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STUDIES OF UREA EXCRETION. V.

THE DIURNAL VARIATION OF UREA EXCRETION IN NORMAL INDIVIDUALS AND PATIENTS WITH BRIGHT'S DISEASE

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In the preceding papers (4, 5, 6) the applicability of the relationship $C_s = \frac{U}{B}\sqrt{V_c}$, as a measure of the urea excreting ability of the kidneys under conditions of low or normal urine volumes, has been demonstrated. This relationship has been called the *standard blood urea clearance* or *standard clearance*, and represents the number of cubic centimeters of blood which are cleared of urea when the urine volume is at the average normal level of 1 cc. per minute. The relative constancy of this measure in a given normal or nephritic individual or in a group of normal individuals shows that the blood urea content and the urine volume are the two factors which appear to be ordinarily of chief importance in regulating the urea output. However, the fact that in a given individual the probable variation of the standard clearance is ±10 per cent and that the maximum variation is much greater indicates that other factors in addition to the blood urea concentration and urine volume affect urea excretion. At high urine volumes, where the rate is uninfluenced by the volume, the effects of some of these factors have been studied (1). Before pursuing a study of the effect of specific factors on the rate of urea excretion at low urine volumes as measured by the *standard clearance* the fluctuation of this value with the ordinary activities of the day and night have been observed. The diurnal variation of the *standard clearance* has been followed in several normal individuals and in a number of patients suffering from Bright's disease.

METHODS

In each experiment observations were made over a 24-hour period, from 6 a.m. one morning until 6 a.m. on the next day. Hourly urine specimens were collected from 6 a.m. until 10 p.m., and then a single specimen was collected between 10 p.m. and 6 a.m. When the subject was unable to void or there was doubt concerning the completeness of voiding the hour period was extended to 2 hours. A sample of blood was drawn by vein puncture at 6:30 a.m., the middle of the first urine collection period, and then at the middle of each second hour thereafter until 8:30 p.m. The blood urea values for the intermediate hours were obtained by interpolation. A sample was drawn at 9:30 p.m. for the last urine period of the day, and another at 6 a.m. on the following morning. The average value of these two samples served as the blood urea concentration from which the standard clearance of the night period was calculated. Urine collections were made within 2 minutes, and the blood samples were drawn within 5 minutes of the stated time. The blood and urine urea concentrations were determined gasometrically (7). The standard clearance, $C_s = \frac{U}{B}\sqrt{V_c}$, where U is the urine urea concentration, B the blood urea concentration, and V the urine volume in cubic centimeters per minute, was calculated as previously described (4, 5). The urine volume, is corrected in each case to V_c by the use of a factor dependent on the ideal body surface of the subject. On the charts the standard clearance has been recorded as the actual value and as a per cent of the normal mean of 54 cc. per minute. When V_c was above the augmentation limit of 2 the rate of urea excretion has been calculated on the basis of the maximum blood urea clearance, $\frac{U\sqrt{V_c}}{B}$ (5). These are recorded in the figures as a per cent of the mean normal, 75 cc. per minute, but have not been used in determining the variability of the rate of urea excretion.

The normal subjects on whom observations were made were up and about during the course of the experiments. All of the patients suffering from Bright's disease were confined to bed. None of the latter received any coffee with their meals, while the normal subjects

had coffee with their breakfast. There were no dietary restrictions in either case although most of the patients happened to be receiving a diet which contained very little sodium chloride.

NORMAL SUBJECTS

In figure 1 have been charted the results obtained on four normal individuals. Although there are many differences between the four

