STUDIES IN DIABETES MELLITUS. II. THE OCCURRENCE OF A DIURESIS IN DIABETIC PERSONS EXPOSED TO STRESSFUL LIFE SITUATIONS, WITH EXPERIMENTAL OBSERVATIONS ON ITS RELATION TO THE CONCENTRATION OF GLUCOSE IN BLOOD AND URINE[1]

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It has been known for many years that the administration of large amounts of glucose to persons with diabetes mellitus may lead to a diuresis. Recent work has amply demonstrated that this effect is attributable to the fact that in the presence of high concentrations of urinary glucose or any other solute there is a limit to the amount of water the renal tubule can absorb—a point where the osmotic pressure of the urine outweighs the work capacity of the tubular epithelium. Brodsky, Rapoport, and West (1) have shown that in this respect the kidney of the diabetic behaves toward glucose in the same manner as the kidney of the non-diabetic individual.

However, there is an increasing body of evidence which suggests that not all of the polyuria which occurs in diabetic persons can be attributed to an increase in the amount of glucose excreted. For example, Tolstoi and Weber (2) observed that diabetic individuals on a metabolism ward, with a fixed regimen of activity, diet, fluid intake, and insulin, excreted widely variable amounts of glucose and water from day to day. The reasons for the fluctuations were not apparent. Meyer, Bollmeier, and Alexander (3), observing two diabetic patients during the course of psychoanalytic treatment, found that these persons developed an increased excretion of glucose and water during acute conflict situations, and that this diuresis could not be related to changes in food intake. More recently, during the course of prolonged observations upon persons with diabetes mellitus of all grades of severity, the present authors (4–7) have repeatedly observed an increase in water and glucose excretion, sometimes associated with ketosis and coma, occurring in association with stressful life situations, and not attributable to infection, trauma, or changes in diet, insulin, or activity. During short term experimental observations (8) it was found that such stresses may induce a marked increase in the ketonemia of both diabetic and non-diabetic persons and significant changes in their blood glucose levels, and that these metabolic changes are frequently accompanied by diuresis. Experimental investigation of this diuresis in non-diabetic persons (9) showed it to be characterized by an increase of up to 500% in the rate of water excretion, accompanied by a fall in the specific gravity of the urine and in the concentration of chlorides and ketone bodies. The changes in the constituents of both the blood and the urine were found to be quite similar to those which take place during the diuresis which occurs during the early stages of a total fast.

The present report describes the results of a study of the phenomenon of "stress diuresis" in persons with diabetes mellitus.

METHODS

Subjects for this study were patients from the Diabetic Clinic of the New York Hospital. The group contained proportionately more persons with severe and labile diabetes than is found in the diabetic population as a whole, but in other respects it was unselected. None of the subjects showed evidence of functional renal impairment, but the possibility that some of them had structural lesions of the kidney cannot be ruled out, inasmuch as several had had diabetes mellitus for a decade or more and showed evidence of generalized arteriosclerosis, diabetic reti-

[1] The authors are indebted to Dr. Edward Tolstoi for making available the facilities of the Diabetic Clinic of the New York Hospital for this study, and for his helpful criticism of this work.

nopathy, or transient episodes of albuminuria. However, a fair proportion of young people with diabetes of recent onset and no evidence of vascular disease were included in the group, and it is probably safe to assume that many of these had no lesions in their kidneys. The patients were subjected to a prolonged study which included a medical history, physical examination, and appropriate laboratory procedures, as well as an evaluation of their personality structures, life histories, cultural backgrounds, present life situations, and significant conscious and unconscious conflicts. The manner in which these studies were made has been described elsewhere (4).

Experiments were performed in the morning after an overnight fast. Those who had been receiving insulin had been on syringe mixtures of Regular and Protamine Insulin usually in a 2:1 ratio, and had received no insulin for 24 hours. All had been consuming at least 125 gm of carbohydrate daily, and there had been no recent major dietary changes. One group of subjects (Table I) received nothing by mouth from the time they retired the night before, and nothing during the experimental period. A second group (Table II) received one glass of water (200 cc) on arising, two hours before the study began, and 200–250 cc per hour by mouth or vein during each experimental hour, as noted in the text. Muscular activity prior to the experimental period was limited to that involved in walking or riding to the laboratory. No smoking was allowed during the experiment. On arising the subject noted the time at which he emptied his bladder; when he arrived at the laboratory he again emptied his bladder, and the time was recorded. Observations were made during three periods of approximately one hour thereafter. Except where otherwise indicated, the procedure was as follows: During the first and third hours the subject "amused himself" reading books or magazines, or was engaged in neutral discussion with the interviewer. During the middle hour he was engaged in a vigorous discussion of topics of significant personal conflict known to be associated with strong and conflicting conscious and unconscious attitudes and feelings. The purpose of this interview was to create a situation which would arouse the feeling states and physiological responses which were usually associated with the important conflict situations in the patient's life.

The reaction of each subject to the procedure was evaluated by observation of his behavior, including both overt manifestations such as facial expression, content of remarks, tone of voice, tears, tachycardia, and sweating, as well as the more subtle clues such as slips of the tongue, figures of speech, and fleeting gestures, which gained significance for the observer from his past familiarity with the subject. The statements of the subject during the interview were recorded, and at later interviews the data were supplemented by his recollections and associations concerning all three of the experimental hours. This precaution was necessary since it could not be assumed that because he was apparently quietly and contentedly reading a magazine during the control hours he was therefore "relaxed" and not reacting to his environment with significant attitudes and emotions.

The control procedures which were carried out were identical with those described above except that no stressful topics were discussed. Because laboratory procedures such as these may in themselves have threatening implications for some people, and because subjects may themselves introduce a stressful stimulus into an intended control procedure through their own ruminations, the subjects for the control procedures were studied as carefully before, during, and after the procedure as the subjects who were exposed to stressful interviews, and their experiences were as carefully evaluated.

The chemical methods used have been outlined in previous papers (8, 9).

RESULTS

Control Studies

As in the studies on the non-diabetic subjects (9), it was found that the variations in posture and the minor variations in activity associated with the interview procedure had no significant effect upon the urine output. In order to facilitate the collection of blood samples at frequent intervals during the interview hour, some of the subjects received a continuous, slow intravenous drip of 0.9% saline during this period at the rate of approximately 1 cc/min. The total amount administered was 60–100 cc. This procedure, which had had no diuretic effect in non-diabetic persons, was likewise found to have no measurable diuretic effect in diabetics. There was no significant difference in the rate of excretion of urine during the hour of neutral interview (second hour) as compared to the average rate of excretion during the first and third hours (Table I). It was also found that there was no significant change in the urinary specific gravity, or in the rate of glucose (Table III), chloride (Table IV), or ketone excretion (Table V), during the interview hour. The rate of urine formation prior to the test was not significantly different from that during the three hours of observation.

The protocol of a control study is presented diagrammatically in Figure 1. At the outset of the study this subject's blood glucose concentration was 134 mg %, and he had 17 mg/cc of glucose in his urine. Subjects for the control studies showed various degrees of glycosuria from 0.0 to 100 mg/cc at the time of their arrival at the laboratory (Table III). Nevertheless, as may be seen here, the rate of water and chloride excretion of 11 out of 14 of them was within the same range as that

found in non-diabetics under similar circumstances (9); likewise their rates of excretion did not vary significantly throughout the morning. Even persons with a high concentration of glucose in their urine and a significant hyperglycemia were observed to develop no polyuria during a morning in which they were not under stress. Figure 2 is the diagram of a study on such a person (Subject

TABLE I

Rate of water excretion (cc/min.)

	Subject	Sex	Age	Insulin requirement	Before arrival	Observation periods			Δ cc./min.	Δ %
						1st	2nd	3rd		
					Control Studies					
1.	J*	F	42	10u		0.2	0.4	0.4	+0.1	+ 33
2.	K*	M	29	110u	0.5	0.6	0.5	0.5	−0.05	− 9
3.	I*	M	15	50u		0.5	0.7	0.7	+0.1	+ 17
4.	S*	F	50	Diet only	0.3	0.5	0.6	0.5	+0.1	+ 20
5.	AB*	M	50	28u	1.4	0.8	0.5	1.2	−0.5	− 50
6.	I	M	15	50u	0.5	0.9	0.7	0.6	−0.05	− 7
7.	U*	F	20	100u	0.2	0.3	0.4	0.4	+0.05	+ 14
8.	P	M	16	60u	0.3	0.5	0.5	0.5	0.0	0
9.	Y	F	16	90u	0.9	1.5‡	1.7‡	1.8‡	+0.05	+ 3
10.	BL	F	38	10u	0.8	0.9	0.8	0.9	−0.1	− 11
11.	Z†	M	20	100u	4.2	4.6	3.3	2.6	−0.3	− 8
12.	BC	F	17	75u	0.2	0.3	0.3	0.3	0.0	0
13.	AJ	F	34	30u	0.7	2.0‡	2.4‡ 2.5‡	2.8‡	0.0	0
14.	O	F	18	100u	0.6	0.5	0.5	0.3	+0.1	+ 25
	Δ cc/min., mean = − 0.04						Standard error of mean ± 0.05			
	Δ % change, mean = − 2						Standard error of mean ± 5			
					Stress Studies§					
1.	AC*	F	52	45u	1.0	**2.0**	**1.8**	0.5	+1.5	+300
2.	Y*	F	16	90u	1.9	**4.5**	**4.7**	3.3	+1.4	+ 42
3.	N*	F	55	10u		**0.7**	**0.5k**	0.4	−0.05	− 9
4.	K*	M	29	110u	1.0	**1.7**	**4.4**	1.2	+3.2	+267
5.	J	F	42	10u	0.4	**1.1**	**0.9**	0.7	+0.4	+ 57
6.	AC*	F	52	45u	0.3	**0.7**	**1.7 3.2**	0.5	+2.7	+540
7.	BC	F	17	75u	0.4	**0.5**	**0.5k**	0.4	+0.05	+ 11
8.	AN	F	40	Diet only	1.0	**1.1**	**2.0 1.9**	0.6	+1.2	+141
9.	BH	M	29	30u	0.7	**0.8**	**1.2**	1.5	+0.7	+ 88
10.	Y	F	16	90u	0.7	**2.9**	**2.8**	1.6	+1.3	+ 81
11.	BI	F	44	Diet only	1.2	**1.0**	**0.9k**	0.7	+0.05	+ 6
12.	AM	F	20	110u		**1.3**	**1.7**	0.5	+1.2	+340
13.	Y	F	16	90u	1.1	**2.8**	**2.7**	1.1	+1.7	+154
14.	AB*	M	50	28u	0.6	**2.1**	**0.5k**	1.1	+1.0	+ 91
	Δ cc/min., mean = + 1.17						Standard error of mean ± 0.27			
	Δ % change, mean = + 149						Standard error of mean ± 42			
	Δ cc/min., mean difference between stress and control studies 1.21 ± 0.27 P < 0.01									
	Δ % change, mean difference between stress and control studies 149 ± 42 P < 0.01									

