the duodenal fluid and a concomitant lowering of the secretory rates of amylase, trypsin, and, to a less extent, the bicarbonate of the pancreatic secretion: the amount of bilirubin in the duodenal contents was also diminished. These changes were maximal approximately 30 minutes after morphine. Soon afterwards there appeared in the blood a lipase that had not previously been present. Lagerlöf interpreted these findings as being due to overaction of the sphincter of Oddi interfering with the delivery to the duodenum of the bile and pancreatic secretion, and leading to absorption of a portion of the latter into the blood stream. He could not, however, exclude altogether the possibility that morphine depresses the function of the pancreas. The procedure just outlined has come to be known as the morphine–secretin test, the focus of attention having shifted to the response on the part of the serum-enzymes (see below). Lagerlöf has also made the arresting suggestion that the nausea and abdominal discomfort, sometimes amounting to pain, which not infrequently follow the administration of morphine, may be symptomatic of a drug-induced pancreatitis.

This paper is principally concerned with the serum-enzyme effects of morphine on healthy humans. Some were investigated in the fasting state, others were given a substantial meal before morphine, and in a third group an attempt was made to exalt the so-called vagus response of the pancreas to food by giving a parasympathetic stimulant before the morphine. Carbaminoylcholine chloride (carbachol *B.P.*) was chosen, since it has been shown to exert a vagus-like action on the pancreatic secretion (Wapshaw, 1952).

Biochemical Studies

Methods.—In most of the experiments both the amylase and lipase estimations were carried out with the same sample of venous blood. For the former the Somogyi iodometric test was employed, for which the normal range of values is 70–200 units per ml. of serum, although for each individual the value varies very little. The lipase activity was determined by the Cherry and Crandall (1932) test. By this method it is unusual for normal values to exceed 1.5 ml. N/20 sodium hydroxide per ml. of serum. A rise in the serum amylase of 50% over the premedication reading was regarded as significant. It was more difficult to decide what constituted a positive lipase response; but in view of results in the literature and after considerable experience an increase of at least 100% over the premedication control reading was taken as a positive result.

Effects of Carbachol.—This was a control study. Twenty-eight normal volunteers were investigated. These were divided into two equal groups. The first group fasted during the experimental period. The second received a meal consisting of soup, a meat dish with potatoes and vegetable, and a milk pudding 45 minutes before the injection of carbachol. Each subject received 0.5 mg. of carbachol intramuscularly, which is twice the upper therapeutic dose. Only lipase estimations were carried out in this series. (*a*) *Fasting Group:* Three out of 14 subjects showed a slight but apparently significant increase in the lipase concentration two to five hours after carbachol. The most pronounced increase was a rise from 0.7 ml. to 1.7 ml. N/20 NaOH per ml. serum. (*b*) *Fed Group:* Only 1 of the 14 subjects had altered readings. The control reading in this case was 0.6 ml., and four hours after carbachol the reading was 1.2 ml.

Effects of Morphine Hydrochloride.—The 84 individuals investigated were divided into three groups, each comprising 28 subjects; all received a subcutaneous injection of ¼ gr. (16 mg.) of morphine hydrochloride. The first group fasted throughout the experimental period. The second group had a meal (see above) 60 minutes before the administration of morphine. The third group received a similar meal and 45 minutes later an intramuscular injection of 0.5 mg. of carbachol; after a further 15 minutes the morphine was injected. Thus it was arranged that the morphine was given at a time when the pancreas was likely to be in a state of active secretion. (*a*) *Fasting Group:* An increase in the amylase and lipase levels was observed in 5 of the 28 subjects (18%). The highest rise for amylase was three times the premedication reading in that subject and the highest for lipase 20 times (see Table I). (*b*) *Fed Group:* Raised levels were noted in 9 of the 28 investigated (32%). The highest rise for amylase was 9.1 times the premedication reading, and the highest for lipase 14.7 times (see Table II). (*c*) *Food plus Carbachol:* Raised levels were observed in 19 subjects (68%). The maximum responses were observed in the same case (No. 15, Table III) and amounted to 22 times and 17 times the premedication values for amylase and lipase respectively. In several the changes were marked within the first hour, but maximum augmentation more usually occurred two to four hours after the morphine injection. A comparison of the two sets of readings indicated that the lipase concentration was more readily affected than the amylase concentration.

