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UROPEPSIN EXCRETION BY MAN. II. UROPEPSIN EXCRETION BY HEALTHY MEN [1, 2]

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In another communication (1) we presented evidence that the excretion of uropepsin in the urine is dependent upon the secretion of pepsinogen directly into the circulation by the peptic cells of the gastric mucosa. Consequently, it was postulated that the amount of uropepsin appearing in the urine might be related to the rate of "intrinsic" or endocrine activity of the peptic cells of the gastric mucosa. The present communication deals with our attempt to define those factors which regulate uropepsin excretion by healthy men.

METHODS

Twenty-seven apparently healthy men were utilized as subjects for this investigation. Urine samples were collected daily from some of these men throughout the entire 24-hour period of the day for as long as three months without interruption. In many cases, the urine formed during the hours of activity was collected separately from that formed during the hours of sleep and separate uropepsin determinations were performed on the individual samples. In other subjects, only the urine formed during the hours of sleep was collected and assayed. Notations of these differences in procedure appear in the appropriate places in the text and protocols. The methods employed for the collection of urine and the determinations of uropepsin activity have been described in the preceding paper (1). Throughout this and subsequent reports of this series, the unit of uropepsin activity will be defined as that amount which, in the standard 10-minute assay, is required to release 1 mg. of acid-soluble tyrosine-like material.

In order to express the uropepsin excretion in terms of units per hour,. the total amount of uropepsin excreted was divided by the number of hours during which the sample was collected. The presentation of uropepsin excretion in rates rather than amounts per sample provides a basis for the comparison of uropepsin excretion using specimens collected over varying periods of time.

Since the collection of specimens of urine formed only during the sleeping hours presents the minimum inconvenience to subjects, the routine collection of such specimens could be obtained for a number of consecutive nights from a large group of men. As will be demonstrated subsequently, such samples may be used accurately to determine the uropepsin excretion for the entire 24-hour period.

RESULTS

Expression of data

The amount of uropepsin excreted per hour by any particular subject was found to vary from day to day. Although such fluctuations in excretion in any one subject were relatively minor in character, it became essential to determine whether or not the different rates of uropepsin excretion from a subject could furnish a reliable estimate of his true excretion pattern. This can be determined by the application of conventional methods of statistical analysis. Since such methods are most efficient when applied to data that can be arranged in the form of a normal distribution frequency curve, it became essential to determine first whether or not the uropepsin excretion values of each subject were so distributed. Inasmuch as the data obtained from the analysis of night specimens of urine will form the basis for a great majority of our conclusions, such data were utilized to investigate the distribution frequency of the uropepsin excretion values in any one subject.

When the cumulative percentage frequency of a variable is plotted on probability paper against the units of that variable, the plot is a straight line when the distribution is normal. A convenient method of making the comparison is to transform the percentages to probability units, or probits (2). Typical results of the probit plots are illustrated graphically in Figure 1 which demonstrates the distribution frequency in the case of three separate subjects. When the data representing the arithmetic units of uropepsin excretion per hour were plotted against the probits, a straight line was not obtained, *i.e.*, the excretion values for uropepsin,