* Subjects received 60–100 cc 0.9% saline i.v. during 2nd observation period.
† This subject was in moderately severe ketosis on arrival (blood ketones 23.8 mg %).
‡ Subjects experienced hunger during these hours.
§ Values in bold type were obtained during stress periods.
Stress periods marked "k" were accompanied by rise in blood ketones despite absence of diuresis. See text.

Derivation of delta:

Δ represents the difference between values obtained during the control periods and those obtained during the interview or stress periods. In control studies, Δ is obtained by subtracting the average of the values obtained during the two control hours from that obtained during the hour of neutral interview (2nd hour). In stress studies, Δ is obtained by subtracting the average of the values obtained during the control hours from the highest value obtained during a stress period. Values obtained "on arrival" were not included as control values except in the few instances where no other control values were available. In a few studies the interview period (2nd hour) was prolonged to include two collection periods of approximately 45 minutes each. In such cases both of the values obtained are printed in the table under "2nd observation period."

TABLE II

Rate of water excretion (cc/min.)

Subject	Sex	Age	Insulin requirement	Before arrival	Observation periods			Δ cc/min.	Δ %
					1st	2nd	3rd		
Control Studies—Fluid intake 250 cc/hr.									
V	F	35	40u		1.3	2.4*	3.3*	+0.1	+ 4
T	M	55	Diet only		0.4	0.6	0.5	+0.1	+ 33
P	M	16	60u		1.1	1.2	1.1	+0.1	+ 8
U	F	20	100u		1.0	2.4*	2.9*	+0.5	+ 30
R	F	21	40u		2.0	2.3	2.2	+0.2	+ 10
Δ cc/min., mean = + 0.20 Standard error of mean ± 0.08									
Δ % change, mean = + 17 Standard error of mean ± 6									
Stress Studies†—Fluid intake up to 250 cc/hr.									
U	F	20	100u		**3.8**	**4.7**	2.1	+2.6	+124
Q	F	14	60u		**0.9**	**0.4**	"none"		
V	F	35	40u		1.1	**5.2**	**2.3**	+4.1	+373
R	F	21	40u		**2.1**	**2.1**k	2.6*	−0.5	− 19
BE	F	47	Diet only	1.0	**4.2**	**6.1**	**5.1**	+5.1	+510
N	F	55	10u	0.4	**0.4**	**0.5**k	0.4	+0.1	+ 25
P	M	16	60u		0.7	1.1	0.5	+0.5	+ 83
I	M	15	50u		0.6	**2.6 1.8**	0.5	+2.1	+373
X	F	55	Diet only		0.5	**1.6**	0.9	+0.7	+129
Δ cc/min., mean = + 1.63 Standard error of mean ± 0.66									
Δ % change, mean = + 177 Standard error of mean ± 64									
Δ cc/min., mean difference between stress and control studies 1.43 ± 0.66 0.1 > P > 0.05									
Δ % change, mean difference between stress and control studies 160 ± 64 0.05 > P > 0.02									

* Subjects experienced hunger during these hours.
† Values in bold type obtained during stress. See Table I footnote for "k".

I) who had a blood glucose of 286 mg %, and 73.4 mg/cc of glucose in his urine, yet excreted water, chlorides, and ketones at a normal rate throughout a three hour period.

Factors which modified results of control studies

Two of the control subjects developed a gradual increase in the rate of excretion of all of the measured urinary constituents during the morning, accompanied by a slight rise in the blood ketone level and a fall in the blood glucose as exemplified in Figure 3. It is of interest that both of these persons developed fairly marked hunger during the morning, accompanied by increasing tension. In some non-diabetic persons under the same circumstances a diuresis associated with similar changes in the blood constituents was observed (9). This phenomenon in diabetic persons resembles the "starvation diuresis" which accompanies the early stages of a total fast in a non-diabetic person. The sensation of hunger appeared to be neither the determining factor nor a necessary accompaniment of these changes; regardless of hunger certain individuals apparently react to the withholding of food with metabolic alterations which include a diuresis.

One of the control studies was done upon a patient (Subject Z) who was in a moderately severe state of ketosis when he arrived at the laboratory. He had had a verbal conflict with his father the evening before—an occurrence which in the past had been followed repeatedly by episodes of ketosis (4). His initial blood ketone concentration was 23.8 mg %, his blood glucose was 206 mg %, and he was excreting water at the rate of 4.2 cc/min. and glucose at the rate of 319 mg/min. He was tense, resentful, and somewhat depressed. No attempt was made to reassure him or to allow him to express his feelings; instead he was lightly diverted in friendly surroundings during the morning. Under these circumstances his polyuria gradually diminished in intensity, but there was no significant change in his blood ketone level.

Another subject (AB) who had a high concen-

TABLE III

Glucose excretion

	Subject	Rate of excretion						Concentration				
		Before arrival	Observation periods			Δ mg/min.	Δ %	Before arrival	Observation periods			Δ mg/cc
			1st	2nd	3rd				1st	2nd	3rd	
						Control Studies						
1.	J	0	0	0	0	0	0	0	0	0	0	0
2.	K	0	0	0	0	0	0	0	0	0	0	0
3.	I	0	0	0	0	0	0	0	0	0	0	0
4.	S	1	4	8	7	+ 3	+ 60	3	8	11	12	+ 1
5.	AB	88	50	30	72	− 31	− 58	64	63	57	61	− 5
6.	I	36	65	56	34	+ 11	+ 24	73	70	75	53	+14
7.	U	0	0	0	0	0	0	0	0	0	0	0
8.	P	6	9	6	5	− 1	− 14	17	17	13	10	− 5
9.	Y	55	105*	118*	113*	+ 9	+ 8	59	70*	69*	64*	+ 2
10.	BL	0	0	0	0	0	0	0	0	0	0	0
11.	Z†	319	339	237	212	− 38	− 14	76	74	72	69	+ .5
12.	BC	2	3	2	2	− 0.5	− 25	9	10	7	7	− 1.1
13.	AJ	55	131*	152* 159*	179*	+ 1	+ 1	77	64*	63* 63*	62*	0.0
14.	O	0	0	0	0	0	0	0	0	0	0	0
15.	V		100	170*	240*	0	0		77	72*	74*	+ 2
16.	T		5	7	6	+ 1	+ 17		12	12	11	+ .5
17.	P		46	23	15	− 7	− 23	49	41	19	13	+ 8
18.	U		52	64*	76*	0	0	62	50	25*	25*	−12
19.	R	96	165	207	188	+ 31	+ 18	100	83	93	86	+ 8

Mean values for subjects with glycosuria:

Δ mg/min., mean = − 1.7 — Standard error of mean ± 4.8
Δ % change, mean = − 0.5 — Standard error of mean ± 8
Δ mg/cc, mean = + 1.3 — Standard error of mean ± 1.8

Subjects Having Stress Diuresis‡

1.	AC	15	10	10	5	+ 5	+100	14	5	6	8	− 2
2.	Y	189	490	485	326	+164	+ 50	95	108	97	98	+10
3.	K	11	31	99	28	+ 71	+254	11	18	23	24	− 1
4.	J	18	40	22	10	+ 30	+300	44	39	26	14	+25
5.	AC	3	6	0 0	0	− 3		12	7	0 0	0	− 3
6.	AN	0	0	0 0	0	0		0	0	0 0	0	0
7.	BH	0	5	10	20	+ 15	+300	0	3	9	14	+11
8.	Y	50	225	250	140	+110	+ 79	78	78	89	85	+ 4
9.	AM	0	0	0	0	0		0	0	0	0	0
10.	Y	62	210	190	87	+123	+142	59	77	72	77	0
11.	AB	6	17	4	7	+ 10	+143	9	8	9	7	+ 1
12.	U		255	376	134	+242	+180		66	80	72	+ 8
13.	V	0	0	0	0	0	0	0	0	0	0	0
14.	BE	0	0	0	0	0	0	0	0	0	0	0
15.	P		46	80	31	+ 42	+ 55	62	70	72	67	+ 3
16.	I		17	80 50	16	+ 63	+394	40	29	31 27	27	+ 3
17.	X	0	0	0	0	0	0	0	0	0	0	0

Mean values for subjects with glycosuria:

Δ mg/min., mean = + 80 — Standard error of mean ± 22.5
Δ % change, mean = + 182 — Standard error of mean ± 35
Δ mg/cc, mean = 5.6 — Standard error of mean ± 2.3

Δ mg/min., mean difference between means of stress and control studies 81.7 ± 23.0 — $P < 0.01$
Δ % change, mean difference between means of stress and control studies 182.5 ± 35.5 — $P < 0.01$
Δ mg./cc, mean difference between means of stress and control studies 4.3 ± 2.9 — $0.2 > P > 0.1$

Analysis of variances reveals no significant difference between stress and control studies with regard to mg/cc (F Test).

