girls the ratio was greater than unity while in all of the postmenarcheal girls it was less than unity, even though all stages of puberty were represented (Table 1).

Previous studies have not disclosed the presence of monthly gonadotropin cycles in premenarcheal girls. However, we found that by using the described autoregressive smoothing techniques on data collected for 60 consecutive days we were able to suppress extraneous variation and allow monthly gonadotropin surges to become more apparent. The validity of the technique is supported by the observation of normal cycles in postmenarcheal girls. By studying five premenarcheal girls, in whom the FSH : LH ratio was appropriate to the pubertal stage, we have observed monthly gonadotropin cycles in at least three of them. This suggests that gonadotropin cycles may have a role even prior to menarche.

JAMES W. HANSEN
HOWARD J. HOFFMAN
GRIFF T. ROSS
Reproduction Research Branch and *Biometry Branch, National Institute of Child Health and Human Development, Bethesda, Maryland 20014*

References and Notes

1. G. T. Ross, *Fertil. Steril.* **25**, 522 (1974).
2. A. B. Rifkind, H. E. Kulin, P. L. Rayford, C. M. Cargille, G. T. Ross, *J. Clin. Endocrinol. Metab.* **31**, 517 (1970).
3. A. Hayes and A. Johanson, *Pediatr. Res.* **6**, 18 (1972).
4. J. W. Hansen and G. T. Ross, in preparation.
5. E. O. Reiter, H. E. Kulin, S. M. Hamwood, *J. Clin. Endocrinol. Metab.* **36**, 661 (1973).
6. Specific FSH antiserums were supplied by the National Institute of Arthritis, Metabolic, and Digestive Diseases.
7. Second international reference preparation of human menopausal gonadotropin was supplied by Derek Bangham for the World Health Organization.
8. R. Boyar, J. Finkelstein, H. Roffwarg, S. Kapen, E. Weitzman, L. Hellman, *N. Engl. J. Med.* **287**, 582 (1972).
9. Y_i is the time series resulting from autoregressing the original data, X_i, in the time forward direction. Z_i, is the time series resulting from autoregressing the derived series, Y_i, in the opposite direction. By performing the autoregression in both directions, the phase shift of the first autoregression is canceled by the exactly opposite phase shift of the second autoregression. The trend is specified by U_i, which is preferred to Z_i, in part because of the resulting simplification in the overall transfer function. W. C. Orr and H. J. Hoffman, *IEEE (Inst. Electr. Electron. Eng.) Trans. Bio-Med. Eng.* **BME-21**, 130 (1974).
10. H. J. Hoffman, D. Guerry IV, D. C. Dale, *J. Interdiscipl. Cycle Res.* **5**, 1 (1974).
11. W. A. Marshall and J. M. Tanner, *Arch. Dis. Child.* **44**, 291 (1969).
12. The Rand Corporation, *A Million Random Digits with 100,000 Normal Deviates* (Free Press, Glencoe, Ill., 1955).
13. The method of data analysis used to define the signal has been accomplished by a combination of autoregressive filters. Each of these autoregressions is a linear filter, and their combined characteristics can be calculated as a transfer function in the frequency domain. The peak frequency admitted by this transfer function is located at $\pi/15$ radians which is equivalent to a period of 30 days. The filter characteristic is broad; the bandwidth, or half-power width, extends from $2\pi/45$ radians (45-day period) to $\pi/5$ radians (10-day period). Also, it should be pointed out that the transmission at the peak frequency is approximately one-third, rather than unity. This attenuation will result in any periodic monthly component in the time series data being reduced to one-third of its true amplitude. For a periodic component near 45 days in length the amplitude is reduced to one-sixth the true amplitude. Since no adjustment has been made for this change in amplitude of the signal due to the filtering procedure, the relative scales provided in the figures do not accurately reflect the amplitude of the LH and FSH surges in the original data.
14. J. S. D. Winter and C. Faiman, *J. Clin. Endocrinol. Metab.* **37**, 714 (1973).
15. A. E. Treloar, R. E. Boynton, B. G. Behn, B. W. Brown, *Int. J. Fertil.* **12**, 77 (1967).
16. B. M. Sherman and S. G. Korenman, *J. Clin. Endocrinol. Metab.* **39**, 145 (1974).
17. We acknowledge the technical assistance of R. V. Reid in analyzing the specimens for gonadotropins and the constructive comments of Dr. D. Alling during the preparation of the manuscript.