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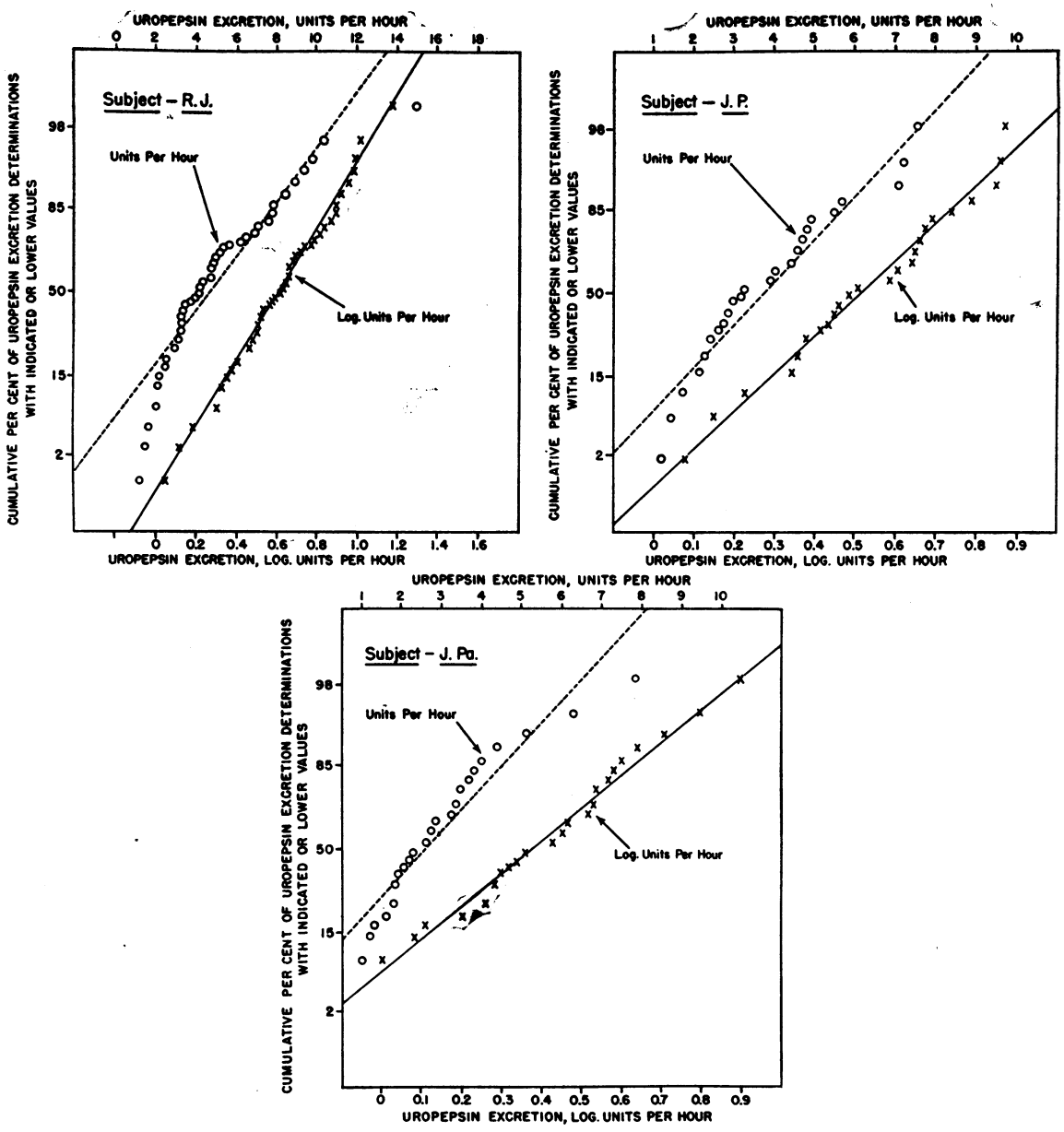

FIG. 1. FREQUENCY DISTRIBUTIONS OF UROPEPSIN EXCRETION VALUES

Probit plots of uropepsin excretions of three subjects in terms of units per hour and logarithms of units per hour. Each point represents an excretion value obtained from the analysis of a "night" specimen of urine. The straight lines have been fitted to the respective data by inspection and indicate that the systematic deviations are removed by the logarithmic transformations.

expressed as units per hour, did not group themselves in the form of a normal distribution curve. However, when the same procedure was repeated but the excretion results expressed exponentially in terms of the Briggsian logarithms of the units of uropepsin per hour, the various data were fitted well by a straight line without the systematic deviation that was uniformly characteristic of the arithmetic plots (Figure 1). Straight lines were obtained from the probit plots of the logarithmic uropepsin excretion values for each of the other subjects. It is worth noting that the use of the values obtained from the analysis of the entire 24-hour urine collection samples yielded similar results to those obtained from night specimens.

The preceding analysis shows that in order to

compare efficiently the uropepsin excretion patterns of different subjects or the excretion values in the same subject from one time to another, the excretion of uropepsin should be expressed in terms of the logarithms of the units (log units), rather than in terms of the arithmetic values. Therefore, all uropepsin excretion values in this and succeeding reports will be expressed in the terms of the logarithms of the units.

Influence of urine volume

Inasmuch as the rate of urine formation often varied markedly during the period of collection of the specimens, it appeared pertinent to determine if the fluctuations observed in uropepsin excretion were due to differences in the rate of urine formation. Toward this end, the results of consecutive uropepsin assays on 13 different subjects were examined in order to determine whether or not uropepsin excretion was a function of the volume of samples of urine. Conventional methods (3) were utilized to determine the linear regression equations expressing the best fit of the data concerning the relation of log units excreted to the volumes of the urine samples.

