Reduced Pupillary Unrest

Autonomic Nervous System Abnormality in Diabetes Mellitus

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Pupillary unrest (fluctuations in pupil size) was measured by infrared television videopupillography in 80 insulin-dependent diabetic patients (age 25–43 yr, diabetes duration 0–35 yr) and 26 control subjects (age 26–39 yr). In darkness, pupillary unrest was 21% less in diabetic subjects than in controls. During prolonged and brief illumination, pupillary unrest was 35 and 37% less in diabetic subjects than in controls, respectively, and in both cases the unrest was inversely correlated to the duration of diabetes. There were inverse correlations between *1*) vibratory perception threshold, long-term high blood glucose levels, and severity of retinopathy, and *2*) pupillary unrest in darkness and during prolonged illumination. The fractional reduction in pupil size (relative miosis) was 19% less during prolonged illumination in diabetic subjects than in controls and was positively correlated to the pupillary unrest in both groups. For a given fractional reduction in pupil size during illumination, diabetic subjects still had a smaller unrest than controls. Pupil size in darkness was 19% smaller in diabetic subjects than in controls, and in diabetic subjects it was positively correlated to the unrest in darkness and during prolonged and brief illumination. None of the pupillary abnormalities showed correlation to biomicroscopic changes in the iris. The autonomic nervous system abnormalities reflected in the pupil in longstanding diabetes are *1*) a reduction in pupillary unrest in light and in darkness, more pronounced in light, *2*) a reduction in the ability to maintain miosis in continuous light, and *3*) a reduction in size. *Diabetes* 37:446–51, 1988

In its role of maintaining homeostasis, the autonomic nervous system is in a state of constant fluctuation. This fluctuation, expressed by spontaneous variations in blood flow and heart rate, for example, has been shown to be reduced or absent in long-term diabetes, thus revealing a functional abnormality of the autonomic nervous system in this disease (1–4). Another example of such fluctuations is the spontaneous variation in pupil size or pupillary unrest. These irregular fluctuations of the pupil have been shown to be reduced in subjects with long-term diabetes (5,6), in diabetic subjects with autonomic neuropathy (7), and in recently diagnosed diabetes during quite severe metabolic derangement (8).

This study of subjects with insulin-dependent diabetes mellitus (IDDM) in their ordinary metabolic state was undertaken to clarify further the occurrence of reduced pupillary unrest in diabetes and the relationship of this autonomic nervous system abnormality to duration and control of the disease and to classic long-term diabetic manifestations (9).

MATERIALS AND METHODS

Subjects. Eighty IDDM subjects (30 women, 50 men) with an average age of 33 yr (range 25–43 yr) and 26 healthy control subjects with an average age of 32 yr (range 26–39 yr) were studied. Mean duration of diabetes was 15.7 yr (range 0–35 yr).

Patient selection was such that there was no correlation between age and duration of diabetes. Patients were not selected with regard to complications of diabetes, including autonomic neuropathy in other organs, with the obvious exceptions that patients with retinopathy within the area stimulated by light and patients with visual acuity less than 6/9 were not examined with light stimuli. None of the patients had received photocoagulation therapy before the study. Pupil size in darkness and its relationship to other long-term manifestations of diabetes (10) and the pupillary response to light (11) have been reported in virtually the same groups of subjects, but subjects in whom pupillary unrest could not be determined because of frequent eye blinks during examination are left out of this study.

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TABLE 1
Long-term diabetic manifestations in 80 young insulin-dependent patients

Diabetes duration	Vibratory perception threshold* (*n* = 79)		Retinopathy (*n* = 80)				Iridopathy (*n* = 60)			Persistent proteinuria (*n* = 80)	
	≤18 V	>18 V	No change	Red dots	Hemorrhage and/or exudates	Neovascularization	No change	Pigment defects†	Rubeosis iridis	Absent	Present
≥15 yr	29	17	17	8	11	11	31	6	1	34	13
<15 yr	26	7	28	4	1	0	22	0	0	33	0

*Arbitrarily expressed in volts; 18 V is highest individual value found in controls.
†Porosity of pigment seam or loss of pigment.