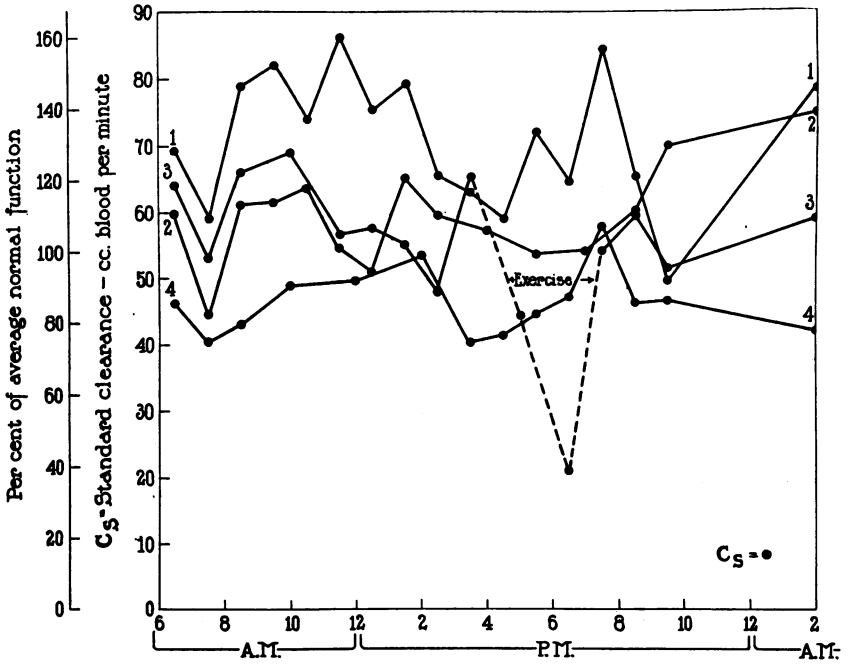

FIG. 1. NORMAL SUBJECTS

curves there are common points characteristic of all of them. In every case the standard clearance is depressed during the first hour after arising. Following this, but commencing before breakfast, there is a regular increase. In a general way this higher level continues through the morning. It is during this period, from 9 to 12 a.m., that the standard clearance shows the least variation, an important consideration in its practical application as a test of renal function, when choosing the time of day during which figures are to be obtained.

After the lunch hour there is a definite drop in the clearance values, which then rise again during the late afternoon and evening. There is no certain effect of meals. In all 4 cases there is a decrease in the clearance an hour after lunch and in 3 cases a similar fall in its value after dinner. The standard clearance for the period of sleep was determined from the actual urine volume and urine urea concentration by the use of the average of the evening and morning blood urea concentrations. The relation of the figures obtained during the night to the daytime values is not constant.

One of the most interesting findings is the observations on subject 3 during the late afternoon, a period in which he indulged in several sets of tennis. A marked depression of his standard clearance occurred. Exercise has been shown (1) to cause likewise a reduction in the maximum blood urea clearance. In both cases this probably follows a decrease in the rate of renal blood flow resulting from the increased blood supply demanded by the muscular tissues. The varying blood supply requirement of different organs and tissues resulting from digestion and other physiological activity, by its influence upon the amount of blood flowing through the kidneys, may well be the cause of much of the variation in the value of the standard clearance. The larger the value of the standard clearance the greater is the variability (table 2) in this figure.

PATIENTS WITH BRIGHT'S DISEASE

Observations of the standard clearance were made each hour during the day on 15 patients suffering from different forms of Bright's disease (figs. 2, 3, and 4). In their grouping Addis' classification (2) has been used. The clinical and laboratory data which form the basis of their separation comprise table 1. The classification of the formed elements of the urine is according to Addis (2).

The two patients with hemorrhagic Bright's disease who had a nearly renal normal function (nos. 5 and 6) showed the same drop in their clearance during the first hour after awakening that was displayed by the normals. In every case the clearance values tend to increase during the course of the day, and they all fall during the period of sleep. The variability of the clearance values decreases in general with the level of the clearance (table 2). Subject 11 was nearly

comatose, and inaccurate voidings probably account for the exceptional variability with such a low function. In percentages of the mean observed clearance values, the variability of the observations on patients is greater than of those obtained on normal subjects. This may be partly due to the fact that the former were all confined to bed where it is more difficult to empty the bladder completely than in the standing posture. Incomplete urine collections could not, however,