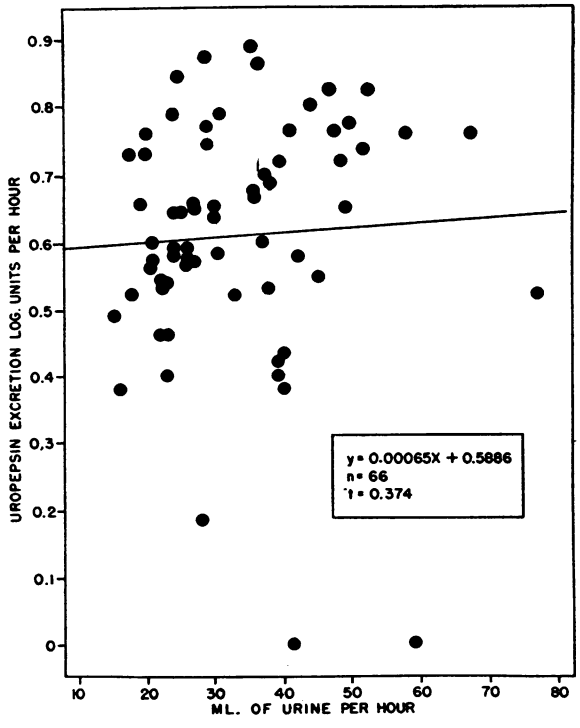

FIG. 2. RELATION OF URINE VOLUME AND UROPEPSIN EXCRETION

Each point represents results obtained from a single specimen of "night" urine. The equation defines the straight line that most closely expresses the relationship between volume of urine and rate of uropepsin excretion for all samples. The "t" test indicates the lack of significance of this relationship. The number of night specimens is given by the figure corresponding to "n."

Figure 2 represents the regression curve corresponding to the experimental observations drawn from assays performed on samples collected for 66 consecutive nights on one subject. Such results are typical of those obtained from all other subjects and no differences were noted, irrespective of whether the data were obtained from the analysis of 24-hour specimens or from analysis of samples representing urine formed during either sleeping or waking hours. Visual inspection indicates the lack of dependence of uropepsin excretion on the rate of urine formation. The calculated regression coefficients for all 13 subjects are recorded in Table I together with the statistics used to test the significance of those coefficients.

Although it is conceivable that uropepsin excretion might be in part a function of the rate of urine formation, the regression may not account for an appreciable portion of the total variation in daily uropepsin excretions even though it is statistically significant. The percentage of the total

TABLE I

The relation between uropepsin excretion and urine volume

Subject	No. of assays	Regression coefficient	"t"	V_1/V_2 *per cent*
I. W.	31	0.00066	0.537	1.0
L. R.	66	0.00065	0.374	1.3
V. G.	15	0.00212	1.191	6.1
W. M.	16	0.01003	3.039*	48.4
J. A.	11	−0.00196	0.797	3.6
H. K.	12	0.00674	3.179*	89.9
J. P.	28	0.00030	0.320	0
J. W.	29	0.00397	1.449	2.8
A. F.	190	0.00046	0.694	2.0
I. H.	26	−0.01228	1.971	11.2
E. J.	26	−0.00055	0.420	3.3
A. S.	15	0.01004	1.764	9.0
E. S.	14	0.00560	1.618	12.4

The uropepsin excretion is expressed as log units per hour. The linear regression coefficient indicates the calculated increase in the rate of uropepsin excretion anticipated from each ml. increase in urine volume. * = Regression coefficient is significant at 5% level; otherwise "t" values indicate no significance of regression coefficients. The ratio between the variance due to the regression and the total variance is listed as V_1/V_2 and is expressed as the percentage of the total variance accounted for by the regression.

variance in uropepsin excretion for each individual that could be accounted for by the regression of the log rate on the volume was calculated. A summary of the results of such calculations appears in Table I. The "t" tests (3) indicate that in only two subjects was uropepsin excretion found to regress to a significant degree on urine volume. Likewise, in only the same two subjects could the calculated, theoretical regression between volume and uropepsin excretion explain an appreciable percentage of the total variance in all of the excretions in any one subject. This fact is illustrated by the statistics in the column "V_1/V_2" which indicate the percentage of the total variance attributable to the theoretical regression (3). These results indicate that, in the overwhelming majority of subjects, variations in urine volume play no significant role in the regulation of uropepsin excretion. Furthermore, in those two subjects in whom it was found to play an apparent role, only a relatively small number of assays had been performed. Consideration of all of these factors leads to the conclusion that for all practical purposes, variations in urine volume can be neglected, and that the formulation of results in terms of rate of excretion furnishes a better index of the various factors regulating uropepsin excretion than does their expression in terms of the concentration of the enzyme as it is found in the urine.