* Subjects experienced hunger during these hours.
† Subject in ketosis on arrival.
‡ Values in bold type obtained during stress.

tration of ketone bodies in his blood (20. 8 mg %) at the time of his arrival was a chronically depressed man who was preoccupied with feelings of loneliness and sadness, and bitter ruminations. During an interview in which he was diverted from these thoughts and reassured by the interest of a friendly physician there was a pronounced fall in his blood ketones, accompanied by a significant fall in his rate of urine output. The concentration of glucose, ketones, and chlorides in the urine did not change significantly, however.

Effect of administering water to control subjects

Because hydropenia is probably in itself associated with strong inhibitory influences on diuresis, a second group of subjects during control procedures were given a moderate amount of fluids in the form of 200–250 cc of 0.9% saline intravenously during the interview hour (Table II). In none of these subjects was there a significant difference in the rate of urine output during the interview hour as compared to the average of the first and third hour values, although two of them

TABLE IV

Chloride excretion

	Subject	Chloride excretion (*mg/min.*)					Chloride concentration (*mg/cc*)				
		Before arrival	Observation periods			Δ mg/min.	Before arrival	Observation periods			Δ mg/cc
			1st	2nd	3rd			1st	2nd	3rd	
					Control Studies						
1.	K	11.5	16.0	14.8	13.7	0.0	23.40	27.50	27.50	30.00	+1.20
2.	I		10.0	11.0	10.0	+ 1.0	16.80	18.00	14.30	13.20	− .70
3.	S	1.2	3.2	4.1	4.9	+ 0.5	5.00	7.65	6.20	8.80	−2.00
4.	AB	6.9	3.6	2.7	6.4	− 2.3	5.00	4.60	5.40	5.40	+ .40
5.	I	2.4	6.7	5.4	4.7	− 0.3	4.90	7.25	7.25	7.40	+ .07
6.	U	1.2	2.8	3.0	4.4	− 0.6	7.45	10.80	8.40	11.05	−1.50
7.	P	2.5	4.9	3.1	3.9	− 1.3	7.20	9.05	7.15	7.40	−1.05
8.	Y	4.1	8.3*	10.8*	14 *	+ 0.3	4.40	5.55*	6.35*	8.90*	+ .77
9.	R	4.2	5.7	8.7	9.5	+ 1.1	4.95	2.87	3.90	4.35	+ .29
10.	BL	7.6	7.8	7.3	8.0	− 0.6	9.00	8.95	8.85	9.10	− .17
11.	Z†	3.2	3.2	2.3	1.9	− 0.3	.76	.70	.68	.63	+ .02
12.	AJ	5.8	11.5*	14.4* 19.8*	22.8*	0.0	8.10	5.70*	6.00* 7.80*	8.00	+ .05
13.	BC	1.8	2.5	3.0	3.0	+ 0.3	8.75	9.35	10.55	10.40	+ .68
14.	O	1.5	1.4	1.2	0.9	0.0	2.66	3.10	2.58	2.59	− .26
		Δ mg/min., mean = − 0.2					Standard error of mean = ± 0.2				
		Δ mg/cc, mean = − 0.16					Standard error of mean = ± 0.24				
					Studies during Stress Diuresis‡						
1.	AC	2.9	**4.5**	**7.8**	3.0	+ 4.8	2.70	**2.20**	**4.10**	4.95	− .85
2.	J	3.2	**5.2**	**5.2**	4.5	+ 0.7	7.65	**5.00**	**6.20**	6.50	− .30
3.	AC		**5.0**	**5.0** 18.0	1.5	+15.0		7.40	**3.05** 5.60	3.20	−1.28
4.	AN	9.0	7.6	**10.6** 7.9	5.3	+ 4.3	8.85	6.75	**5.25** 4.25	9.45	−3.35
5.	BH	5.1	5.9	**9.0**	12.2	+ 6.3	7.68	7.05	**7.32**	**8.35**	+ .78
6.	Y	1.0	**4.5**	**4.5**	4.2	+ 0.3	1.40	1.60	1.60	2.60	−1.00
7.	Y	3.6	**8.8**	**11.4**	4.2	+ 7.2	3.35	**3.20**	**4.35**	3.75	+ .02
8.	BE	7.0	**11**	**11**	12.7	+ 5.7	7.05	**2.60**	**1.75**	**2.50**	−4.77
		Δ mg/min., mean = + 5.4					Standard error of mean ± 1.6				
		Δ mg/cc, mean = − 1.34					Standard error of mean ± 0.65				

Δ mg/min., mean difference between means of stress and control studies 5.6 ± 1.6 $P < 0.01$
Δ mg/cc, mean difference between stress and control studies 1.18 ± 0.69 $0.2 > P > 0.1$

* Subjects experienced hunger during these hours.
† Subject was in ketosis on arrival.
‡ Values in bold type obtained during stress.

developed a gradual increase in urine output during the three hour period. Both of these subjects developed moderate hunger during the morning. It is possible that this diuresis may in part represent a "starvation diuresis" as described above. Another subject (R) had a somewhat elevated rate of urine formation at the outset of the study.

Stress Studies

In 11 of the 14 subjects who were exposed to stressful situations there was a significant diuresis (Table I), accompanied by an increase in chloride excretion (Table IV). In subjects who had glycosuria, there was an increase in glucose excretion which was parallel to the increase in water excretion and was not accompanied by significant changes in urine glucose concentration (Table III). This diuresis was nearly always associated with feelings of anxiety and apprehension, although other feelings might be present also. The conflict situation which aroused these feelings was often initiated by the attitude and actions of the interviewer during the initial waiting period, and sometimes, as in Subject BH, could not be allayed during the final period. Stress periods, therefore, were not confined solely to the second hour. The

TABLE V

Ketone excretion (expressed as acetone recovered)

	Subject	Ketone excretion (*mg/min.*)						Ketone concentration (*mg/cc*)				
		Before arrival	Observation periods			Δ mg/min.	Δ %	Before arrival	Observation periods			Δ mg/cc
			1st	2nd	3rd				1st	2nd	3rd	
						Control Studies						
1.	K	.020	.015	.010	.005	0.000	0	.042	.028	.020	.013	−0.005
2.	I		.009	.010	.017	−.003	− 30	.017	.017	.015	.022	− .004
3.	S	.006	.025	.027	.028	−.001	− 3	.023	.057	.040	.044	+ .011
4.	AB	.045	.032	.022	.050	−.019	− 19	.034	.041	.043	.042	+ .0015
5.	I	.020	.049	.040	.038	−.003	− 7	.041	.053	.053	.060	− .004
6.	U	.014	.028	.036	.045	−.001	− 3	.085	.107	.108	.114	− .002
7.	P	.010	.009	.011	.012	+.001	+ 10	.028	.018	.025	.025	+ .004
8.	Y	.019	.066*	.129*	.114*	+.039	+ 43	.019	.043*	.075*	.066*	+ .021
9.	BL	.008	.011	.010	.010	−.001	− 10	.010	.012	.012	.011	+ .0005
10.	Z†	1.930	2.340	1.700	1.650	+.299	+ 15	.461	.510	.520	.540	+ .005
11.	O	.028	.023	.026	.016	+.007	+ 37	.050	.051	.056	.056	+ .003

Δ mg/min., mean = + 0.029 Standard error of mean ± 0.027
Δ % change, mean = + 3 Standard error of mean ± 7
Δ cc/min., mean = + 0.0032 Standard error of mean ± 0.0022

Subjects Having Stress Diuresis

1.	AC	.025	.011	.026	.009	+.017	+189	.023	.005	.014	.013	− .005
2.	J	.052	.160	.150	.200	−.050	− 25	.132	.157	.179	.195	− .016
3.	AN	.021	.009	.014	.016	+.006	+ 50	.021	.008	.007	.027	− .008
				.022						.012		
4.	BH	.011	.013	.020	.009	+.001	+ 8	.017	.015	.017	.006	− .003
5.	Y	.050	.450	.450	.250	+.200	+ 80	.094	.158	.163	.156	+ .004
6.	Y	.125	.278	.256	.143	+.135	+ 94	.117	.101	.097	.126	− .027
7.	AB	.004	.016	.006	.021	−.005	− 31	.006	.008	.013	.020	− .009
8.	BE	.005	.017	.012	.064	+.026	+520	.005	.004	.002	.012	+ .001

Δ mg/min., mean = + 0.041 Standard error of mean ± 0.029
Δ % change, mean = + 111 Standard error of mean ± 64
Δ mg/cc, mean = − 0.0079 Standard error of mean ± 0.0035

Δ mg/min., mean difference between stress and control studies = 0.012 ± 0.040 1.0 > P > 0.5
Δ % change, mean difference between stress and control studies 108 ± 64 0.2 > P > 0.1
Δ mg/cc, mean difference between stress and control studies 0.0111 ± 0.0041 0.05 > P > 0.02

* Subjects experienced hunger during these hours.
† Subject in ketosis on arrival.
‡ Values in bold type obtained during stress.