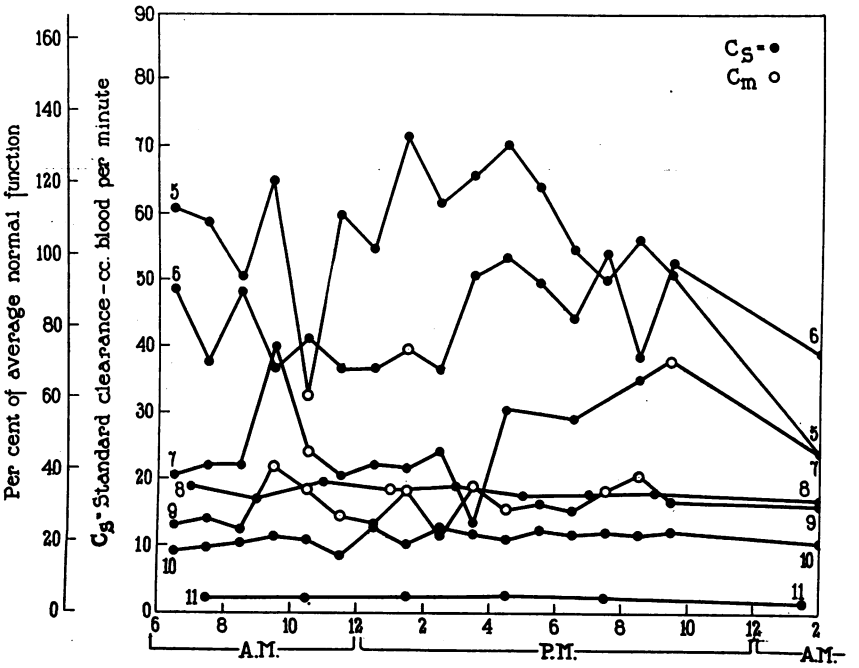

FIG. 2. HEMORRHAGIC BRIGHT'S DISEASE

account for all of the difference. As in the case of the normals the least variable standard clearances occur in every case between the hours of 9 and 12 a.m.[1]

[1] Some of the observations recorded in figs. 2, 3, and 4 were made when the urine volumes exceeded the augmentation limit, and accordingly yielded maximum instead of standard clearances. The C_m values, represented as hollow circles, are given in percentages of the mean normal C_m of 75 cc. blood per minute. The outer scale at the left of each figure applies both to C_s and C_m values, the inner scale only to C_s.

Observations on 5 patients with degenerative Bright's disease are given in figure 3. With the exception of case no. 12, one on whom

TA
Clinical and labor

Case number	Hospital number	Diagnosis		Complications	Age	Sex	Heart size	Blood pressure	Eye grounds	Ede
		Bright's disease								
		Type	Stage							
5	6458	Hemorrhagic	Initial—latent	Acute sinusitis	49	M.	Normal	155/106	Normal	0
6	6164	Hemorrhagic	Healed		31	M.	Normal	125/65	Normal	0
7	6475	Hemorrhagic	Active		25	F.	Normal	168/114	Normal	++
8	6139	Hemorrhagic	Latent		19	M.	Normal	152/ 94	Normal	0
9	6162	Hemorrhagic	Latent		20	F.	Slightly increased	202/115	Normal	0
10	6238	Hemorrhagic	Initial—terminal		16	M.	Increased	136/ 86	Normal	0
11	6166	Hemorrhagic	Terminal	Cardiac insufficiency	34	F.	Increased	203/118	Retinitis with hemorrhages	+
12	6184	Degenerative cryptic	Active		18	M.	Normal	106/ 77	Normal	+++
13	6473	Degenerative cryptic	Initial		12	M.	Normal	115/ 70	Normal	+++
14	6172	Degenerative cryptic	Active	Pulmonary tuberculosis	29	M.	Normal	110/ 68	Normal	+
15	5949	Degenerative cryptic	Terminal	Empyema	20	M.	Normal	128/ 83	Normal	+++
16	5505	Degenerative cryptic	Terminal		11	M.	Normal	116/ 60	Normal	++
17	6446	Arteriosclerotic			49	F.	Normal	234/154	Normal	0
18	6102	Arteriosclerotic			51	F.	Slightly increased	148/ 86	Normal	0
19	6466	Arteriosclerotic		Cardiac failure	49	F.	Greatly increased	242/145	Retinitis	+
20	5210	Hemorrhagic	Terminal	Otitis media	30	M.	Normal	148/190	Normal	0
21	5482	Hemorrhagic	Active		12	M.	Normal	152/110	Normal	+

highly variable figures have always been obtained, the results are essentially similar. Except for one case they all show the fall in the clearance in the morning after awakening. The increase in the clear-

ance during the course of the day, which was evident in all of the normals and the patients with hemorrhagic Bright's disease, is absent