Similarly, analysis of the results has indicated the essential independence of uropepsin excretion on factors such as the pH or the specific gravity of the urine.

Constancy of uropepsin excretion

The expression of uropepsin excretion in terms of the rate forms the basis for an efficient method for the analysis of samples collected over varying fractions of the same or different days with the provision that uropepsin is excreted at a relatively constant rate throughout the 24-hour period.

The constancy of the rate of excretion of uropepsin was investigated by two procedures. In the first of these, a comparison was made between uropepsin excretion by the same subject during the night and during the day. For this purpose, the urine formed by individual subjects during the waking hours ("day urine") was collected and assayed separately from that formed during the hours of sleep ("night urine") for a number of consecutive 24-hour periods. The significance of the differences between the log units of uropepsin excreted per hour in the night and day urines of five subjects chosen at random was estimated by calculation of the "t" values corresponding to the differences between the means of the uropepsin excretion for all of the waking and all of the sleeping hour specimens. These results and their interpretations are found in Table II.

The number of consecutive 24-hour periods during which urine was collected in separate day and night fractions for the above-mentioned subjects averaged 31 days with extremes of nine and 53 days. In none of these subjects was the difference between the mean day and night excretions found to be significant at the 5% level. Indeed, the dif-

TABLE II

Comparison of uropepsin excretion during waking and sleeping hours

Subject	No. of days	Uropepsin excretion (*log units per hour*)				Difference of means	"t"	"Probabilities"†		Significance of Differences
		Waking hours		Sleeping hours						
		Mean	S.D.*	Mean	S.D.*			5%	1%	
A. M.	9	0.35	0.24	0.37	0.20	0.02	0.185	2.12	2.92	none
H. W.	21	0.64	0.14	0.64	0.14	0	0	2.02	2.70	none
L. R.	53	0.66	0.39	0.60	0.44	0.06	0.53	1.98	2.63	none
J. F.	36	0.87	0.49	0.74	0.41	0.13	0.91	1.99	2.65	none
S. B.	37	1.01	0.13	0.94	0.15	0.07	1.538	1.99	2.65	none

Uropepsin excretion values obtained from separate analyses of specimens of urine formed during waking and sleeping hours of the same 24-hour period.

* S.D. $= \pm \sqrt{\frac{S(x - \bar{x})^2}{n - 1}}$.

† The probabilities listed are the values of "t" at which the differences between uropepsin excretion during the waking and sleeping hours become significant at the 1% and 5% levels (3).

ferences did not even approach significance except in the case of one subject. In all four other instances, the significance of the differences was found to be so low as to permit them to be completely ignored. In other words, the differences between uropepsin excretion per hour during the waking and sleeping periods were not significantly greater than the differences found to occur among excretions per hour during consecutive waking or during consecutive sleeping periods. The lack of difference between day and night uropepsin excretion was found to exist irrespective of the individual subject's characteristic rate of excretion. Thus, in these five subjects, the mean uropepsin excretion rate varied from 0.35 log units per hour to 1.01 log units per hour, a range which nearly covers the entire range of dispersion of the mean uropepsin excretion values of healthy men (Table III).

In the preceding analysis, one variable has been temporarily neglected. Since the average duration of the waking period was 16 hours and of the sleeping period only eight hours, it is conceivable theoretically that the absence of a combined effect of the variables "day" and "night," on the one hand, and of length of time of collection of urine, on the other hand, could be due to an interaction between the two factors. In other words, if the amount of uropepsin excreted were found to be some function of the duration of the period of collection of the urine sample, the influence of wakefulness or sleeping (or night or day) alone might have been concealed.

However, the constancy of the rate of uropepsin excretion and the lack of its dependence on the length of the time interval corresponding to the duration of excretion of urine in the sample was demonstrated in yet another manner. In some subjects, samples of urine, representing collections for some fraction of the 24-hour period, were obtained for a number of consecutive days. No attempt was made to advise these subjects to standardize the duration of the period of collection of the urine samples. As a consequence, the times of collection of the urine samples on consecutive days varied from as little as two hours to as much as the entire 24-hour day. When all of these data were analyzed no effect of the duration of collection of urine was revealed. Figure 3 illustrates the data obtained from one such subject and demonstrates the lack of a significant regression. This indicates clearly that fluctuations in uropepsin excretion per hour are not influenced appreciably by the time of the day during which the urine is collected or by the duration of the period of the collection of urine.