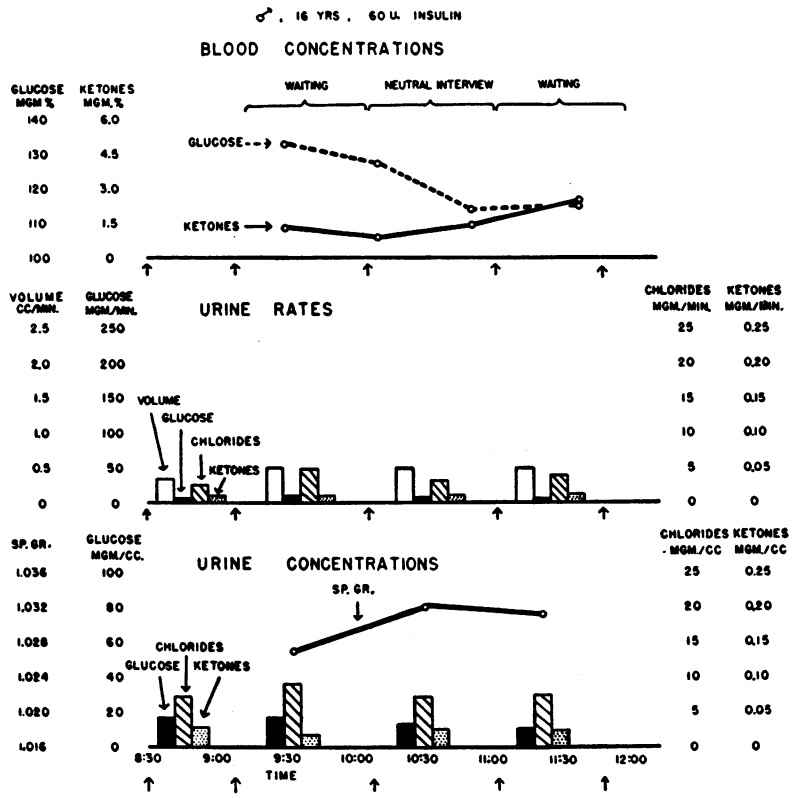

FIG. 1. CONTROL STUDY. URINE GLUCOSE CONCENTRATION 17 MG/CC

Normal rate of excretion of water, chlorides, and ketones; no significant change in concentration of these substances in the urine.

three subjects who developed a significant rise in their blood ketone concentration but had no diuresis showed little evidence of anxiety or apprehension. They were predominantly angry, depressed and resentful. Figure 4 is a diagram of such a study.

Stress diuresis occurred in diabetic subjects even without glycosuria (Figure 5). In such persons the diuresis could not be distinguished from stress diuresis as seen in the non-diabetic (9). It was characterized by an increase in the rate of water excretion, accompanied by a fall in the specific gravity of the urine and in the concentration of chlorides and ketones; but the rise in urine output usually offset the fall in chloride concentration, and resulted in an increased rate of chloride excretion. Accompanying the diuresis there was usually a rise in the blood ketone level, a fall in the blood glucose level, and a decrease in the number of circulating eosinophiles.

When glucose was present in the urine in small or moderate concentrations, the rate of glucose output rose *pari passu* with the rate of water output (Figure 6), but there was no significant change in the concentration of glucose in the urine, and the specific gravity of the urine occasionally fell. When glucose, ketones, and chlorides were initially present in the urine in high concentration, the rate of output of all of these substances also rose in parallel with the rate of water output (Figure 7), again without significant change in their concentrations. It appeared, therefore, that the diuresis was not dependent upon the development of a urine maximally concentrated with regard to glucose or any other substance.

That this diuresis was not dependent upon the level of the blood sugar or upon changes in it was evident from the fact that it occurred in persons with "normal" blood glucose levels (Figure 5) and was most often seen in association with a

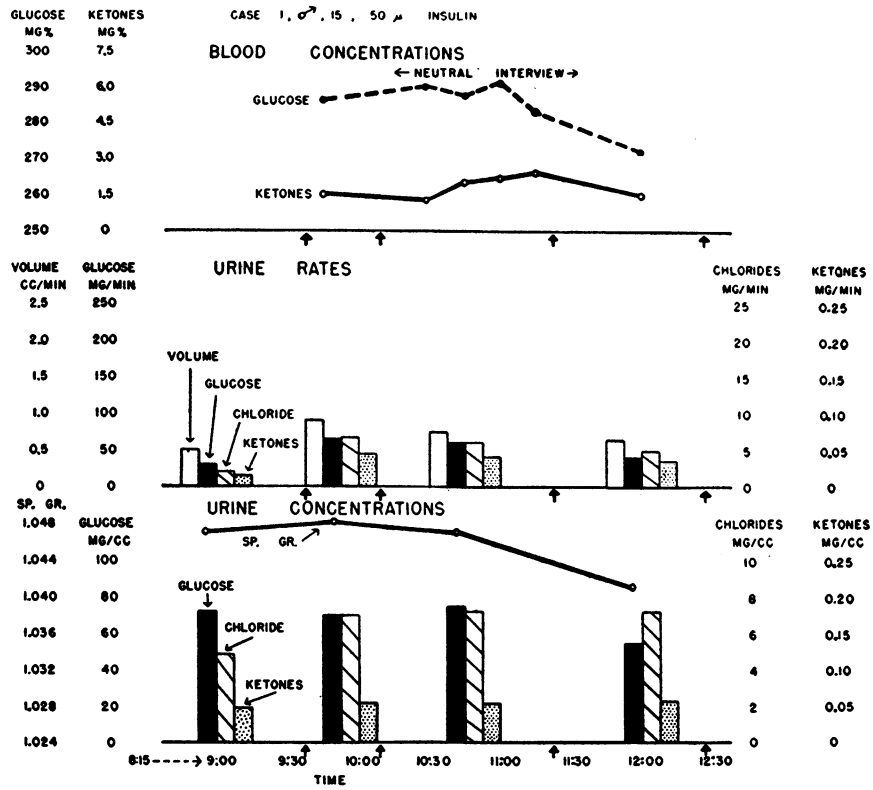

FIG. 2. CONTROL STUDY. HYPERGLYCEMIA AND HEAVY GLYCOSURIA NOT ASSOCIATED WITH POLYURIA

Blood glucose 286 mg%, urine glucose concentration 73.4 mg/cc. Normal rate of output of water, chlorides, and ketones.

falling blood glucose concentration (Figures 6 and 7). On the other hand, it was also seen to occur in persons in whom the blood glucose rose significantly (Figure 8). The subject of this study, who had no glycosuria at the outset of the experiment, developed hyperglycemia, glycosuria, and a slight diuresis after he learned that nothing could be done to prevent him from rapidly losing his eyesight. (This knowledge, which made him predominantly apprehensive and depressed, but did not cause him to feel resentful of the physician or deprived of his support, led to somewhat different feeling states from those aroused by the stresses to which most of the subjects were exposed.) His diuresis probably could not be explained on an osmotic basis, for his urine was at no time maximally concentrated.

Experiments such as that on Subject Q demonstrated that a rise in the blood glucose concentration was not necessarily accompanied by a diuresis. This subject developed a hyperglycemia during a stressful interview, but at the same time developed an oliguria, despite the fact that her urine contained 7.1% glucose and despite the fact that she received 790 cc of fluids during the three hour period. (See below.) A diminution in urine output (cessation of diuresis) also occurred in Subject AB as previously mentioned, during the course of a stress-relieving interview in which his blood sugar level fell. From such studies it appeared that changes in the blood glucose concentration of endogenous origin were not a controlling factor in the development of either a rise or a fall in the urine output of these diabetic subjects, even when their urine was maximally concentrated with regard to glucose.

The magnitude which a stress diuresis may attain was demonstrated by Subject Y. This girl un-

der stress developed a urine output rate of 4.7 cc/min. (282 cc/hr.) and a glucose excretion rate of 490 mg/min. (29.4 gm/hr.). During a four-hour period under stress she excreted 1016 cc of water and 98.25 gm of glucose, whereas on a comparable control day, when her urine contained an equivalent concentration of glucose (90 mg/cc) she excreted only 353 cc. of water and 22.85 gm of glucose during the same period of time. She had not eaten for 14 hours and had presumably been excreting glucose at a relatively high rate prior to the experiment. According to Soskin and Levine (10), the liver of a well fed man of 70 kg contains only 108 gm of glucose as glycogen. Although some of the glucose which this girl excreted probably represents that dissolved in extra-cellular fluid which was mobilized during the period of diuresis, it is a reasonable assumption that a good part of it was derived not only from liver glycogen, but also by gluconeogenesis from protein.