LE 1
ory data on patients

Blood									Urine (excretion per 12 hours)											Renal function	
		Plasma		Plasma proteins						Formed elements											
												Casts									
Urea nitrogen	N.P.N.	Creatinine	Cholesterol	Hemoglobin	Albumin	Globulin	Total	A/G ratio	Protein	Erythrocytes	Leucocytes and epithelial cells	Total	Hyaline	Blood	Fatty	Epithelial	Granular	Waxy	Failure	Phthalein excretion (2 hours)	Standard urea-clearance
mgm. per cent	*mgm. per cent*	*mgm. per cent*	*mgm. per cent*	*volumes per cent O_2*	*per cent*	*per cent*	*per cent*		*gms.*	*millions*	*millions*	*millions*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*cc. per minute*
10.6	35.0	1.30	500	18.5	3.54	3.13	6.67	1.13	1.8	19.15	11.74	0.31	100	0	0	0	0	0	0	66.9	55.8
12.7	29.0	1.42	250	19.2	4.52	2.16	6.68	2.10	0.0	1.01	0.11	0.01	100	0	0	0	0	0	0	60.6	43.9
8.8	27.0	1.36		15.0	1.23	2.68	3.91	0.46	2.9	25.46	26.80	12.46	90	0	8	0	2	0	0	56.4	24.9
23.8	48.0	1.97		16.1	4.32	2.54	6.86	1.70	1.6	13.49	11.48	1.08	83	3	0	0	14	0	0	37.0	18.1
12.5	28.0	1.58	457	17.0	3.06	2.08	5.14	1.47	2.5	11.02	3.39	1.75	100	0	0	0	0	0	0	41.0	14.3
46.1	64.0	4.39	279	11.5	3.07	2.54	5.61	1.21	4.6	190.68	77.20	4.48	67	13	0	0	12	0	8	14.1	11.2
100.0	259.0	16.00	344	10.9	3.47	2.72	6.19	1.27	2.5	8.19	8.77	0.76	0	0	0	0	100	0	100	1.0	2.2
6.6	20.0	1.33	539	10.1	1.34	3.47	4.81	0.39	6.5	0.31	6.82	1.86	70	0	20	10	0	0	0	67.8	44.8
18.8	28.0	1.36	600	13.0	1.65	2.32	3.97	0.71	3.8	0.06	14.11	0.88	65	0	35	0	0	0	0	50.1	24.7
12.7	33.0	1.67	839	17.1	1.92	2.72	4.64	0.70	7.5	0.33	24.48	5.30	80	0	16	4	0	0	0	54.6	18.1
37 [2]	50.0	3.10	682	10.5	1.96	2.90	4.86	0.68	3.7	0.39	38.53	7.57	10	0	10	10	25	5	40	7.0	16.6
[illegible].3	49.0	3.16	648	19.9	1.29	3.12	4.41	0.41	3.9	0.40	4.29	1.48	30	0	0	0	43	0	27	10.2	12.0
[illegible].4	14.0	1.36	313	20.0	4.46	2.81	7.27	1.59	0.3	0.58	0.32	0.32	100	0	0	0	0	0	0	74.0	47.7
[illegible].7	36.0	1.67		19.0	4.32	3.05	7.37	1.42	0.1	0.58	0.43	0.14	100	0	0	0	0	0	0	50.0	42.2
[illegible].1	57.0	1.76		15.7	3.21	2.79	6.00	1.15	0.8	3.04	0.23	0.08	50	0	0	0	50	0	0	28.9	6.0
[illegible].2	61.0	4.50	288	12.1	2.35	2.22	4.57	1.06	3.2	21.12	4.93	0.67	35	17	13	26	0	0	9	16.0	8.0
[illegible].1	22.0	1.50		16.7	1.70	2.79	4.49	0.61	5.6	7.05	4.70	6.30	90	0	10	0	0	0	0	35.7	16.0

in this group, and in two cases quite the reverse occurs. Here again the variability decreases with the decrease in the standard clearance (table 2). In case no. 17, who suffered from enuresis, the variability

is rather high due to our inability to obtain accurate specimens. In 4 of the 5 subjects the standard clearance fell during the period of sleep.