The above results have definite practical as well as theoretical implications. The collection of 24-hour specimens of urine day after day from a number of subjects presents certain practical difficulties. On the other hand, the collection of specimens formed during the sleeping hours only is far less objectionable to the subject and constitutes an entirely feasible project. For this purpose, the subject is instructed to void and discard his urine before going to sleep. In the morning he is advised to empty his bladder completely and collect the entire specimen. The times of the two voidings are noted and it then becomes possible to determine the excretion per hour during the sleeping hours. Since such values are representative of uropepsin excretion throughout the entire 24-hour period, they constitute a valid index for the comparison of excretion between subjects and in the same subject from day to day. It was thus found possible to utilize "night specimens" of urine for the determination of each subject's uropepsin excretion pattern.

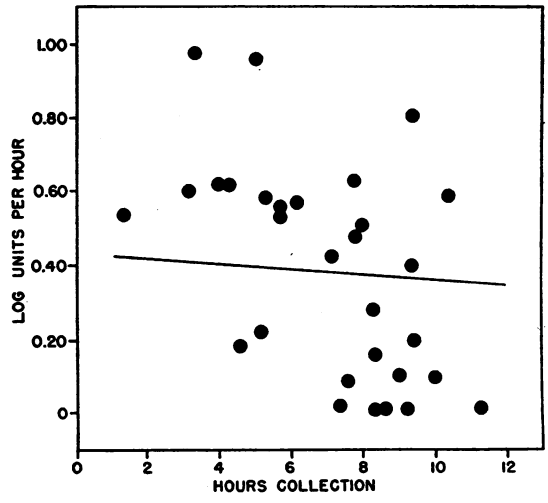

FIG. 3. EFFECT OF DURATION OF COLLECTION ON UROPEPSIN EXCRETION

Each point represents the results obtained from the assay of one of a series of consecutive night urine collections. The coefficient of linear regression is: $b = 0.0064$; $t = 0.333$.

TABLE III

Uropepsin excretion of healthy men

Subject	Age	First four assays					All assays	
		1	2	3	4	Mean	Number	Mean
S. B.	24	0.77	0.73	0.72	0.81	0.76	44	0.93
W. B.	30	0.49	0.69	0.11	0.15	0.36	5	0.41
A. D.	28	0.51	0.18	0.68	0.34	0.43	45	0.34
C. H.	27	0.59	0.52	0.08	0.97	0.54	55	0.78
M. J.	21	0.58	0.46	0.20	0.42	0.42	11	0.25
R. J.	31	0.20	0.65	0.18	0.44	0.37	127	0.62
D. J.	27	0.52	0.26	0.70	0.20	0.42	13	0.52
R. J.	31	0	0.58	0.32	0.15	0.26	5	0.21
L. L.	24	0.62	0.51	0.69	0.65	0.62	6	0.64
C. M.	29	0	0.45	0.57	0.20	0.31	49	0.35
I. A. M.	41	0.53	0.43	0	0.49	0.36	11	0.41
S. O.	24	0.36	0	0.40	0.56	0.33	47	0.36
J. P.	52	0.43	0.45	0.08	0.58	0.39	33	0.39
J. P.	24	0.60	0.64	0.23	0.65	0.53	31	0.54
L. R.	26	0.74	0.76	0.73	0.42	0.66	71	0.61
R. S.	24	0.08	0.08	0.15	0.51	0.21	4	0.21
T.	—	0.64	0	0.72	0.23	0.40	14	0.29
I. H. W.	25	0.34	0.46	0.73	0.63	0.54	83	0.65
N. W.	23	0.82	0.48	0.65	0.45	0.60	8	0.52
I. Y.	26	0.65	0.92	0.82	0.75	0.79	4	0.79
R. McC.	26	0.58	0.52	0.68	0.20	0.50	8	0.46
M. H.	24	0.38	0.42	0.65	0.62	0.52	14	0.58
B. M.	21	0.60	—	—	—	0.60	1	0.60
G. G.	50	0.07	0.71	—	—	0.39	2	0.39
K.	—	0.59	0	—	—	0.30	2	0.30
R. D.	19	0.52	—	—	—	0.52	1	0.52
H. T.	33	0.32	—	—	—	0.32	1	0.32
Mean excretion for entire group		0.46	0.45	0.46	0.47	0.46		0.48

From the preceding considerations, it is evident that the uropepsin excretion of any one subject varied from day to day but that the fluctuations were such as to cause all of the values (in terms of log units per hour) to be arranged in the form of a normal distribution curve. It then became pertinent to inquire whether or not the differences among the subjects were greater than the differences within the subjects. Furthermore, since it was not possible always to obtain specimens for the same number of consecutive periods of sleep, it became important to determine also how many consecutive collections were required to form a valid basis for the characterization of an individual's uropepsin excretion and for the comparison of excretions between different subjects. The pertinent data and conclusions are presented in Tables III and IV.