Effect of stress on subjects given fluids

Among the group of nine patients under stress who received fluids at the rate of 200 cc/hr., six developed a significant degree of diuresis (Table II). Two of these subjects, neither of whom was anxious, developed no diuresis, and one who was intensely afraid became oliguric. As mentioned above, this subject developed a hyperglycemia during the stressful interview, but she became oliguric despite this and despite the fact that she received 790 cc of fluids during the three-hour period.

That oliguria may occur during fear or pain has been known for some time. The phenomenon has been studied extensively in animals by Verney

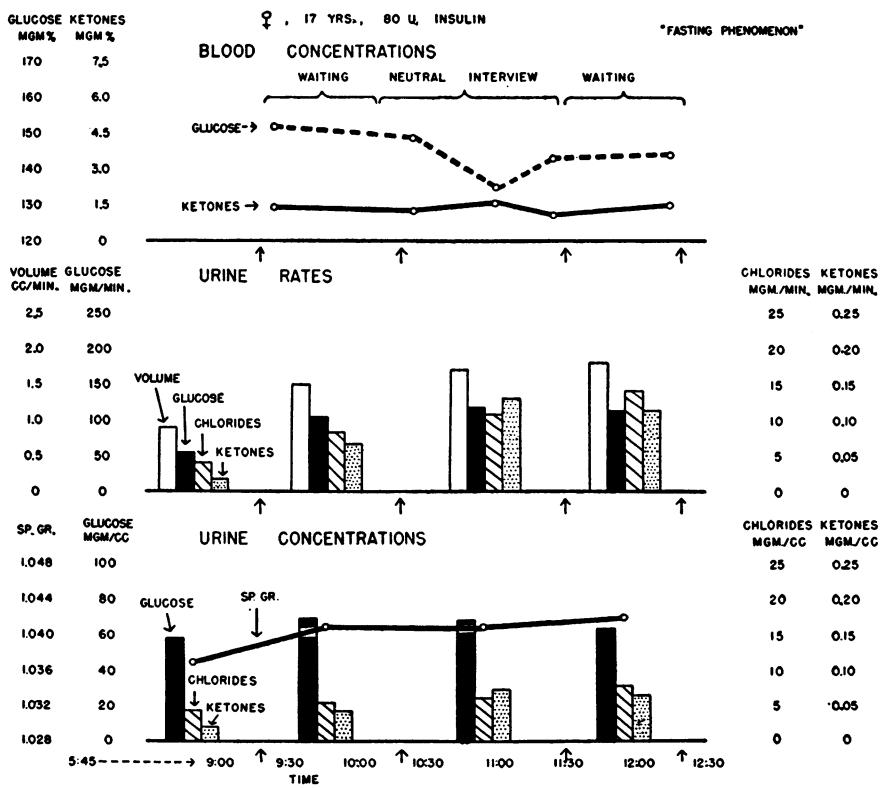

FIG. 3. CONTROL STUDY. "FASTING PHENOMENON" IN A DIABETIC

Gradual rise in the output of water, chlorides, glucose, and ketones associated with increasing hunger and tension. Slight fall in blood glucose, and no significant change in urine glucose concentration.

(11), and in man it has been described by Wolf (12) and Kelsall (13). It appears to be the physiological response which is the opposite of the diuresis of stress, and to be induced by circumstances which imply a different sort of threat to the subject from those which elicit a diuresis. The relation between "stress diuresis" and "stress oliguria" seems to be analogous to the relation between the vascular hypertension and hypotension which may occur in stressful situations. That is to say, just as an individual who may develop a marked rise in blood pressure when angry, may on the other hand develop acute hypotension and faint at the sight of blood, so the same individual may develop diuresis under one set of circumstances, and oliguria under another. (See discussion of Subject AB, below.)

Effect of stress on persons ingesting concentrated glucose solution

Two other subjects were given 500 cc of 50% glucose by mouth after initial blood and urine samples had been obtained (Table VI). Control and stress studies were made upon each subject. The procedures were physically identical, and were separated by an interval of one month during which there was no significant change in the patient's diet, insulin intake, average daily activity, or state of general health. Subjects had received their last insulin injection 24 hours before the procedure. The control studies were made on days when the subjects were feeling relatively cheerful and secure, and when their personal problems were not especially pressing; during the neutral interviews they were lightly diverted by friendly talk with a physician whom they knew and liked, including a discussion of topics and situations which they had associated with hypoglycemia ("insulin reactions"). The stress studies, on the other hand, were made on days when the subjects were feeling depressed, resentful, anxious, and unloved, and when their personal problems were acutely obtruding themselves. Subject V, for example, had recently been passing through a period of con-

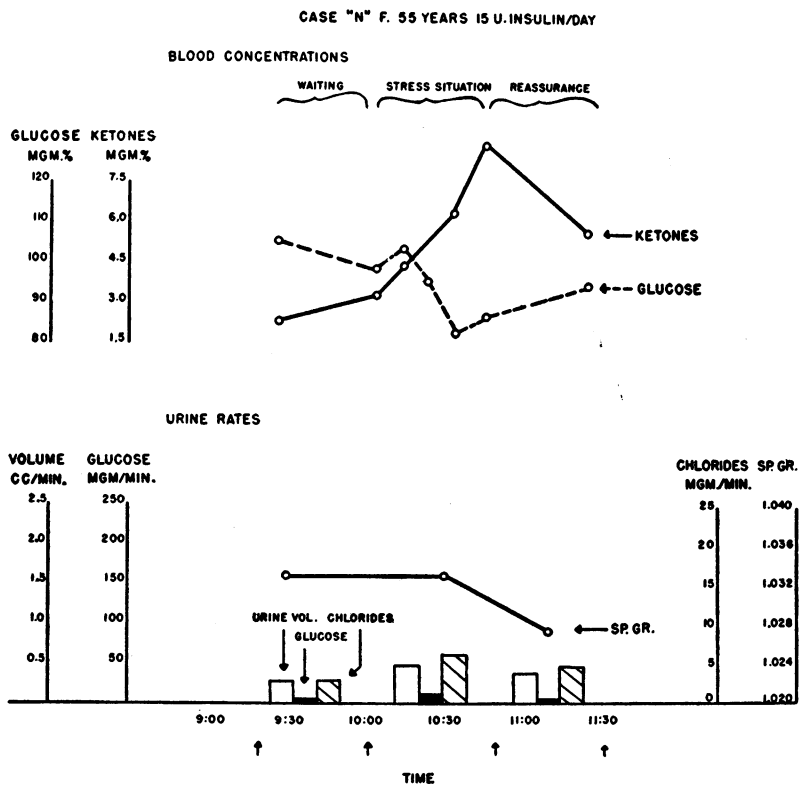

FIG. 4. STRESS STUDY. RISE IN BLOOD KETONES OCCURRING DURING STRESS, NOT ACCOMPANIED BY DIURESIS

TABLE VI

Effect of ingesting 500 cc of 50% glucose solution

	On arrival	Glucose P.O.	Observation periods* 1st	2nd	3rd	4th	Total excreted	Increment over baseline†
Subject V								
Control Studies								
Volume, cc/min.	1.8		1.2		5.5	5.1	812 cc	+445 cc
Glucose excr., mg/min.	0		0		365.	645.	73.2 gm	+ 73.2 gm
Chloride excr., mg/min.	11.0		4.1		11.7	17.5	2.36 gm	+ 0.12 gm
Ketone excr., mg/min.	.034	↓	.028		.017	.017	2.56 mg	− 4.26 mg
Stress Studies								
Volume, cc/min.	0.4		**2.2**	**7.7**	**5.2**	**7.2**	1058 cc	+976 cc
Glucose excr., mg/min.	8		**118**	**279**	**350**	**511**	61.34 gm	+ 59.71 gm
Chloride excr., mg/min.	3.2		**9.3**	**16.3**	**16.2**	**25.2**	3.28 gm	+ 2.626 gm
Ketone excr., mg/min.	.025	↓	**.046**	**.093**	**.052**	**.072**	13.39 mg	+ 8.29 mg
Subject K								
Control Studies								
Volume, cc/min.	0.5		0.8 0.6	0.4	0.7	1.8	180.3 cc	+ 71 cc
Glucose excr., mg/min.	0		0 0	7.7	25.9	112	6.36 gm	+ 6.36 gm
Chloride excr., mg/min.	4.4		9.0 6.6	3.2	2.2	4.2	0.987 gm	+ .022 gm
Ketone excr., mg/min.	.010	↓	.007 .009	.014	.014	.057	4.220 mg	+ 2.03 mg
Stress Studies								
Volume, cc/min.	2.0		**2.4**	**4.35**	**4.33**	**4.72**	845 cc	+407 cc
Glucose excr., mg/min.	135		**177**	**336**	**354**	**342**	64.0 gm	+ 29.6 gm
Chloride excr., mg/min.	6.6		**10.0**	**15.8**	**13.5**	**14.8**	2.919 gm	+ 1.479 gm
Ketone excr., mg/min.	0.24	↓	**0.43**	**0.42**	**0.43**	**0.46**	96.4 mg	+ 43.8 mg

* Values in bold type obtained during stress.