TABLE I.—*Effects of ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Fasting Subjects (only the 5 instances of positive responses are shown)*

No.	Amylase (units/ml.)						Lipase (ml. N/20 NaOH/ml.)					
	Fasting Reading	Hours after Morphine					Fasting Reading	Hours after Morphine				
		1	2	3	4	5		1	2	3	4	5
1	100			180								
2	180				460		0·5				1·8	
3	177			530			0·3			4·6		
4	220			260			1·8			3·2		
5	160			320			0·1			2·0		

TABLE II.—*Effects of Food and ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Subjects (only the 9 instances of positive responses are shown)*

No.	Amylase (units/ml.)							Lipase (ml. N/20 NaOH/ml.)						
	Fasting Reading	Hours						Fasting Reading	Hours					
		1	2	3	4	5	6		1	2	3	4	5	6
1	177				200			0·2				2·6		
2								0·1					2·6	
3	84					188		0·4					1·2	
4	114				640			0·4				5·9		
5	100	400		914				0·8	6·4		7·6			
6	100			640				1·1			5·3			
7	123			530				1·3			3·1			
8	139			800				0·5			3·4			
9	160			800										

TABLE III.—*Effects of Food, 0.5 mg. of Carbachol, and ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Subjects (only the 19 instances of positive responses are shown)*

No.	Amylase (units/ml.)											Lipase (ml. N/20 NaOH/ml.)									
	Fasting Reading	Hours										Fasting Reading	Hours								
		1	2	3	4	5	6	7	8	9	10		1	2	3	4	5	6	7	8	9	10
1	100	94	213									1·2	1·3	4·6								
2	80	85			220							0·7	0·7			3·9						
3	40	44			53							0·7	1·4			2·4						
4	50					88						1·1					2·4					
5	66			177							106	Zero			2·5							0·9
6	46				145							,,				1·6						
7	55					114						,,				0·6						
8	66	118		172								0·6	4·0		2·7							
9	80	340		420								0·4	5·2		5·1							
10	100	710	1,600									0·8	8·0	9·6								
11	60	760	940									0·7	3·5	6·6								
12	168	530		650								1·1	7·0	6·5								
13	94	200		578								1·6	4·5		6·0							
14	123	640		1920								0·9	7·4		10·1							
15	70				1600				800			0·6				10·2				4·3		
16	55	96		320								1·2	7·5		10·7							
17	160	400			580							0·9	5·0			1·6						
18	73					920						0·9					8·5					
19	80				580							1·3				5·8						

Bodily Reactions

Carbachol.—The somatic effects varied from case to case. Some subjects were apparently unaffected. Others complained of flushing of the face and neck, diaphoresis, salivation, a desire to void urine or go to stool, and one suffered from fairly severe precordial distress.

Morphine Hydrochloride.—One-fifth of all the subjects complained of nausea and about half of those affected vomited. The detailed incidence of sickness in the three groups was as follows : fasting, 21% ; fed, 18% ; fed and received carbachol, 25%. In some the feeling of sickness, often with giddiness, came on soon after the injection of morphine ; in others it did not come on for one to two hours. It passed off after about two hours.

There was no correlation between the occurrence of sickness and the enzyme findings in the blood.

Pain developed in the epigastrium in three subjects. One belonged to the fasting group and the other two to the group which received food and carbachol. One of the latter was in great distress when examined, not only with pain that radiated in the lumbo-dorsal region but also with vomiting and retching. None of the three, however, showed signs of intra-abdominal irritation, and all the unpleasant effects had passed off within a few hours.

The serum enzymes were slightly raised in two of the three affected with pain. The one with the severe pain was No. 4 in Table III, and the other No. 2 in Table I.

Discussion

It is generally accepted that the amylase concentration in the blood remains constant irrespective of the state of nutrition or the relative abundance of carbohydrate in the diet (Carlson and Luckhardt, 1908 ; Cohen, 1925 ; Somogyi, 1934). Opinions differ, however, whether or not the blood is normally endowed with the capacity to split the glyceryl esters of the more complex fatty acids, and there is no agreement on what effects the ingestion of fat may have on this property. Crandall (1935) and Lagerlöf (1945) hold that the olive-oil-splitting esterase or lipase is normally confined to the pancreatic secretion and that it finds its way into the general circulation only when the gland becomes the seat of disease. Others believe that its presence in the blood is consistent with sound health (Comfort and Osterberg, 1940 ; Johnson and Bockus, 1940, Wapshaw, 1948).

There is evidence that certain parasympathetico-mimetic drugs modify the digestive activity of the blood. Thus, the beta-methyl derivative of acetylcholine (methacholine *B.P.*, "mecholyl") was administered intramuscularly to dogs by Antopol, Schifrin, and Tuchman (1934), and by Friedman and Thompson (1936), and observed to cause a rise in the amylase titre, which attained maximal levels within a few hours. Friedman and Thompson tied off the pancreatic ducts in dogs and found that the subsequent response on the part of the serum amylase to methacholine diminished *pari passu* with the degree of acinar atrophy which resulted from that procedure. In similar experiments Popper, Olson, and Necheles (1943) were likewise able to correlate their serum-lipase findings with the amount of parenchymatous loss. Indeed, the latter authors went so far as to suggest that the serum-enzyme response to methacholine, especially when administered together with secretin, might serve as a means of detecting pancreatic insufficiency.

Myhre, Nesbitt, and Hurly (1949) performed the methacholine–secretin test on a group of 24 healthy subjects. Only 70% of them yielded positive responses in the blood, which is obviously too low a normal register for a test that is intended to discover faulty function. The impression gained from the present investigation was that carbachol would also be unsuitable for this purpose.