14 March 1975; revised 20 June 1975

Somatostatin Suppresses Secretin and Pancreatic Exocrine Secretion

Abstract. *Somatostatin, a hypothalamic peptide, suppresses hydrochloric acid–stimulated release of secretin, pancreatic flow rate, and bicarbonate and protein secretion in fasted, conscious dogs. It also reduces nonstimulated pancreatic exocrine secretion but does not affect basal secretin concentrations. Suppression of HCl-stimulated secretin release is complete, whereas pancreatic flow rate and bicarbonate and protein secretions are only partially inhibited. The action of somatostatin is rapid in onset and quickly reversible.*

Somatostatin (somatotropin-release inhibiting factor, SRIF), a tetradecapeptide isolated from ovine hypothalamic extracts, inhibits the release of growth hormone from the pituitary gland (*1*). SRIF was also found to suppress thyrotropin (TSH) release stimulated by thyrotropin-releasing factor (TRF) (*2*), both basal and arginine-stimulated insulin and glucagon release from the pancreas (*3*), and basal as well as food-stimulated gastrin release from the stomach (*4*).

We have investigated the effect of SRIF on the release of immunoreactive secretin (IRS) from the proximal small intestine and have found that SRIF suppresses both the HCl-mediated IRS release and the pancreatic secretion of water, bicarbonate, and protein. All experiments were performed on conscious dogs that had been fasted overnight and that had long-term pancreatic fistulas. The fistulas had been prepared 3 weeks earlier according to the technique of Herrera (*5*) with two modifications: (i) the minor pancreatic duct was ligated and (ii) the continuity of stomach, duodenum, and jejunum was reestablished after the preparation of the duodenal pouch.

Figure 1 shows data obtained from six experiments in four dogs. Synthetic SRIF (200 μg, the cyclic form) infused continuously for 30 minutes into a hind leg vein had no significant effect on IRS concentrations (*6*). However, somatostatin suppressed further the low basal pancreatic flow and bicarbonate (*7*) and protein (*8*) secretion to barely detectable amounts ($P < .05$). This observation raised the possibility that SRIF may inhibit basal pancreatic secretion through secretin-independent mechanisms. In contrast, HCl-mediated IRS release was completely suppressed by SRIF. When SRIF (200 μg/30 minutes) was infused concurrently with HCl (9.6 meq/30 minutes, intraduodenally), there was no statistically significant rise in IRS concentrations. By comparison, when HCl was infused without SRIF, IRS rose from 610 ± 61 μunit/ml to 1110 ± 187 μunit/ml ($P < .001$) (*9*).

HCl-stimulated pancreatic flow rate and bicarbonate and protein secretion were all partially suppressed by somatostatin. When SRIF was infused concurrently with HCl, the incremental increases were 7.3 ± 2.6 ml/15 minutes for flow rate, 0.60 ± 0.26 meq/15 minutes for bicarbonate secretion, and 83 ± 22 mg/15 minutes for protein secretion. However, considerably greater increases were observed when HCl was infused alone. Flow rate increased by 21.8 ± 1.2 ml/15 minutes, bicarbonate secretion increased by 2.06 ± 0.31 meq/15 minutes, and protein secretion increased by 232 ± 25 mg/15 minutes. Thus, SRIF had reduced the HCl-stimulated increase in pancreatic flow rate by 67 percent, bicarbonate secretion by 72 percent, and protein secretion by 64 percent. These reductions were statistically significant ($P < .001$ for flow rate and bicarbonate secretion and $P < .05$ for protein secretion). Therefore, it appeared that SRIF affected HCl-stimulated IRS release more than pancreatic exocrine function. This was particularly evident in three dogs whose IRS responses were completely abolished but, nevertheless, showed distinct increases in pancreatic secretions during HCl plus SRIF infusions. The observation that the pancreatic secretions were only partially suppressed was not surprising. The stimulation of pancreatic exocrine function by HCl is a complex phenomenon. It involves the release of secretin, cholecystokinin-pancreozymin, and prob-

