Effect of Aging on Pancreatic Secretion in Rats

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Gut function changes with aging, but the exact mechanisms responsible for these changes are largely unknown. We have been very interested in pancreatic physiology and the means of control of pancreatic secretion for years. Previous studies have documented evidence of digestive dysfunction and pancreatic insufficiency in elderly patients [*1,2*], but as far as we can ascertain, the influence of aging on pancreatic exocrine secretion in man and laboratory animals is unclear [*3–5*]. Previous investigations have described a reduction of pancreatic exorine cell mass in elderly people [*6,7*] and in senile laboratory animals [*8,9*], as well as a significant incidence of senile chronic pancreatitis in elderly people [*2*]. These findings suggest that pancreatic exocrine function is compromised in the aged population. Whether pancreatic exocrine responsiveness to cholecystokinin and secretin is altered by aging is unknown.

The objective of this study was to characterize the effect of aging on the pancreatic exocrine secretory response to the normal stimulatory hormones, secretin and cholecystokinin, in rats.

Material and Methods

Young (6 months old, 700 to 850 g) and aged (26 months old, 900 to 1,060 g) male Sprague-Dawley rats (Zivic-Miller, Allison Park, PA) were maintained in an air-conditioned, temperature-controlled room with a lighting schedule of 14 hours of light and 10 hours of dark (lights were on from 5:00 AM to 7:00 PM). Rats had free access to laboratory rat chow and tap water. All aged rats were healthy.

The animals were prepared with pancreatic fistulas according to the method described by Colwell [*10*]. After an 18 hour fast, the rats were anesthetized with ether. A polyethylene catheter (50, inside diameter 0.58 mm, outside diameter 0.96 mm, length 15 cm) was introduced into the duodenum and then into the pancreatic duct through a duodenostomy 5 cm distal to the opening of the duct and secured with a ligature. The main bile-pancreatic duct was ligated just proximal to the point at which it becomes surrounded by pancreatic tissue. The bile was then rerouted directly into the duodenum by cannulation of the bile duct 2 to 3 mm above the ligature with a Silastic® tube (inside diameter 0.61 mm) with a Teflon® tip. This tube was then inserted into the duodenum to near the opening of the pancreatic duct through another duodenostomy, which was closed with a pursestring suture. The rats were also prepared with gastric and duodenal fistulas. The pancreatic and duodenal tubes were brought to the exterior through the lower end of the wound. Rats were placed in Bollman cages [*11*], and a tail vein was cannulated using a 23 gauge catheter. They were kept under a heat lamp until they recovered and then were maintained at room temperature (23 ± 2°C). The pancreatic and duodenal fistulas were connected to allow the pancreatic juice to enter the duodenum. All rats were given a continuous infusion of 5 percent dextrose in lactated Ringer's solution through the tail vein (1 to 2 ml/kg per hour) until completion of the cholecystokinin and secretin challenge studies. All rats were studied 24 hours after surgery. We have previously shown that 24 hours after operation is an acceptable time to perform such studies [*12*].

During the experiments, the pancreatic and duodenal fistulas were disconnected to allow collection of pancreatic fluid. Pancreatic juice was collected in nonheparinized capillary tubes (inside diameter 1 to 1.2 mm, outside diameter 1.4 to 1.6 mm, length 74 mm). The pancreatic flow rate was measured every 10 minutes and recorded in microliters every 10 minutes. Three 10 minute specimens of pancreatic juice were combined, and 120 ml was saved and placed into sealed plastic tubes for bicarbonate and protein determinations. Surfeit juice was infused into the duodenum through the duodenostomy tube during the next 30 minutes. To avoid possible error because of differences in size between young and aged rats, all pancreatic secretory data are expressed as output per unit of time, as well as output per kilogram-unit of time (Tables I and II). Since the animals all weighed between 700 and 1,060 g, the differences between the two means of expression were not great.