The results of 695 uropepsin excretion determinations performed on the night specimens of urine obtained from 27 healthy adult male subjects for from one to 127 consecutive nights are summarized in Table III. It is evident by inspection that irrespective of whether only the first assay, the mean of the first four assays or the mean of all of the available assays for each subject is used, the mean value of the entire group is essentially the same. Therefore, there is no sampling error and one or any number of assays on each individual can be used for making comparisons between different groups. Naturally, the usual methods for weighting for a possibly different number of assays on each individual must be used in making such comparisons, in order not to bias the estimate of group performance by giving the various individuals unequal weight.

The preceding conclusion is confirmed in more elegant form by an analysis of variance (3). The quantitative estimate of the degree of variance in uropepsin excretions within and among the various subjects is tabulated in Table IV. These statistics were derived by analysis of the data obtained from

TABLE IV

Analysis of variance of uropepsin excretion of healthy men

The variance was calculated from data obtained from the first four and the first ten consecutive assays of specimens from all subjects with the corresponding or greater number of assays.

Source of variation	Sums of squares		Degrees of freedom		Mean variance			F		
	Four samples	Ten samples	Four samples	Ten samples		Four samples	Ten samples		Four samples	Ten samples
Among all men	1.9506	3.3955	21	14	A	0.0929	0.2425	A/B	1.96*	5.91†
Within all men	3.1259	5.5317	66	135	B	0.0474	0.0410			
Among samples	0.0033	0.0212	3	9	C	0.0011	0.0024	C/D	0.02	0.05
Interaction	3.1226	5.5529	63	126	D	0.0496	0.0441			

* Significant at 5% level.
† Significant at 0.1% level.

the results of the first four consecutive night urine specimens of all subjects from whom four or more such specimens were obtained, and from the first ten consecutive night urine specimens of all subjects from whom ten or more specimens were obtained. In that manner, the bias that comes from unequal weighting is avoided.

It is apparent that the mean variance within the subjects in the rate of uropepsin excretion (0.0474) is smaller than the mean variance in uropepsin excretion among all the subjects (0.0929). The ratio of these two variances ($F = 1.96$) is greater than would be expected on the basis of chance, 95 times out of 100. In other words, each man has a uniform pattern of excretion that is characteristic for him. Also, the differences in the mean uropepsin excretion of different subjects far exceed those that could be attributable to the fluctuations in uropepsin excretion that occur from day to day in the group, as well as in each man. This conclusion is derived from the lack of a significant ratio ($F = 0.02$) of the variance among samples to the variance due to "interaction." The "interaction" is the mean variation remaining after the principal sources of variation (among and within men, and among samples) have been removed, and is due to uncontrolled sources which are assumed to act at random. Thus, the analysis shows that men differ significantly from each other in the rate at which they excrete uropepsin and that there is no first or subsequent sample effect.

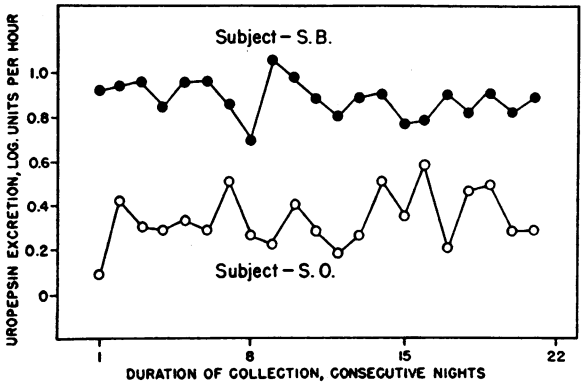

FIG. 4. UROPEPSIN EXCRETION PATTERNS OF TWO SUBJECTS

Each point represents a value obtained from analysis of a "night" specimen of urine. The figure illustrates results obtained from such urines collected for 21 consecutive nights.