ably still other unidentified factors. Complete suppression of all these factors by SRIF would be unlikely.

While the achievement of complete hormone suppression may depend on the dose of SRIF used, the timing of administration of somatostatin also has been shown to play a role. Johnson *et al.* reported complete suppression of arginine-stimulated insulin release by prior treatment for 5 minutes with somatostatin while only partial suppression was observed when somatostatin and arginine were administered concurrently (*10*).

In our study we found the inhibitory effect of somatostatin on IRS release and exocrine pancreatic secretion to be short-lived and completely reversible. In three of our six experiments, HCl administration preceded SRIF infusion, whereas in the remaining three the sequence was reversed and HCl was given 60 minutes after the end of SRIF infusion. IRS responses to HCl in both series were identical; that is, they were the same before or 60 minutes after SRIF administration, an indication that the suppressive effects of somatostatin were no longer demonstrable 1 hour after the infusion was discontinued. Rapid onset and reversibility of action has been the general experience of all investigators studying the influence of somatostatin on a variety of different hormonal systems (*10–12*).

Our findings have added secretin, a gut hormone, to the list of other hormones whose release is inhibited by somatostatin. The physiologic significance of these findings is uncertain. So far, SRIF has not been detected in peripheral blood. However, Arimura *et al.* (*13*) have demonstrated the presence of SRIF in rat pancreas, stomach, and duodenum. These findings suggest the possibility that somatostatin may have a physiologic role in the secretion of pituitary, pancreatic, gastric, and duodenal hormones.

The amounts of somatostatin that we and others have used are most likely pharmacologic. Nevertheless, SRIF is now being tried as a therapeutic agent in acromegalic (*12*) and diabetic patients (*14*). In addition, it may be useful in the medical treatment of gastrin-secreting tumors. Its capacity to suppress exocrine pancreatic function may be of potential use in the treatment of acute pancreatitis. Conversely, these inhibitory actions may also lead to undesirable side effects such as maldigestion and malabsorption.