Young and aged rats (six rats in each group) were prepared as already described. Basal pancreatic exocrine secretions were collected every 10 minutes for 60 minutes. Graded doses of synthetic secretin (0.03, 0.06, and 0.12 nmol/kg; Peninsula Laboratories, Belmont, CA) were given intravenously in the tail vein to six young and six aged rats. In a separate study, an additional six young and six aged

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TABLE I Pancreatic Secretion Before and After Graded Doses of Secretin in Young and Aged Male Rats

Secretin Dose* (nmol/kg)	Secretion Volume		Bicarbonate Output		Protein Output	
	μl/min	μl/kg/min	μEq/30 min	μEq/kg/30 min	mg/30 min	mg/kg/30 min
			Group I (6 months old)			
Basal	8.1 ± 1.5	10.8 ± 2.0	7.4 ± 0.7	9.8 ± 0.8	2.5 ± 0.7	3.3 ± 1.1
0.03	12.4 ± 0.9	16.5 ± 1.3	15.9 ± 0.8	21.2 ± 1.1	4.2 ± 1.0	5.6 ± 1.2
0.06	14.2 ± 1.2	18.9 ± 1.6	20.1 ± 1.2	26.8 ± 1.9	5.2 ± 1.0	6.9 ± 1.4
0.12	16.1 ± 0.8	21.4 ± 1.0	23.8 ± 2.0	31.7 ± 3.1	5.9 ± 0.9	7.9 ± 1.5
			Group II (26 months old)†			
Basal	5.3 ± 0.9	5.9 ± 1.0	4.1 ± 0.4	4.5 ± 0.5	1.4 ± 0.3	1.5 ± 0.3
0.03	6.7 ± 0.7	7.4 ± 0.8	7.7 ± 0.9	8.6 ± 1.1	1.7 ± 0.6	1.9 ± 0.6
0.06	7.8 ± 1.0	8.7 ± 1.1	9.5 ± 1.0	10.5 ± 1.1	1.8 ± 0.6	2.0 ± 0.6
0.12	8.0 ± 0.8	8.9 ± 0.9	11.4 ± 1.2	12.7 ± 1.4	1.9 ± 0.5	2.1 ± 0.5

* Values are expressed as the mean ± standard error of the mean maximal response.
† $p < 0.05$ versus Group I.

TABLE II Pancreatic Secretion Before and After Graded Doses of Cholecystokinin-8 (CCK-8) in Young and Aged Male Rats

CCK-8 Dose* (nmol/kg)	Secretion Volume		Bicarbonate Output		Protein Output	
	μl/min	μl/kg/min	μEq/min	μEq/kg/30 min	mg/30 min	mg/kg/30 min
			Group I (6 months old)			
Basal	7.4 ± 0.7	9.8 ± 1.0	6.1 ± 1.2	8.1 ± 1.5	2.9 ± 1.1	3.9 ± 1.4
0.3	9.7 ± 0.7	12.9 ± 0.9	8.2 ± 1.7	10.9 ± 2.3	7.8 ± 0.8	10.4 ± 1.2
0.6	11.6 ± 0.7	15.5 ± 1.0	9.8 ± 1.7	13.0 ± 2.2	10.7 ± 0.8	14.2 ± 1.3
1.2	12.9 ± 0.8	17.2 ± 1.2	10.9 ± 1.6	14.5 ± 2.2	13.1 ± 1.2	17.5 ± 1.6
			Group II (26 months old)†			
Basal	5.7 ± 0.8	6.3 ± 1.0	3.8 ± 0.8	4.2 ± 0.9	1.7 ± 1.2	1.9 ± 1.3
0.3	6.8 ± 0.6	7.5 ± 0.7	5.7 ± 0.9	6.3 ± 1.1	3.5 ± 1.5	3.9 ± 1.7
0.6	7.7 ± 0.7	8.5 ± 0.8	6.8 ± 1.1	7.5 ± 1.4	6.3 ± 2.0	7.0 ± 2.2
1.2	5.8 ± 0.7	6.4 ± 0.8	5.3 ± 1.0	5.9 ± 1.2	5.2 ± 1.4	5.8 ± 1.6

* Values are expressed as the mean ± standard error of the mean maximal response.
† $p < 0.05$ versus Group I.

rats received intravenous graded doses of synthetic cholecystokinin-8 (0.3, 0.6, and 1.2 nmol/kg; BACHEM, Torrance, CA). Pancreatic secretions were collected every 10 minutes for 60 minutes after secretin and cholecystokinin-8 challenges. Each dose of secretin and cholecystokinin-8 was separated by a 30 minute basal period to allow pancreatic secretions to return to basal output levels.