TABLE 2

Values for standard clearance

Case number	Number of observations	C_s average	Variability*
Normal subjects			
		cc. per minute	*per cent*
1	17	71.3	17.9
2	15	59.4	12.9
3	13	58.2	10.5
4	14	46.2	10.2
Hemorrhagic Bright's disease			
5	17	55.8	20.3
6	16	43.9	15.0
7	13	24.9	28.7
8	8	18.1	4.9
9	9	14.3	12.5
10	17	11.2	10.6
11	6	2.2	12.1
Degenerative Bright's disease			
12	15	44.5	30.5
13	17	24.7	24.2
14	17	18.1	22.9
15	17	16.6	11.7
16	10	12.0	20.4
Arteriosclerotic Bright's disease			
17	15	47.7	38.0
18	14	42.2	32.3
19	15	6.0	28.3

* The average variation of the individual observations from the mean value for each series expressed as a per cent of the mean.

Three patients with arteriosclerotic Bright's disease were examined (fig. 4). The characteristics of the other curves are entirely missing here, and the variability of the observations (table 2) is by far the greatest of any of the groups. Subject 17 showed the largest fluctua-

tions. This patient had a rather unstable vaso-motor system and a variable but constantly high arterial blood pressure. The second patient (no. 18) was a phlegmatic individual with only a slight hypertension. The third subject (no. 19) had a very low function produced in part by a complicating cardiac insufficiency. The low variability associated with a low standard clearance in the other groups is lacking here. Whether a high variability of the standard clearance values is

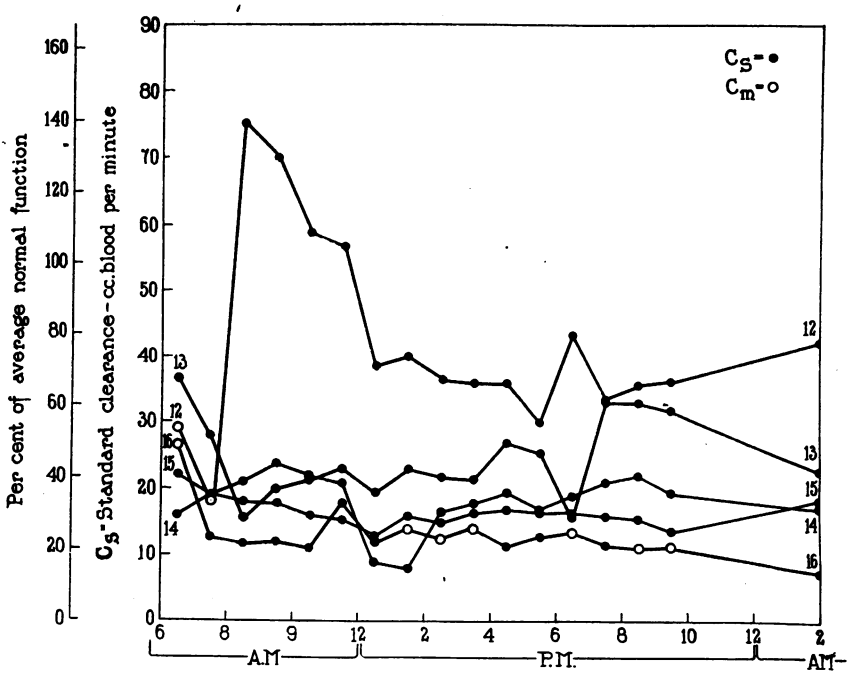

FIG. 3. DEGENERATIVE BRIGHT'S DISEASE

always associated with this type of renal lesion is not certain. That it should be the case is not surprising for the clearance figures are probably largely dependent on the state of the renal vascular system, and both the superficial and visceral blood vessels of individuals with hypertension are known (3) to be hypersensitive to normal stimuli.

THE EFFECT OF MEALS

In nearly every normal subject or patient, on whom observations of the standard clearance during the day have been made, the least

variable values occur between the hours of 9 and 12 a.m. It is during this period that observations for clinical use have always been made on patients in our wards. This period follows the breakfast hour, and from the point of view of the practical use of the standard clearance as a measure of renal function it becomes important to determine whether or not meals, especially breakfast, have any effect upon the clearance figures. In the normal individuals who were examined