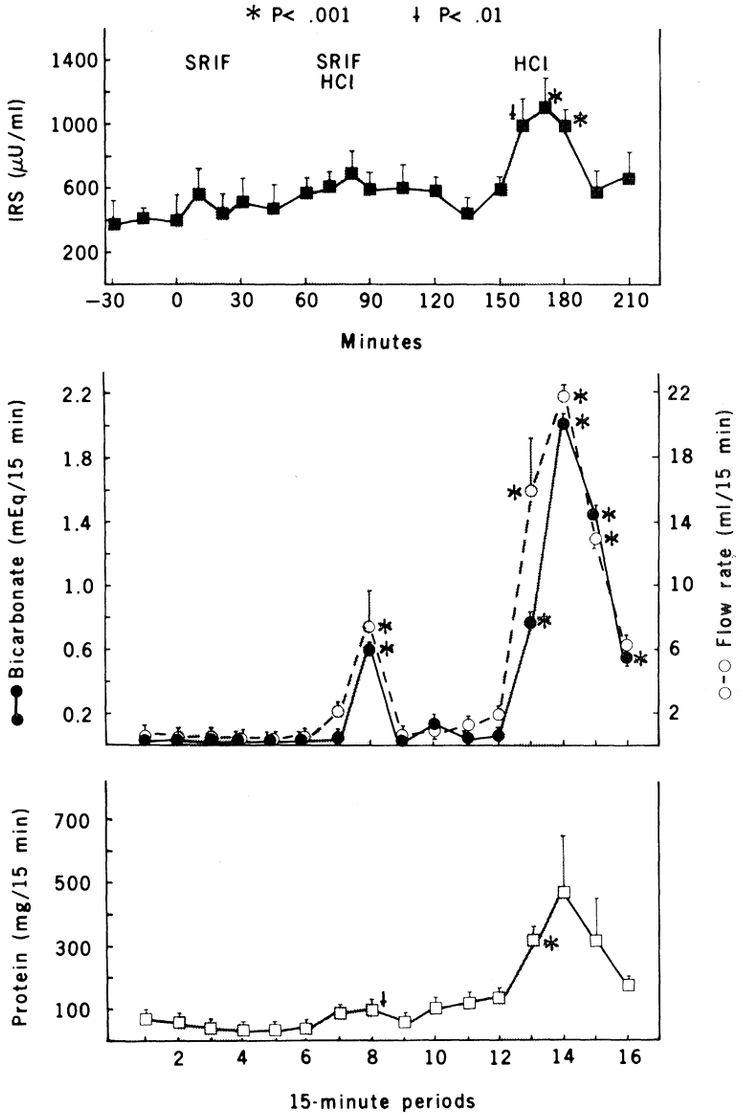

Fig. 1. Effects of infusions of somatostatin (SRIF), somatostatin plus HCl, and HCl alone on serum immunoreactive secretin (IRS), pancreatic flow rate, and bicarbonate and protein secretion. Shown are means ± the standard error of the mean of six experiments in four conscious dogs. Somatostatin was infused intravenously (200 μg/30 minutes), HCl was administered intraduodenally (9.6 meq/30 minutes). In three experiments somatostatin plus HCl was preceded by somatostatin and followed by HCl. In the remaining three experiments, the order of infusions was reversed (HCl preceded somatostatin plus HCl which was followed by somatostatin). For statistical evaluation (paired Student's *t*-test) data during infusions were compared to those immediately preceding the respective infusions. Somatostatin did not change basal secretin concentrations but did suppress basal flow rate and bicarbonate and protein secretion. Somatostatin caused complete suppression of HCl-stimulated secretin release and partial suppression of pancreatic flow rate and bicarbonate and protein secretion.

GUENTHER BODEN
MICHAEL C. SIVITZ
OLIVER E. OWEN
Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140
NOORJEHAN ESSA-KOUMAR
JOHN H. LANDOR
College of Medicine and Dentistry of New Jersey, Piscataway 08854

References and Notes

1. P. Brazeau, W. Vale, R. Bargus, N. Ling, M. Butcher, J. Rivier, R. Gullemin, *Science* **179**, 77 (1973).
2. R. Hall, G. M. Besser, A. V. Schally, D. H. Coy, D. Evered, D. J. Goldie, A. J. Kastin, A. S. McNeilly, C. H. Mortimer, C. Phenekos, W. M. G. Turnbridge, D. Weightman, *Lancet* **1973-II**, 581 (1973).
3. K. G. M. M. Alberti, S. E. Christenson, J. Iversen, K. Sayer-Hansen, N. J. Christensen, A. Prange-Hansen, K. Lundbrek, H. Ogskov, *ibid.* p. 1299; D. J. Koerker, W. Ruch, E. Chideckel, J. Palmer, C. J. Goodner, J. Ensinck, C. C. Gale, *Science* **184**, 482 (1974).
4. S. R. Bloom, C. H. Mortimer, M. O. Thorner, R. Hall, A. Gomez-Pan, V. M. Roy, R. C. G. Russell, D. H. Coy, A. J. Kastin, A. V. Schally, *Lancet* **1974-II**, 1106 (1974).
5. F. Herrera, D. R. Kemp, M. Tsukamoto, E. R. Woodward, L. R. Dragsted, *J. Appl. Physiol.* **25**, 207 (1973).
6. IRS was determined in serum by a previously published radioimmunoassay technique [G. Boden and W. Y. Chey, *Endocrinology* **92**, 1617 (1973); G. Boden, in *Methods of Hormone Radioimmunoassay*, E. M. Jaffe and H. Berman, Eds. (Academic Press, New York, 1974), p. 275].
7. Bicarbonate in pancreatic juice was determined as described [G. Boden, N. Essa, O. E. Owen, F. A. Reichle, *J. Clin. Invest.* **53**, 1185 (1974)].
8. Protein concentration in pancreatic juice was estimated by measuring the absorbance at 280 nm in a Zeiss spectrophotometer, with bovine serum albumin as standard.
9. Data are presented as mean ± S.E.M. Statistical evaluation was performed with the Student's *t*-test for paired samples.