Pancreatic juice protein concentrations were measured by the method of Lowry et al [13]. Pancreatic juice bicarbonate concentrations were measured by adding 1 ml of 0.01 N hydrochloric acid to 0.1 ml samples of pancreatic juice, swirling the mixture, and back titrating to pH 7 with 0.01 sodium hydroxide using an automatic titrator with a pH meter (Radiometer, Copenhagen, Denmark). Total protein and bicarbonate outputs were calculated by multiplying their concentrations by the volume of pancreatic juice collected in 30 minutes.

Data are expressed as the mean ± the standard error of the mean. Significant differences were identified by the Student's t test. Differences with a p value of less than 0.05 were considered significant.

Results

There were no deaths in the operated rats. Basal pancreatic secretion volume and bicarbonate and protein outputs are shown in Figures 1 through 4. Basal pancreatic secretion volume in aged rats was significantly reduced ($p < 0.05$) in comparison to that of young rats (Figures 1 and 2). For instance, the pancreatic secretion volume of aged rats was 5.9 ± 1 μl/kg/min, whereas the basal pancreatic secretion volume of young rats was 10.8 ± 2.0 μl/kg/min (Table I). In addition, the basal pancreatic outputs of protein (Figure 4, Tables I and II) and bicarbonate (Figure 3, Tables I and II) were significantly decreased in aged rats compared with those of young rats.

Administration of graded doses of secretin (0.03, 0.06, and 0.12 nmol/kg) to young and aged rats resulted in dose-related elevations of pancreatic secretion volume (Figure 1), bicarbonate (Figure 3),

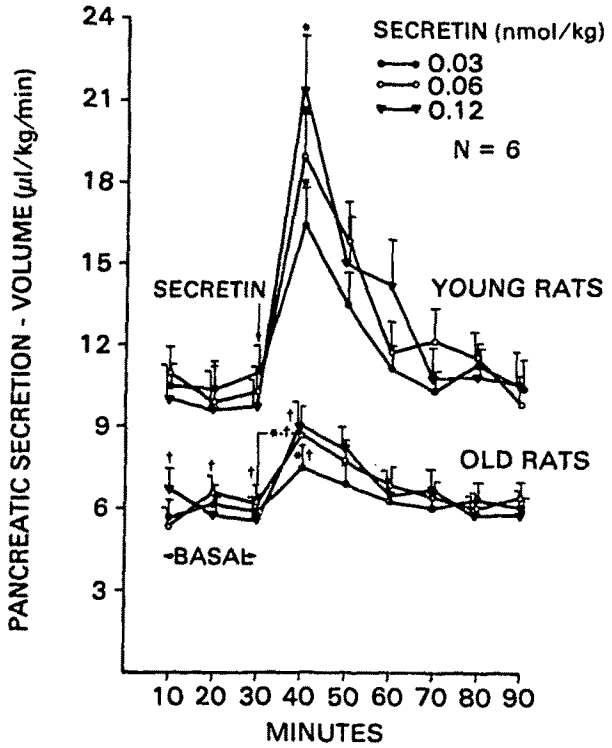

Figure 1. Pancreatic secretion volume before (basal) and after secretin challenge in young and aged rats. Asterisks indicate significant difference versus basal or a lower dose; daggers indicate significant difference versus young rats.