† "Increment over baseline" represents the actual amount of each substance which was excreted during the four hour period after the ingestion of glucose, over and above the amount which would have been excreted during the same period if the subject had continued to excrete at the rate which obtained during the initial control period.

flict with her alcoholic husband and her domineering mother-in-law (4), while Subject K was unemployed, discouraged by rude rebuffs when he attempted to find a job, and brooding over the fact that he would be unable to buy his children any toys for Christmas. During the stress interviews the physician assumed a cool and detached manner, and pressed the discussion of these unpleasant situations depite the subject's desire to avoid them.

A diuresis ensued in each of these experiments, although in Subject K the diuresis during the control procedure was delayed and small in magnitude. In each of these subjects the diuresis during stress was much greater in terms of loss of water, chlorides, and ketones. The two studies made on Subject V are diagrammed in Figures 9 and 10, and have been discussed in another paper (4). Although she excreted almost the same amount of glucose on each occasion, she lost 39% more water, and 57% more chlorides during the stress procedure. Her chloride excretion rose to 25.2 mg/min., which is the equivalent of a loss of 1.5 gm/hr. or 36.3 gm in 24 hours. The incremental excretion of glucose was actually greater during the control procedure (73.2 gm) than during the stress procedure (59.7 gm), but during the control study the increment of water excretion (445 cc) was less than half as much as that during the stress study (976 cc). The diuresis on the control day was associated with a negligible increment of chloride loss (0.12 gm), while that on the stress day was associated with a large increment of chloride loss (2.626 gm). On the control day the ingestion of glucose led to a significant decrease in ketone excretion, whereas on the stress day it was followed by a slightly increased ketonuria.

Closely similar changes were observed in the two studies on Subject K.

DISCUSSION

It seems to be clear from these observations that in the evaluation of diuresis in diabetes it is

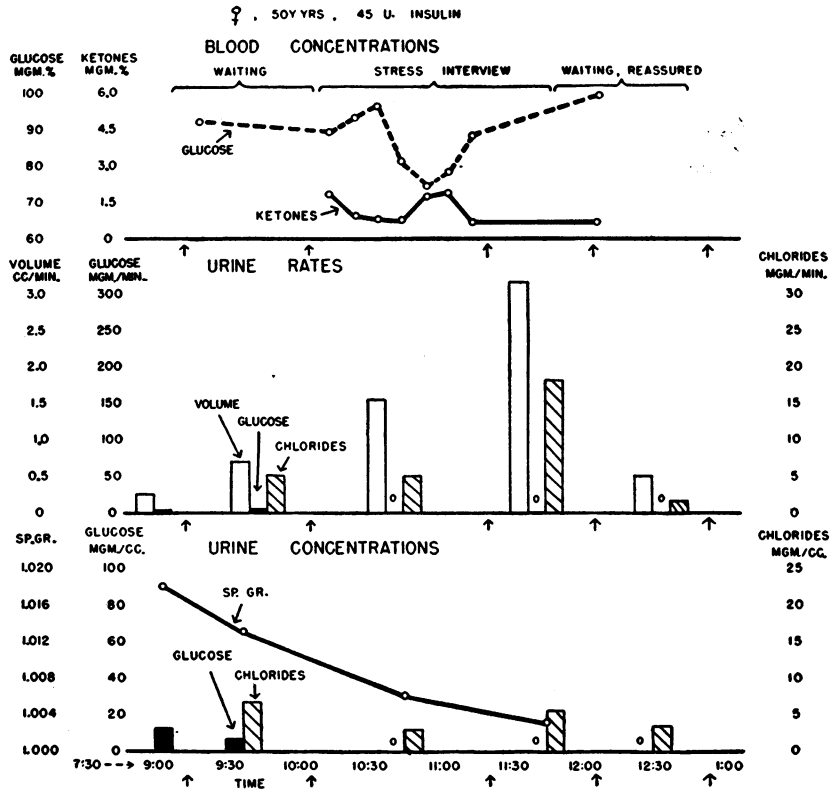

FIG. 5. STRESS STUDY. DIURESIS OCCURRING IN THE ABSENCE OF GLYCOSURIA

Rate of chloride excretion rises in parallel with rise in rate of water excretion, although specific gravity of urine and concentration of chlorides falls.

necessary to consider factors other than the concentration of glucose in blood and urine, since diuresis involving loss of water and chlorides may occur independently of changes in glucose and ketone excretion. In this respect diabetics behave in a fashion similar to non-diabetic individuals.

The occurrence of a "diuresis of stress" in persons who do not have diabetes mellitus appears to have little or no adverse effect upon their health; but when this phenomenon occurs in a diabetic it may have serious consequences. The loss of glucose, water, and chlorides which may occur under circumstances of stress may cause a severe degree of dehydration if it continues. In an earlier communication it was pointed out that stressful situations may also lead to a direct augmentation of the blood ketone concentration in both diabetic and non-diabetic persons(8). A simple elevation of the ketone concentration in the blood does not appear to be toxic to either diabetics or non-diabetics; but when a rise in ketonemia is accompanied by diuresis and dehydration, it may be a potent factor in the development of diabetic acidosis and coma. It is probable that this reactivity of the diabetic to the stresses of daily life explains many of the hitherto obscure fluctuations in the course of diabetes. In extended clinical studies published elsewhere (4–7) it has been observed repeatedly that not only episodes of ketosis and coma, but also changes in insulin requirement of short or long duration, occurring in diabetics of all grades of severity, show an intimate temporal correlation with the significant events in their lives. In adolescents many instances of ketosis have been seen to occur within a relatively few hours after a severe conflict with parents, quite in the absence of infections or of significant changes in their diet or insulin intake. Dolger (14) states that he observed an adolescent girl on a hospital ward who, in a conflict situation, within six hours developed

severe ketosis requiring over 400 units of insulin for its treatment.

The fact that the ingestion of large amounts of glucose and water during a period of stress serves to increase the magnitude of the diuresis may explain another frequently observed phenomenon. Clinicians have long noted that persons with diabetes often are admitted to the hospital in coma after an "eating spree." For a long time it was felt that the ingestion of food was the cause of the ketosis, but Mirsky and others (15, 16) have conclusively demonstrated that a simple ingestion of food cannot cause ketosis. The present study indicates that during periods of calm and security, in the absence of stressful situations, a diabetic person may tolerate the ingestion of large amounts of glucose and water quite well; but that the ingestion of similar amounts of glucose and water in the face of an established stress diuresis increases the loss of chloride and has a potentially deleterious effect. Moreover, the investigations cited above (4, 5) have indicated that diabetic persons tend to respond to stress with an increased desire to eat. It appears, therefore, that diabetic persons do not "eat themselves into coma," but rather that diabetic persons when subjected to stress respond with ketonemia, diuresis and an increased ingestion of food, and that under these circumstances

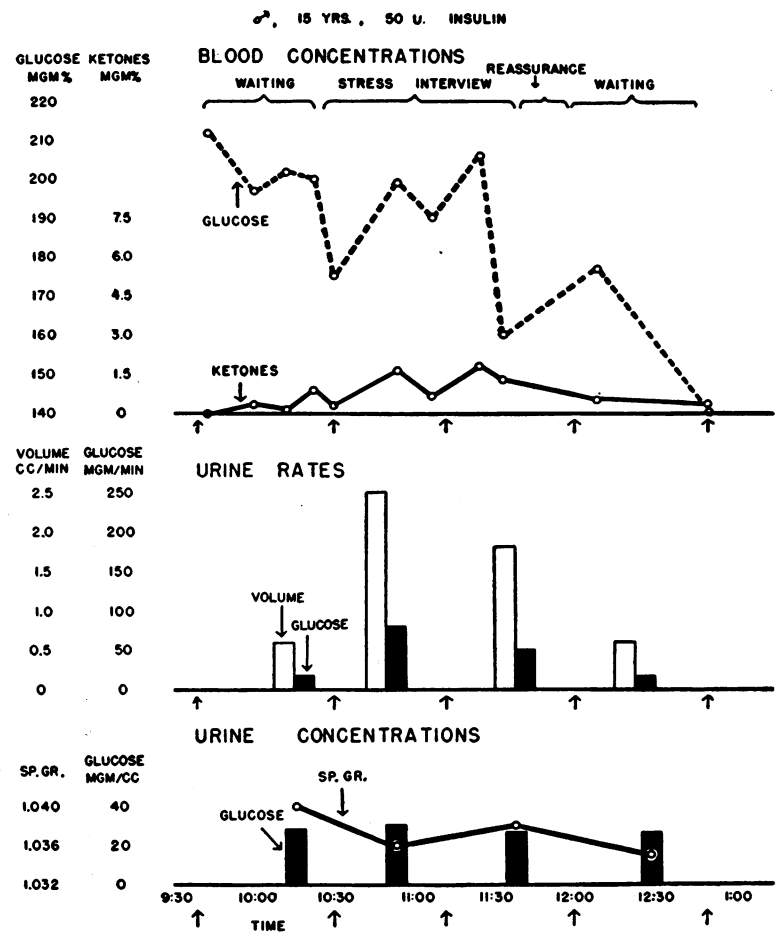

FIG. 6. STRESS STUDY. DIURESIS OCCURRING IN A SUBJECT WITH MODERATE GLYCOSURIA

Rate of glucose excretion rises in parallel with rate of water excretion; concentration of glucose in urine does not change significantly. Diuresis accompanied by large fall in blood glucose associated with marked fluctuations in the level.

the ingestion of large amounts of water and concentrated carbohydrate may aggravate the diuresis.