10. D. G. Johnson, J. W. Ensinck, D. Koerker, J. Palmer, C. J. Goodner, *Endocrinology* **96**, 370 (1975).
11. H. Sakurai, R. Dobbs, R. H. Unger, *J. Clin. Invest.* **54**, 1395 (1974); J. E. Gerich, R. Lovinger, G. M. Grodsky, *Endocrinology* **96**, 749 (1975).
12. G. M. Besser, C. H. Mortimer, A. S. McNeilly, M. O. Thorner, G. S. Batistoni, S. R. Bloom, K. W. Kastrup, K. F. Hanssen, R. Hall, D. H. Coy, A. J. Kastin, A. V. Schally, *Br. Med. J.* **4**, 622 (1974).
13. A. Arimura, H. Sato, A. DuPont, N. Nishi, A. V. Schally, *Fed. Proc.* **34**, 273 (1975).
14. J. E. Gerich, M. Lorenzi, V. Schneider, J. H. Karam, J. Rivier, R. Guillemin, P. Forsham, *N. Engl. J. Med.* **291**, 544 (1974).
15. We thank Dr. R. Deghengi, Ayerst Research Laboratories, Montreal, Canada, for the gift of synthetic somatostatin. We thank W. Saraga, D. Thompson, and E. Silver for technical assistance. Supported by PHS grants 1R01 AM 16348-02 MET, AM 16102-01, AM 16520-03, and 5 M01 RR 349.

2 April 1975; revised 13 May 1975

Food Preference and Length of Life

Abstract. *When random-bred rats were given freedom of dietary choice throughout postweaning life, their life-span correlated with the dietary practices before midlife, particularly those exhibited during early life.*

The relationship between diet and longevity was established when it was demonstrated experimentally that a regimen of caloric restriction imposed throughout postweaning life increased the length of life (*1*). Under natural conditions, however, the quantity or composition (or both) of the diet consumed may change with age and differ from individual to individual. Thus it is important to determine whether, and to what extent, self-determined dietary practices correlate with life-span.

We reported that when rats were given freedom of choice, the composition of the diet selected varied from rat to rat in a manner that maximized the risk to the individual of developing a neoplasm and other diseases associated with aging (*2*). The longevity data presented here were obtained from the same animals.

The self-selection regimen of the 121 individually housed male Charles River COBS rats, which are genetically relatively heterogeneous, was begun at 21 days of age and maintained throughout life. Each rat was provided with three complete isocaloric purified diets in separate containers. Inasmuch as these diets differed in protein (casein) and carbohydrate (sucrose) content only (*3*), the number of dietary variables was limited to the quantity of food consumed and the relative and absolute intakes of protein and carbohydrate. The amounts of each of the three diets consumed and the preference data derived from these values were determined daily. Mean values for successive weekly, 50-day, and 100-day periods were used for actuarial (*4*) and statistical (*5*) analyses.