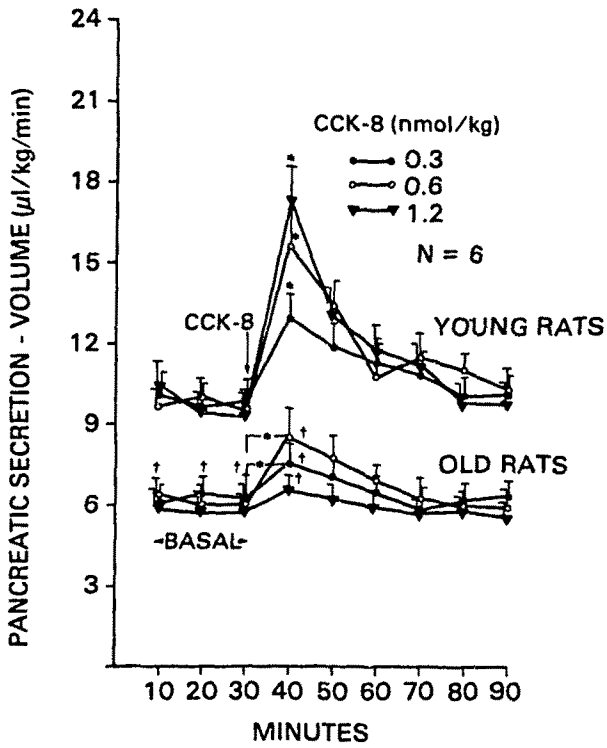

Figure 2. Pancreatic secretion volume before and after cholecystokinin-8 (CCK-8) challenge in young and aged rats. Asterisks indicate significant difference versus basal or a lower dose; daggers indicate significant difference versus young rats.

and protein outputs (Table I) in comparison to the basal levels. The pancreatic secretion volumes of aged rats in response to all doses of secretin were significantly reduced in comparison to those of young rats (Figure 1 and Table I). The pancreatic outputs of bicarbonate (Figure 3 and Table I) and protein in response to all doses of secretin were significantly depressed in the aged rats in comparison to those of young rats.

Administration of graded doses of cholecystokinin-8 (0.3, 0.6, and 1.2 nmol/kg) resulted in dose-related elevations in pancreatic secretion volume (Figure 2) and in bicarbonate (Table II) and protein outputs (Figure 4) in young and aged rats. Figure 2 shows that the pancreatic secretion volumes of aged rats in response to all doses of cholecystokinin-8 were significantly reduced in comparison to those of young male rats. In addition, the maximal pancreatic output of protein in response to all doses of cholecystokinin-8 was significantly diminished in aged rats in comparison to that of young rats (Figure 4). The maximal pancreatic output of bicarbonate in response to all doses of cholecystokinin-8 was significantly depressed in aged rats in comparison to that of young male rats (Table II).

In Tables I and II, the pancreatic volume and bicarbonate and protein outputs per unit of time are expressed as absolute values and per kilogram body weight to eliminate any effect of the lower body weights of the young rats. However, the values of pancreatic volume and bicarbonate and protein outputs in the aged rats were significantly lower than those of the young rats, regardless of how the data were expressed.

Comments

As far as we know, this is the first report to compare the responsiveness of the exocrine pancreas to cholecystokinin and secretin challenges in aged rats to that of young rats. It is noteworthy that investigators using rodents select the 50 percent survival age (median longevity time) and older as the "aged" populations [*14*]. The reported median length of life of Sprague-Dawley male rats is between 23.2 and 25.3 months [*15,16*]. The 26 month old rats used in this study have been properly classified as aged. The results of the present study indicate that in senescent rats, the basal pancreatic secretion volume and protein and bicarbonate outputs are significantly reduced, as are the pancreatic secretion volume and