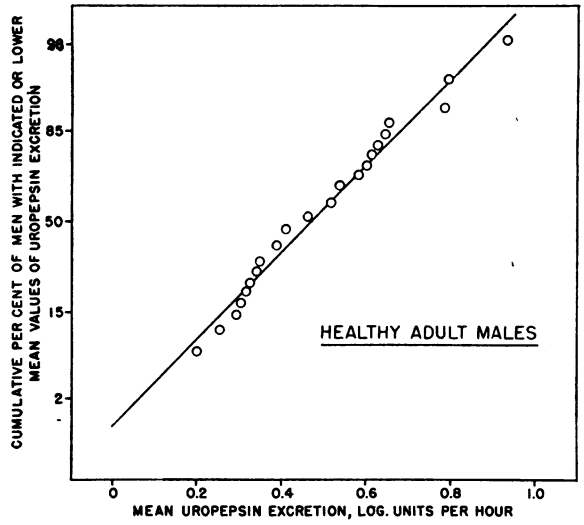

FIG. 5. FREQUENCY DISTRIBUTION OF MEAN UROPEPSIN EXCRETIONS OF HEALTHY MEN

Probit plots of the mean uropepsin excretion values of all assays for each subject. The straight line corresponding to these points has been fitted by inspection.

The data obtained from the first ten night urine specimens of all subjects with ten or more consecutive night specimens reveal essentially the same mean variance within each subject but a greater variance among the subjects, so that the ratio of the variance among subjects to that within subjects becomes even more significant. Thus it is evident from the analysis of both four and ten samples that there is a relatively small variance in uropepsin excretions per hour within each subject and therefore that the daily uropepsin excretion pattern appears to be characteristic of the individual. This fact is illustrated graphically in Figure 4 in which two uropepsin excretion rates during consecutive nights are compared. For this example, two subjects were chosen, one of whom excreted uropepsin at a high rate, the other of whom excreted uropepsin at an appreciably lower rate.

In order to investigate the nature of the observed variance among subjects, the probit transformation was utilized; the means of all of the available assays of the night urines of each subject, in terms of log units per hour, were plotted against their cumulative frequencies (Figure 5). The lack of systematic deviation and the relatively small scatter makes it evident that the population is distributed normally. Since the previous analyses indicate

that the group of subjects chosen is representative of the entire population of healthy adult males and constitutes a random sample chosen without bias, the distribution of their mean uropepsin excretions in the form of a normal curve indicates that the subjects are a homogeneous group with a mean rate of uropepsin excretion of 0.48 log units per hour.

DISCUSSION

A number of observations indicate that uropepsin is excreted at a fairly constant rate by the healthy adult male. The constancy of the rate of excretion throughout the same 24-hour period is indicated by the lack of a significant difference between excretion rates during the waking and sleeping hours (Table II) and by the fact that the excretion rate is not appreciably affected by wide differences in the duration of the collection period of the urine (Figure 3). This fact justifies the determination of the uropepsin excretion rate from analysis of a sample of urine representing the urine excretion of but a fraction of the entire day and also validates the comparison of excretion rates as determined from samples of urine obtained during different lengths of periods of collection and at a different time of the day. The constancy of the rate of excretion of any one subject from day to day was demonstrated by the analysis of the data summarized in Tables III and IV and presented graphically in Figure 4.

The small variance within subjects is extremely significant in spite of the fairly wide fluctuations in daily excretion rates that may be noted in some instances. It indicates the reliance that may be placed on the results obtained from analysis of a single specimen of urine. Thus, if the expected uropepsin excretion rate was calculated from the assay of only one specimen from a healthy man, the result would, on the average, have a relative standard deviation of $\pm$ 62 per cent. That is, it would closely approximate his true uropepsin excretion rate. This figure may be compared to the relative standard deviation of the differences among the men of $\pm$ 58 per cent.

The degree of constancy demonstrates that the rates are grouped in a characteristic excretion pattern. However, failure to utilize the true extent of random fluctuation may easily lead to false conclusions such as that "night" excretions may differ from "day" excretions. Furthermore, the degree of constancy of the rate of uropepsin excretion may be concealed by expressing it in terms of units per day or per hour if the logarithmic nature of the distribution is neglected. Comparisons using statistics based on the assumption that the rates are distributed normally arithmetically are not efficient and, furthermore, expression of values as log units "smooths out" apparent differences.