Without exception, the rats consumed some food daily from each container, but no two rats had the same feeding habits. After an initial period of adjustment, the quantity and composition of the composite diet selected by an individual usually stabilized within narrow limits. The durations of the adjustment period and of the stable peroid differed from rat to rat.

The stable phase for amount of food consumed persisted as long as 300 days. At any time during this period, the food intake values nearly fit a normal distribution curve (*6*). The time required for the protein/carbohydrate ratio of the diet selected (*6*) to stabilize was more variable than that for either component separately. Some rats attained a stable ratio as early as the second week of feeding; approximately 50 percent reached it by the fifth week. Once the ratio was established, it was maintained by some rats throughout most of life. However, a number of rats failed to establish a stable ratio, and from the beginning exhibited a slow and progressive change in the protein/carbohydrate ratio of the preferred diet.

If the dietary preferences of the animals are not considered, their life expectancy at time of weaning was age 630 days. The largest number of deaths per 100-day age period, 32 percent, occurred between ages 600 and 699 days. The death ages were nearly normally distributed, ranging from 317 to 1026 days.

Data presented below show that (i) longevity was related to the dietary habits of the animal, (ii) the correlations were limited to age periods before midlife, and (iii) the age when a correlation was first found, as well as the duration and direction of the correlation, differed for each dietary variable.

Actuarial analyses demonstrated that rats that chose to consume large amounts of food were more likely to be short-lived than rats whose intake was smaller (Table 1). The earliest indication of an association between appetite and life-span was found when the rats had been on the self-selection regimen for only 5 weeks. During the period of relatively constant intake, a 10 percent difference in intake was associated with an 8 percent difference in the probable length of life.

For a more critical appraisal, ungrouped data were used (simple correlation values in Table 2). Inasmuch as a strong association of life-span with one variable may mask an association with another, or may interact to give rise to an apparent but invalid correlation, partial correlation coefficients were computed (Table 2). This method of analysis permits singling out the character of a correlation between two variables while another or other variables are held constant. To assess the combined effects of two or more dietary variables, multiple correlation values were also derived (Table 2).

Simple correlations. In agreement with the actuarial analyses, simple correlations indicated that length of life was inversely related to the amount of food consumed. However, the magnitude of the food intake effect, as determined from the regression equations, changed with age. It was maximal during age period 100 to 199 days (26-day loss in life-span for a 1-g daily difference in food intake), and by midlife it was negligible. If the level of food intake still later in life related to life-span, it was not detected in this study.

If the amount of food consumed is not considered, low-protein diets early in life were more likely to be associated with

Table 1. Life-span of rats permitted freedom of dietary choice: relationship to food intake. Rats are classified according to the mean daily food intake during age period 100 to 199 days. The age for 50 percent survival was estimated from survival curves. The mortality ratio reflects the relative death risk at all ages. It is computed as 100 times the actual number of deaths divided by the expected number of deaths. Values < 100 indicate the extent of reduction in risk relative to "standard" population; those > 100 indicate the extent of increase in relative risk. Age-specific mortality rates for all rats (N = 121) were used as standard rates in deriving the expected number of deaths at consecutive age periods for each of the subclasses.

Food intake (g/day)		N	Life-span (days, mean ± S.E.)	Age for 50% survival (days)	Mortality ratio
Mean ± S.E.	Range				
18.3 ± 0.8	16.2 to 19.2	20	733 ± 117	690	62
19.8 ± 0.3	19.4 to 20.2	20	653 ± 126	650	97
20.7 ± 0.3	20.3 to 21.1	20	630 ± 111	630	103
21.6 ± 0.2	21.2 to 21.9	20	612 ± 115	610	108
22.4 ± 0.4	22.0 to 22.9	20	600 ± 113	580	121
24.1 ± 1.0	23.0 to 26.6	21	556 ± 106	540	162