The fact that a diuresis of stress is associated with an increased excretion of chloride may have an important bearing upon the loss of fixed base which occurs in diabetic acidosis. In 1933 Atchley and associates (17) observed that when diabetic subjects on a metabolism ward were allowed to develop ketosis because of lack of insulin, the early stages of the ketosis were accompanied by a loss of chloride as well as sodium and potassium in the urine. Such a chloruresis would appear to be "contraindicated" from a homeostatic point of view, inasmuch as a loss of chloride entails a loss of fixed base, while the acidotic state of the ketotic person appears to demand a maximal conservation of fixed base. Others, however, have confirmed this finding (18, 19) and it has now been established that chloruresis probably accounts for a large part of the loss of fixed base which occurs during the early stages of ketosis (18, 20). Atchley and co-workers attributed this loss of chloride to the heavy glycosuria. Although experimental attempts to cause chloride depletion in diabetics by giving them glucose have not always been successful (21), recent studies indicate that the administration of glucose to diabetics leads to a significant chloride loss (20). The present studies indicate that some of the loss of chloride which occurs in a diabetic may be a concomitant of the diuresis of stress, and that it may occur even in the absence of glycosuria. The administration of glucose without insulin to a diabetic in a setting of stress appears to cause a

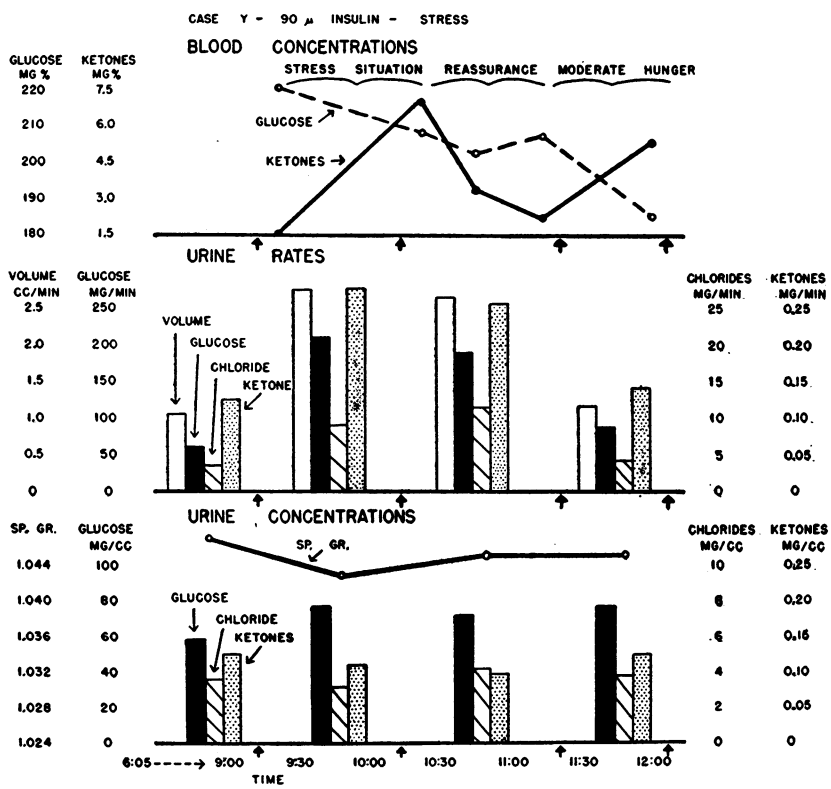

FIG. 7. STRESS STUDY. TYPICAL STRESS EFFECT ON A DIABETIC WITH HYPERGLYCEMIA AND A HEAVY GLYCOSURIA

Diuresis, characterized by rise in rate of excretion of water, chlorides, glucose, and ketones, but not associated with significant change in the concentration of these substances in the urine. Rise in blood ketones associated with a fall in blood glucose.

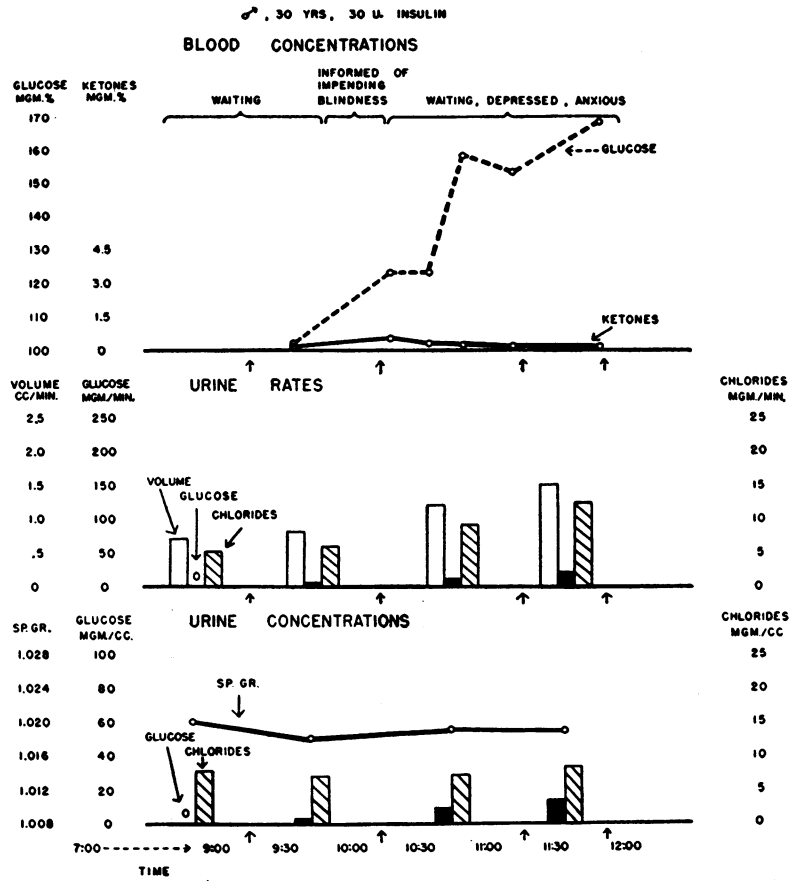

FIG. 8. STRESS STUDY. DIABETIC SUBJECT DEVELOPING HYPERGLYCEMIA, GLYCOSURIA, AND DIURESIS DURING STRESS

greater loss of chloride than occurs when glucose is administered in the absence of stress.

From the present studies it seems safe to conclude that the rate of urine output in diabetic subjects may bear no direct relation to the level of the blood glucose. Many of these subjects developed a ketonemia and a massive diuresis at a time when their blood glucose level was falling steadily, while others with an elevated blood glucose and a heavy glycosuria were obviously in good equilibrium during a morning in which they were under no special stress. Thus it would appear that despite the common clinical reliance on the level of fasting blood sugar as an indicator of "diabetic control," the rate of urine formation is in general a much more reliable reflector of the immediate degree of equilibrium of the diabetic person, if it is evaluated in the light of the general clinical state of the patient and the presence or absence of glycosuria and ketonuria (and, of course, with due consideration of the amount of food or fluids recently ingested).

In order to explain the lack of correspondence between fluid output and the concentration of glucose in the blood and urine, it is necessary to consider the renal mechanism involved. It has been customary to regard the glomerular filtration rate (GF) and the maximal rate of tubular reabsorption of glucose (Glucose Tm) as relatively unvarying in each individual (22–25). Some diabetic persons have been found to have an elevated glucose Tm (26, 27), but this, too, has not been thought to change greatly. The present observations suggest that one or both of these values may change under stress. In fact it is a reasonable assumption that not only the glomerular filtration

and the glucose reabsorption, but the entire renal hemodynamics and all of the reabsorptive capacities of the renal tubule may change under the influence of stress. Smith (28), G. A. Wolf (12), and Stewart Wolf and associates (29), have shown that changes in glomerular filtration, in the filtration fraction, and in the renal blood flow, may occur in response to stressful life experiences, although the changes in glomerular filtration which they described were not of the magnitude which we suggest may have occurred in these studies. Conn and his co-workers (30) have indicated that ACTH depresses the tubular reabsorptive capacity for glucose, while Ingbar and his associates (31) have shown that ACTH and cortisone cause an increase in renal blood flow and glomerular filtration. It has been mentioned that the response to stress of the patients in the present study was often accompanied by a significant fall in the eosinophile count, the details of which will be described elsewhere. It is reasonable to assume that adrenal corticosteroids were elaborated during these procedures. It is of further interest that Verney (11) has shown that the secretion of posterior-pituitary anti-diuretic hormone is under the control of the central nervous system and may be affected by "emotional stress." Some such mechanism must probably be invoked to explain the changes in wa-