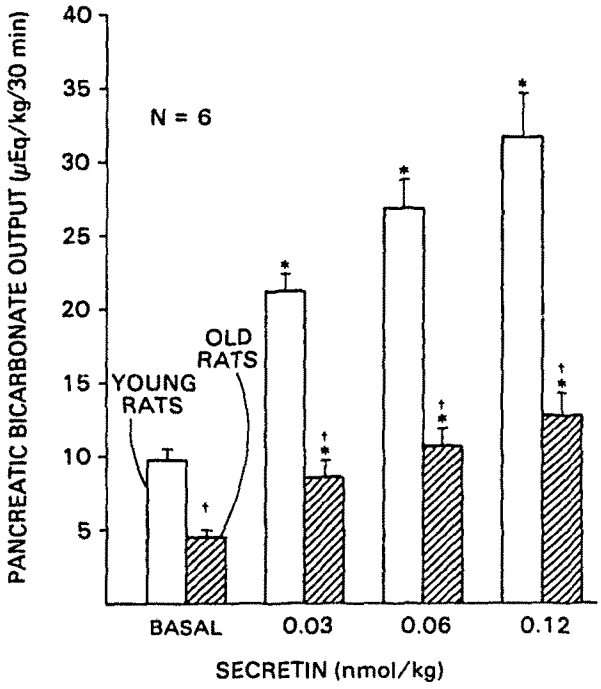

Figure 3. Maximal pancreatic bicarbonate secretion after secretin challenge in young and aged rats. Asterisks indicate significant difference versus basal or a lower dose; daggers indicate significant difference versus young rats.

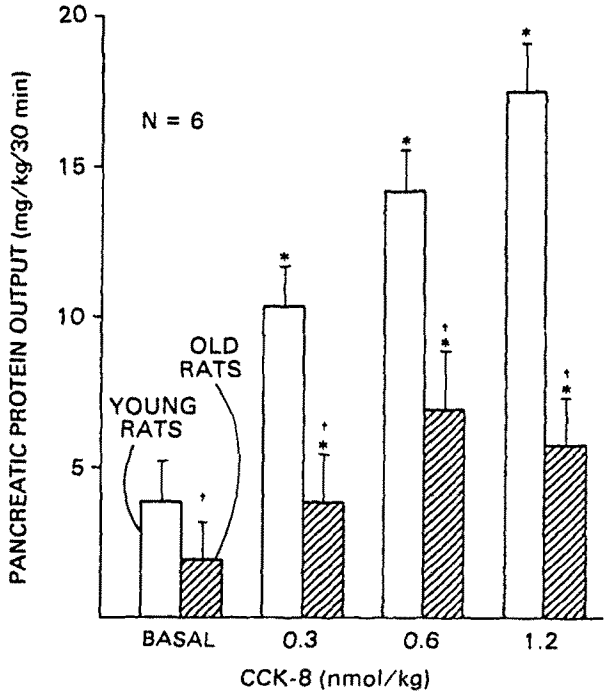

Figure 4. Maximal pancreatic protein secretion after cholecystokinin-8 (CCK-8) challenge in young and aged rats. Asterisks indicate significant difference versus basal or a lower dose; daggers indicate significant difference versus young rats.

protein and bicarbonate responses to exogenous cholecystokinin-8 and secretin challenges.

The influence of aging on exocrine pancreatic function in human subjects and laboratory animals has not been studied previously in depth. Meyer and Necheles [3] observed that the duodenal contents of aged human subjects while fasting showed reduced levels of pancreatic exocrine enzymes (trypsin, amylase, and lipase). Stimulated levels of lipase in the aged group were also found to be reduced in comparison to those of the young group. Rosenberg and colleagues [4] and Tiscornia and co-workers [5] reported that the peak pancreatic secretion volume and bicarbonate output failed to decline significantly with age in human subjects. It is worth mentioning, however, that these investigators did not monitor the loss of pancreatic juice due to intestinal absorption or peristalsis. In another study, Price and colleagues [1] found that malabsorption and pancreatic insufficiency existed in 30 percent of the patients older than 65 years of age. Ammann and co-workers [2] have described 38 patients with senile chronic pancreatitis. The disease started at an advanced age, was common in male patients, and was accompanied by pancreatic calcification. Autopsy examination of some of these patients showed acinar atrophy and fibrosis. The well-known association between pancreatic calcification and alcoholism must raise the question of a possible role of alcohol in the syndrome of senile pancreatitis. Morgan and Feldman [6] reported in an autopsy study of 74 subjects (ages 76 to 95 years) that in 8 percent, the pancreas was atrophic (weight 18 to 40 g), and evidence of degenerative disease was noted in the pancreas of a majority of the patients.