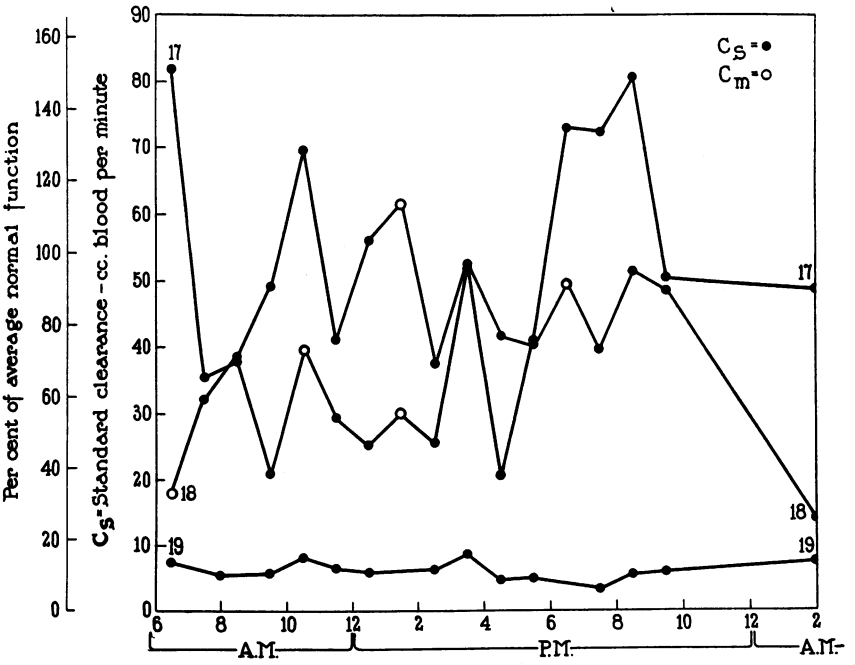

FIG. 4. ARTERIOSCLEROTIC BRIGHT'S DISEASE

there appeared to be a decrease in the value of the clearance after both breakfast and lunch. From the observations on patients no conclusion can be reached on this point.

In order to ascertain whether it is necessary to carry out this urea excretion test in the fasting state a series of observations were made on two patients with hemorrhagic Bright's disease. Observations were made for two hours, from 6 to 8 a.m. before breakfast, and for two other hour periods, 9 to 11 a.m. after breakfast. The tests were

TABLE 3

Testing effect of breakfast on standard clearance

Case number	Breakfast protein content	C_s		Effect
		Before breakfast	After breakfast	
	grams			*per cent*
21	11	10.4	11.0	+5.8
	15	9.9	10.4	+5.1
	24	9.1	8.2	−9.9
	35	8.4	8.3	−1.9
	41	7.3	7.8	+6.9
	35	7.1	9.2	+29.6
	27	7.9	7.5	−5.1
	18	6.6	6.6	0.0
	10	5.6	6.7	+19.6
Average		8.0	8.4	+5.1
22	19	15.2	14.6	−3.9
	23	16.5	16.5	0.0
	28	12.8	12.3	−3.9
	34	18.6	20.7	+11.3
	21	13.0	12.7	−2.3
	23	16.5	18.1	+9.7
	15	19.1	21.2	+11.0
Average		16.0	16.6	+3.1

TABLE 4

Testing effect of breakfast on standard clearance

Case number	Number of observations	C_s	
		Breakfast given	Breakfast omitted
		cc. per minute	*cc. per minute*
2	1	64.0	—
	2	—	64.5
	3	62.6*	—
	4	—	58.3
	5	56.4	—
	6	—	57.4
Average		61.0	60.1
14	1	18.5	—
	2	—	18.7
	3	22.4	—
	4	—	20.5
	5	19.6*	—
	6	—	21.0
Average		20.2	20.1

* Coffee taken.

made four days apart. No coffee was given. The results are given in table 3. Breakfast has no effect, for the volume of blood cleared of urea per minute was in each subject consistently the same before and after the meal. The average figures show a slight increase in the post-breakfast figures, but it is not significant. It is accordingly unnecessary to limit measurements of the standard clearance to fasting periods. As additional proof that breakfast has no demonstrable effect, daily observations of the standard clearance were made between 8 and 10 a.m. on a normal subject (no. 2), and a patient (no. 14) with degenerative Bright's disease. On alternate days breakfast was omitted. The results in table 4 show that there was no effect.

The experiments detailed in table 3 indicate that there is less variability in a series of observations made on an individual on different days, but at the same time each day, then in a series of observations all made on the same day.

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