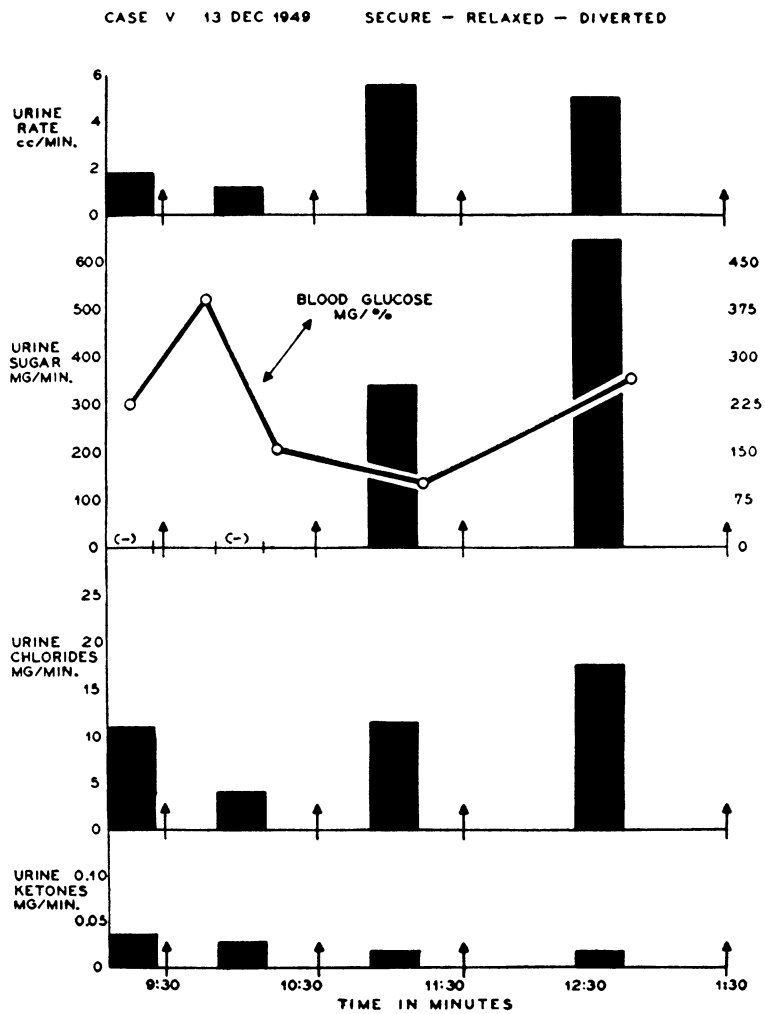

FIG. 9. CONTROL STUDY. EFFECT OF INGESTION OF 500 CC OF 50% GLUCOSE SOLUTION IN THE ABSENCE OF SIGNIFICANT STRESS

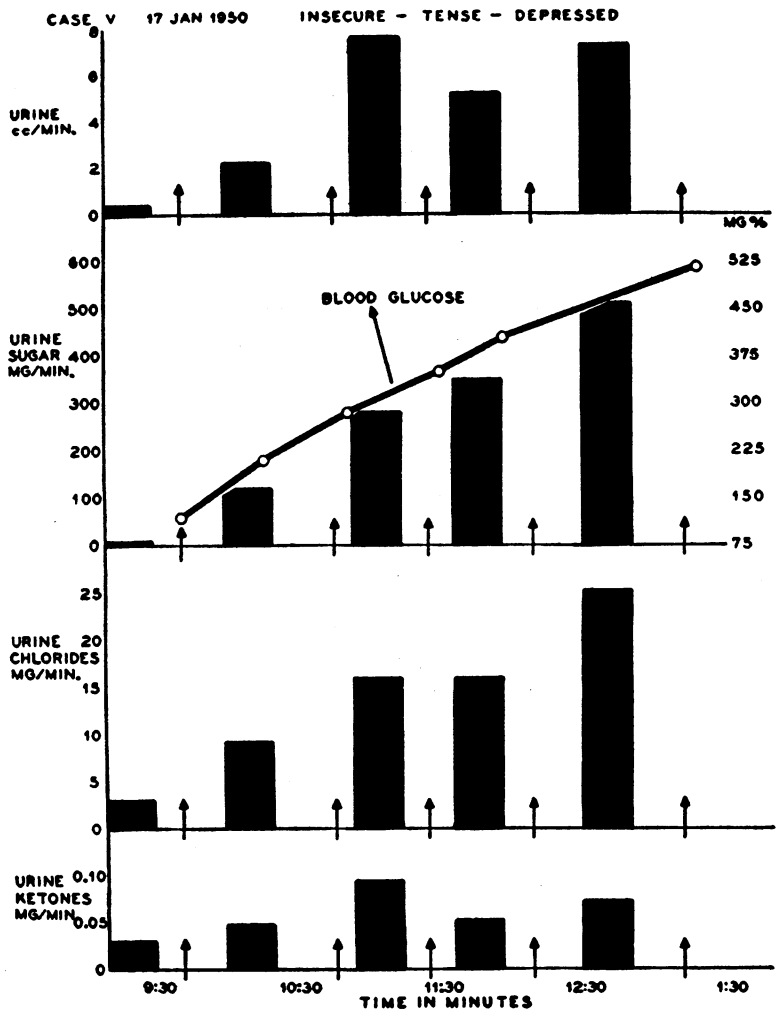

FIG. 10. STRESS STUDY. EFFECT OF INGESTION OF 500 CC OF 50% GLUCOSE SOLUTION IN A SETTING OF STRESS

ter excretion which occurred in both these and the non-diabetic persons previously studied, since present evidence indicates that changes in water excretion cannot be explained upon the basis of changes in glomerular filtration (32).

With regard to the connotation of the commonly used expression "emotional stress," it may be said that situations such as these persons faced quite commonly arouse strong emotions, but it is unnecessary to consider that these emotions are the "cause" of the physiological changes which were observed. It appears, rather, that the situation—the words and actions of the interviewer—was the stimulus; that the patient's interpretation of these words and actions, made on the basis of his past experience of which he was partly conscious and partly unconscious, endowed them with a threatening meaning for him, and converted them into a "stress"; and that he responded to this stress with a change in feeling state, a change in behavior, and a change in many aspects of his metabolism. The emotion and the bodily change, therefore, were both a part of the response to stress, and it is not profitable to consider that either caused the other. Despite this lack of causal relationship between the two it is of interest that there did appear to be a high degree of correlation between certain feeling states and specific metabolic changes. Since the

significance of the experimental situation to the individual concerned appeared to be the determining factor with regard to the type of response which occurred, and since the way in which he considered this situation to affect his welfare would naturally be reflected in his attitude, one would expect a fairly high correlation between feeling states which are appropriate to this or that attitude and a particular type of bodily change.

Stress diuresis, for example, most often occurred in a setting of anxiety and apprehension, but intense fear was associated with oliguria, as in Subject Q. Subject AB (Table I, Stress Study) was anxious and apprehensive during the initial hour of observation, and had a diuresis; during the second hour his anxiety turned to great fear, and he became oliguric; during the final hour his urine output returned to its original level. A rise in blood ketones was usually associated with feelings of resentment, hostility, and depression, and of being deprived of the friendship and support of the physician. When mixed feeling states were present, several types of metabolic change might occur also. Measurements of these emotional changes cannot be made as precisely as need be, but conscious and unconscious attitudes and feelings can nevertheless be reasonably satisfactorily assessed with suitable experience and recourse to the methods outlined in the beginning of this communication.

The reasons why a diuresis should occur in a diabetic person in a setting of stress are not at present clear. Usually bodily reactions which develop in situations of stress appear to have an adaptive value for meeting specific threats to the homeostatic integrity of the organism; but the specific threat which they are designed to meet may not actually be a part of the stress to which the subject is now exposed (33). In line with this thought, it is well known that the normal individual adapts to starvation with metabolic changes which involve the preferential use of fat rather than carbohydrate as the fuel for muscular work. This shift is accompanied by a rise in the blood ketones and a diuresis (9, 34), and its development may be accelerated and augmented by exposing the individual to various forms of non-specific stress (9). The fact that the diabetic metabolism has many qualitative similarities to the metabolism of starvation (6), the psychological evidence that diabetes often occurs in persons who have suffered repeated emotional deprivations and who react psychologically as if they were "starved" (4–6), and the similarity of the stress reaction in the diabetic to the reaction of a non-diabetic person to early starvation (9), all have led us to conjecture that perhaps the diabetic individual reacts to the specific stressful situations with which he is confronted "as if they represented threats of starvation," and responds with an exaggeration of the metabolic changes which would be appropriate to actual starvation. The diuresis of stress appears to be a part of this response.

CONCLUSIONS

(*1*) In persons with diabetes mellitus, exposure to stressful life situations may lead to a diuresis. This diuresis is characterized by a 200–500% increase in the rate of water excretion, accompanied by a rise in the excretion of chlorides and ketone bodies.

(*2*) The stress diuresis which occurs in aglycosuric diabetic persons is similar to that observed in non-diabetic individuals.

(*3*) When stress diuresis occurs in diabetic persons who are glycosuric, the rate of glucose excretion rises in parallel with the rate of water excretion, and there is no major change in the glucose concentration of the urine.

(*4*) Stress diuresis is not dependent upon osmotic changes associated with the excretion of glucose in the urine, or upon changes in the concentration of glucose in the blood.

(*5*) A stress diuresis may lead to a rapid loss of large amounts of water, glucose, and chlorides, and may be an important factor in the development of diabetic acidosis and coma.

(*6*) The ingestion of concentrated glucose solutions is well tolerated by diabetic persons in the absence of stress; but in a setting of stress the ingestion of concentrated glucose solutions may accentuate the loss of water and chlorides.

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