Several morphologic studies have reported certain changes that occur frequently in aged dogs [8], rats [9], and human subjects [7], which are probably a normal accompaniment of aging. These observations include metaplasia of the duct epithelium and dilation of the acini and ducts which lead to flattening of the epithelium, giving locules that often contain a keratin-like material. There are also areas of tissue in which the nuclei are small, shrunken, and hypochromatic, with the cytoplasmic basophilic material diminished.

Taken together, these earlier studies indicate that age-related alterations occur in the secretory capacity of the exocrine pancreas of human subjects and laboratory animals. It is not known, however, whether these age-related changes of the exocrine pancreas are associated with alterations in the responsiveness to cholecystokinin-8 and secretin.

The results of this study indicate that the responsiveness of the exocrine pancreas is depressed

in aged rats. Whether the duodenal release of cholecystokinin and secretin in aged rats is enhanced to compensate for the diminished pancreatic responsiveness is not known. Unpublished studies from our laboratory have shown that fasting levels of cholecystokinin-33 in aged subjects (older than 60 years of age) are significantly elevated in comparison to levels in young adults. Furthermore, we have shown that the response of isolated pancreatic acini of aged rats to carbachol, cholecystokinin-8, or secretin is reduced significantly in comparison to the response of young rats [unpublished observations].

The present study indicates that the pancreatic exocrine function of aged rats is reduced to approximately 50 percent of that of young rats. A preliminary investigation showed that the median effective dose (half maximal dose) of secretin and of cholecystokinin-8 in young rats is 0.06 and 0.6 nmol/kg, respectively. This dose of secretin caused an elevation of 175 percent in pancreatic secretion volume, an elevation of 263 percent in bicarbonate output, and an elevation of 209 percent in protein output in young rats. In contrast, an identical dose of secretin in aged rats resulted in an elevation of 147 percent in pancreatic secretion volume, an elevation of 233 percent in bicarbonate output, and an elevation of 133 percent in protein output. Similarly, cholecystokinin-8 (0.6 nmol/kg) caused elevations of 158 percent in pancreatic secretory volume, of 364 percent in protein output, and of 160 percent in bicarbonate output in young rats. In aged rats, an identical dose of cholecystokinin-8 caused elevations of 135, 368, and 178 percent in volume, protein, and bicarbonate outputs, respectively. In brief, the maximal pancreatic secretion volume and the bicarbonate and protein responses to the median effective dose of secretin in aged rats were 46, 39, and 29 percent, respectively, of those observed in young rats. Similarly, the maximal pancreatic secretion volume and bicarbonate and protein responses to the median effective dose of cholecystokinin-8 in aged rats were 55, 49, and 58 percent, respectively, of those observed in young rats.

Parenthetically, it is important to compare the pancreatic secretory response of our young rat model with that of previous reports. Several investigators have reported basal pancreatic secretion volumes similar to those given in the present report [*17–20*]. In contrast, other investigators [*21–24*] have reported lower pancreatic secretion volumes. The pancreatic bicarbonate outputs in the present study are comparable to those reported by de Smul et al [*19*] and Roze et al [*25*], but some studies yielded lower [*20,21*] and some higher [*26,27*] outputs. The pancreatic protein outputs in the present study are similar to those of several groups of investigators [*22,25,28*], but Petersen and Grossman [*26*] have reported higher levels. All of these studies describe secretory data from young rats. Unfortunately, there are no comparable studies reporting basal pancreatic secretion in aged rats.

Summary

We have characterized the effects of aging on the pancreatic exocrine secretory response to the normal stimulatory hormones, secretin, and cholecystokinin. Young (6 month old) and aged (26 months old) male Sprague-Dawley rats were prepared with pancreatic fistulas and challenged with different doses of secretin (0.03, 0.06, and 0.12 nmol/kg) and cholecystokinin-8 (0.3, 0.6, and 1.2 nmol/kg) intravenously. The pancreatic secretion was measured for volume and bicarbonate and protein outputs. Our results show that in aged rats, the basal pancreatic secretion volume and protein and bicarbonate outputs were significantly reduced, and the pancreatic secretion volume and protein and bicarbonate responses to graded doses of secretin or cholecystokinin-8 were significantly reduced. This study demonstrates that pancreatic exocrine function in rats diminishes with age.