Table 1 shows clinical characteristics of the patients. Twenty-four (30%) had peripheral neuropathy as evidenced by an abnormally elevated vibratory perception threshold (12); 35 (44%) had diabetic retinopathy, 11 (14%) of whom had proliferative changes; 7 (12%) of 60 patients who underwent slit-lamp examination had evidence of minor diabetic iridopathy, 1 of whom had a mild rubeosis iridis; and 13 (16%) had diabetic nephropathy as evidenced by persisting proteinuria. The diabetic subjects, most of whom were attending the outpatient clinic, had nonfasting blood glucose of 194 ± 85 mg/dl (mean ± SD) at the time of the study. Patients with hypoglycemia or excessive hyperglycemia (>360 mg/dl) during the examination, patients with a history of iridocyclitis and diseases unrelated to diabetes, and subjects with myopia or hypermetropia >2 diopters were excluded from the study. None of the participants received any drug known to influence the pupil. Care was taken to ensure that the patients were fully awake during the examination. Informed consent was obtained from all participants in the study, which was performed in accordance with the principles of the Declaration of Helsinki.

Methods. Pupillography was performed with an infrared-sensitive television camera (Iriscorder, Hamamatsu, Hamamatsu, Japan), measuring the area of the left pupil, and after analog-to-digital conversion (Schlumberger, Solarthron, FRG) the measurements were handled off-line on a central computing facility (CDC Cyber 173, Aarhus University, Denmark). The pupillographic examination took place in a completely dark room. A red fixation light placed at an optically infinite distance was used to prevent accommodation. [For further details of the technique, see Gundersen (13)].

Pupil unrest (so-called hippus) was recorded during darkness and during continuous illumination. The normal pupil is always undergoing fluctuations in size (14). In darkness these fluctuations are minimal but increase markedly in light (Fig. 1) and during accommodation (15), i.e., when the pupil is small. After adaptation to complete darkness for 15 min, pupil area was measured at 10-Hz sampling rate for several consecutive periods of 15 s each. The ordinary standard deviation of the mean of these continuous measurements was calculated by the computer and used to express the degree of variation in pupil area, i.e., pupillary unrest (8). Day-to-day intraindividual coefficient of variation (C.V.) of this parameter in darkness was 12.5% estimated from investigations <1 mo apart. The same procedure was used for measuring the pupillary unrest in light but with continuous illumination to the right eye with a beam of light of an intensity of 512 μlm emitted by a photostimulator (13) and converging to a width of 1 mm in the plane of the pupil. Thus, any influence of the pupil size on the stimulus intensity delivered to the retina (so-called open-loop approach) was avoided. On the retina, the light beam covered an area about the size of the optic disk, located one papillary diameter above the optic disk. The absence of retinopathy (except for a few red dots) within this particular area was determined by ophthalmoscopy in all patients (11). Pupillary unrest in light was determined in two ways: *1*) during prolonged illumination, with each recording starting 90 s after the onset of light stimulus (Fig. 2); and *2*) during brief illumination, with each recording starting 15 s after the onset of light stimulus. Day-to-day C.V. for pupillary unrest during prolonged illumination was 20.9% and during brief illumination was 14.7%. Fractional reduction in pupil size (degree of miosis) caused by continuous illumination was also calculated. Day-to-day C.V.