As regards the effects of morphine, the serum-enzyme levels were raised in 33 of the 84 subjects examined—that is, 39%. Taking each group separately, positive responses occurred in 18% of the fasting group, in 32% of those furnished with a meal, and in 68% of those who received carbachol in addition to food. Peak levels were reached between the second and the fourth hours, and by the tenth hour the readings approached normal. Some very remarkable findings were recorded; in fact, judging from previous experience (Wapshaw, 1948) the increments in certain instances were of such a high level as to justify a biochemical diagnosis of acute pancreatitis; but the lack of supporting clinical evidence allayed any misgivings on that score. Lagerlöf expressed the view that although a certain parallelism exists between the lipase and amylase responses the former is the more pronounced. The present findings agree with this.

The increased incidence of positive findings in the third group of the morphinized series—that is to say, those on whom presumably the most testing conditions were imposed—corresponds with that reported by others. Thus, Myhre *et al.* (1949) found that morphine and secretin modified the amylase levels in 70% of 30 normal subjects. It would appear that Burke, Plummer, and Bradford (1950) subjected the pancreas to a still greater stress by giving concurrently morphine, methacholine, and secretin, since, according to their results, 79% of the 68 individuals so treated exhibited raised enzyme readings. In the present series the disparity between the results in the three groups of subjects, all of whom had morphine, leads to the view that the mobilization of the serum enzymes is conditioned by (1) the potent action of the drug on the sphincter of Oddi and the surrounding duodenal musculature, and (2) the functional state of the pancreas at the time when the morphine takes effect. The proportionately higher readings in the carbachol group was also regarded as evidence that this drug enhances the natural secretory response to food. Whether or not carbachol, itself a powerful excitant of visceral muscle, reinforces the action of morphine on unstriped muscle, thereby increasing the compression of the *pars intestinalis* of the pancreatic ducts, is a matter for further study. The findings with carbachol alone suggest that it does not seriously hamper the flow of the pancreatic secretion, which it stimulates, though, judging from the data, methacholine may conceivably have such a dual effect.

The nausea that so often affects those under the influence of morphine has been ascribed variously to one or several of the following actions—excitation of the vomiting centre in the medulla (Goodman and Gilman, 1941), pyloric spasm (Schroeder, 1933), a more general effect on the motility of the intestinal tract (Plant and Miller, 1926; Carlson, 1933; etc.), and biliary side-effects (Lueth, 1931; McGowan, Butsch, and Walters, 1936). Clinical support for Lagerlöf's assumption that the nausea may be of pancreatic origin is lacking. None of the subjects in the investigations of Myhre *et al.* showed symptoms which were referable to the pancreas. Burke *et al.* cited one instance of epigastric pain following morphine, but it is noted that this particular subject had previously undergone cholecystectomy and the pain could well have been due to a rise in the intrabiliary pressure. The overall incidence of nausea in the present series was 21% and did not bear any obvious relation to the functional state of the pancreas at the time when the morphine was given. There were three instances of associated epigastric pain—one in the fasting group, and the other two in the carbachol group; in two the enzyme levels showed a rise, but only of slight degree. All three were completely free of pain and nausea within a few hours, and enjoyed their evening meal.

It would be premature to conclude that these findings have any direct bearing on the aetiology of acute pancreatitis. They do infer, however, that morphine may cause the pancreas a considerable degree of embarrassment, although these short-term experiments indicate that the disturbance was largely functional.

Summary

The influence of morphine on the pancreas was investigated in 84 normal subjects. The observations included a study of (1) the ensuing changes in the amylase and lipase levels in the blood, and (2) the somatic effects of the drug.

The serum-enzyme concentrations were significantly raised in 39% of the series. These changes appear to be due mainly to a state of secretion-retention within the pancreas, for which the excitant action of morphine on the sphincter of Oddi and contiguous muscularis, with consequent absorption of the ferments into the general circulation, is responsible. The present findings suggest that this effect is conditioned also by the functional state of the pancreas.

Carbachol alone does not materially affect the enzyme concentration of the blood, though it would appear to intensify the effect of morphine in this respect.

The incidence of nausea among the morphinized group was 21%. Three instances of transient epigastric pain are recorded. It is questionable if these bodily reactions, though attributable to morphine, have a pancreatic basis.

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The rapidity with which exchange of information on influenza has taken place since the first signs of the present epidemic has made it possible to determine with certainty that the virus concerned in 1953 is the A-prime virus. This, in turn, has made possible the immediate use of vaccines prepared from it and the carrying-out of large-scale vaccination, whose results may prove of great value in the prevention of the disease. Thus, in Holland, workers and employees in large works and factories have been vaccinated. In the United States, Canada, and Great Britain mass vaccination has been carried out, mainly in barracks and hospitals, ideal places for the transmission of the infection. World Health Organization experts now hope that when they meet in Geneva in 1954 they will be able to announce that they have mastered this disease, thanks to the work carried out by the network of W.H.O. laboratories established throughout the world, and thanks also to the fact that for the first time it has been possible to use in good time a vaccine prepared in advance.