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Discussion

Ronald Greenberg (New York, NY): Dr. Khalil, was a pancreatic histologic study performed? Clearly, a decrease in pancreatic secretion occurred. Do you have an explanation for the mechanism of that, whether it might be a decreased sensitivity of the hormone receptor, decreased pancreatic content of enzymes, or decreased enzyme release? Lastly, pancreatic secretion was expressed as a flow rate per kilogram of rat weight. Are you suggesting that there is a physiologic relationship between pancreatic function and total rat weight in this instance?

Edward Passaro, Jr. (Los Angeles, CA): Were there any morphologic changes, for example, in body weight? Was there any correlation between gland weight and body weight that may be pertinent to your observations?

Michael McMahon (Leeds, England): Dr. Khalil, can both quantitative and qualitative aspects of the diet induce morphologic and secretory changes in the rat in the long term? Perhaps some of the changes seen in this study reflect the type of diet the rats were placed on in the 26 months during which they were aging, rather than a specific response to age itself. Was there any evidence of dietary effects over this period of time?

P. R. Holt (New York, NY): I would like to extend the questions by Dr. Greenberg. I do not think in your studies you really achieved maximum secretion. Could you have given more hormone to determine whether maximum secretion differed in the young and aging rats? One of the reasons I am asking the question is that the aged rat tends to be much bigger and presumably has a larger volume of body distribution of the hormones that were infused. Could this have played a role in some of the results?

Paul H. Jordan, Jr. (Houston, TX): Dr. Khalil, in your summary you indicated that there was a relationship between these findings and gastrointestinal function. Would you tell us what functions?

Andrew L. Warshaw (Boston, MA): This study has real clinical relevance. It has been observed in human subjects that there is increased fibrous tissue and decreased glandular tissue in the old pancreas compared with the young one, and endoscopic retrograde cholangiopancreatic findings in older patients have shown a definite trend toward an enlarged pancreatic duct, which would be consistent with atrophy of the gland. There is the potential for confusion with the diagnosis of chronic pancreatitis if one is not aware of this phenomenon.

R. Scott Jones (Charlottesville, VA): There is abundant evidence that cholecystokinin exerts a trophic influence on the pancreas. I would like to extend the discussion further in terms of mechanisms. Is there any evidence that older rats secrete less cholecystokinin in response to feeding than do young rats? In other words, could there be alterations in intestinal hormone secretion as well as in end organ secretion?

Richard H. Bell (Cincinnati, OH): The stimulated protein output in the older rats was lower than in the young rats. However, as a multiple of their basal secretion, it seemed to be considerably higher. Would you comment on that?

Talaat Khalil (closing): Dr. Greenberg and Dr. Holt, we did not do any histologic studies on these rats. However, there are reported morphologic changes that occur in the pancreas in conjunction with aging in rats. These are mainly degenerative changes. This is a preliminary study. We have to study this phenomenon further to determine whether it is due to depressed secretory function or to reduced protein synthesis.

In regard to the effect of weight on pancreatic secretin, we have chosen two different age groups, 6 month old and 26 month old rats, with no drastic difference in their weights. The average weight of the young rats was 750 g and the average weight of the old rats was 950 g. If we express the difference in pancreatic secretory difference per animal and per kilogram body weight, we still get a significant difference between the two age groups.

All of the rats were maintained on a normal rat chow diet; however, we do not have any data on the effect of diet.

We did not measure the maximal stimulated secretion. We chose to stimulate with the median effective dose of both cholecystokinin-8 and secretin, and a lower and a higher dose than the median effective dose.

The observation of the high incidence of indigestion in aged subjects is well established. Whether this is a pathologic or a normal physiologic change that occurs with aging is not clearly understood. The work we have presented shows that pancreatic function in aged rats is compromised with aging. If this could be reproduced in human subjects, it would explain some of the reported clinical and morphologic changes that occur in the gastrointestinal tract with aging.