It is pertinent to inquire concerning the causes of this constancy of uropepsin excretion. At the onset of our study, we anticipated that marked differences might be found between day and night excretions as was suggested by Gottlieb's data (4). Bucher also conceded the possibility that higher than usual rates in the daily uropepsin excretion of some of her subjects could be attributed to increased wakefulness coincident with the pressure of classroom examination (5). However, examination of our data (Table II) reveals no significant diurnal variation. Furthermore, regardless of variations in the number of hours during successive days, during which our subjects were awake or asleep, each subject exhibited a fairly constant rate of excretion. Thus, it is evident that sleep and wakefulness per se exert very little influence on uropepsin excretion. Furthermore, in spite of variations, from day to day, in the amount and type of work, exercise or recreation, the constancy of the rate of uropepsin excretion is indicative of the lack of influence of these latter factors on the regulation of uropepsin excretion.

The lack of diurnal fluctuations also suggests that the influence of the usual meal, varying as it does from day to day in quality and quantity, on uropepsin excretion must be minimal for otherwise, if eating had caused either an increase or decrease in the uropepsin excretion rate, the day and night urine values would have been different. It is conceivable that if no food had been ingested during the daytime, the uropepsin excretion rates would have been lower than those found at night. In an attempt to examine more closely the effect of eating, fractional urine specimens have been collected from a few subjects throughout the waking hours and assayed for uropepsin. These experiments failed to reveal any significant fluctuations that could be attributed to the ingestion of food.

However, the influence of food on the secretion of gastric juice is well-known. Since our data indicate that the ingestion of food does not play any significant role in the regulation of uropepsin ex-

cretion, it becomes evident that a dissociation may exist between the stimulation of the secretion of gastric juice into the stomach and the excretion of uropepsin. Such a conclusion is in accord with the observation that caffeine and histamine, both of which are powerful stimulants of gastric secretion, exert no influence on the excretion of uropepsin by the cat (6).

The apparent dissociation between gastric secretion and uropepsin excretion may reflect a dissociation between the rates of pepsinogen secretion into the circulation and pepsinogen secretion into the lumen of the stomach. Consequently, such factors as do influence uropepsin excretion may do so by affecting the endocrine-like function of the peptic glands of the stomach rather than the exocrine functions of these glands.

Another factor that appears to exert very little influence on uropepsin excretion is the rate at which urine is formed by the apparently healthy kidney. The data in Table I and Figure 2 indicate that the amount of uropepsin excreted is independent of marked variations in the volume of urine excreted. This conclusion is supported also by the lack of diurnal fluctuation in uropepsin excretion (Table II) in spite of the fact that night urine generally is more concentrated and lower in volume per unit of time than is urine excreted during waking hours. Furthermore, very little fluctuation has been observed in uropepsin excretions by the same subject from winter to summer even in the presence of marked changes in urine concentrations.

All of these findings substantiate the conclusion of Bucher (5), that the total amount excreted per unit of time, rather than the concentration, characterizes uropepsin excretion by the human subject. However, all of our data, particularly that presented in Table II, fail to support Bucher's contention that a single specimen of urine cannot be used with validity for the determination of the rate of uropepsin excretion. Our own observations support the conclusion that, if the duration of the time of collection of the specimen is known, the rate of uropepsin excretion can be calculated accurately for the entire day from the analysis of a single specimen containing the urine formed during some fraction of the entire 24-hour period.

As yet, it has not been possible to ascribe to any single factor the responsibility for the differences in excretion rates exhibited by different people. However, the very fact that all of these subjects comprise a homogeneous group in regard to their uropepsin excretion (Figure 5) would tend to indicate that the same group of factors operate to regulate the uropepsin excretion of all the subjects.

SUMMARY AND CONCLUSION

1. Uropepsin excretion by healthy men is best expressed in terms of rates of excretion. Comparisons among rates may be made efficiently by using the logarithms of the rates.

2. Healthy men excrete appreciable quantities of uropepsin at a fairly constant rate throughout the day and from day to day. This rate is not markedly affected by the volume, specific gravity or acidity of the urine or by factors such as wakefulness, sleeping, or ordinary exercise and the usual fluctuations in dietary habits. The ingestion of food does not appear to stimulate uropepsin excretion.

3. The rate of uropepsin excretion is characteristic of the individual subject.

4. Healthy men form a homogeneous group in regard to their rates of uropepsin excretion.

5. Evidence is presented that uropepsin excretion is a function of the endocrine rather than the exocrine activity of the peptic glands of the stomach.

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