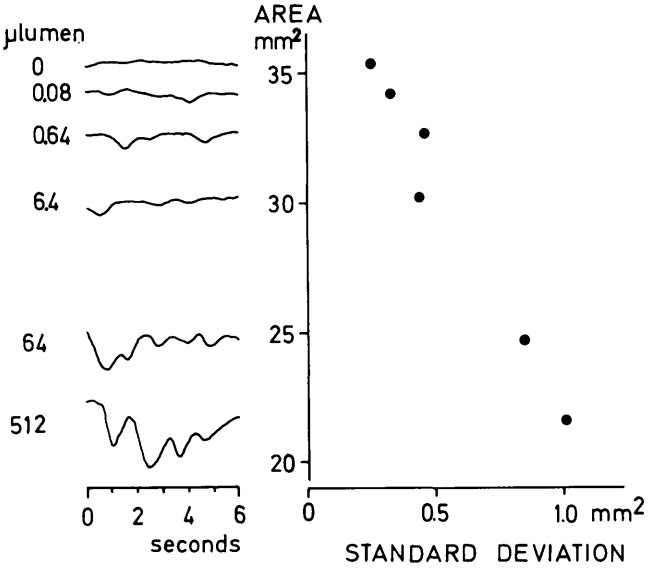

FIG. 1. *Left*: pen recorder tracings of pupil area in control subject in periods of 6 s in darkness (0 μlm) and at different light intensities (0.08–512 μlm). *Right*: pupil area and standard deviation of measurements of pupil area, i.e., pupillary unrest. At 512 μlm, pupil area is reduced from 35 to 22 mm² (relative miosis 40%), and standard deviation or pupillary unrest is increased from 0.2 to 1.0 mm².

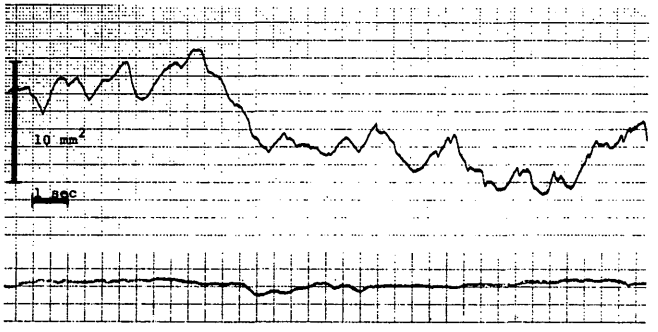

FIG. 2. Pen recordings of pupillary unrest in darkness (*lower curve*) and in continuous illumination (512 μlm, *upper curve*) in normal subject.

was 19.7% for the relative miosis in prolonged illumination and 11.7% in brief illumination.

Ophthalmoscopic examination was made in mydriasis and reported on a 4-point scale: 0, no changes; 1, red dots only (microaneurysms or punctate hemorrhages); 2, larger hemorrhages and/or exudates; 3, neovascularization (16). Biomicroscopy was performed with a Zeiss slit lamp in 60 patients, and the observed changes were reported as rubeosis iridis (neovascularization at the surface of iris), porosity or defects of the pigment seam at the pupillary margin, and loss of pigment from the pigment epithelium with the criteria described by Ohrt (17,18). Nephropathy was defined as persistent proteinuria (Albustix and sulfosalicylic method) on at least five consecutive attendances to the outpatient clinic. As a simple measure of peripheral nervous function, the vibratory perception threshold at 100 Hz (12) was determined on the great toe with a biothesiometer with a variable amplitude arbitrarily expressed in volts (range 0–50; Biomedical, Chagrin Falls, OH). For most of the long-term diabetic subjects (duration ≥15 yr), long-range mean annual blood glucose, based on values from at least the preceding 5 yr, was determined as a measure of the quality of metabolic control obtained over the years of diabetes (10).

Statistical analysis. Student's *t* test was used for comparison between groups. For testing the strength of correlations, analysis of the ordinary parametric least-square regression was used, except for determining the relationship between pupillary unrest and the discontinuous variables retinopathy, iridopathy, and nephropathy, in which Kendall's τ (19) was used. A 5% two-sided limit of significance (2*P*) was used throughout the study.

RESULTS

Table 2 shows mean values of pupillary measures in diabetic and control subjects. In darkness the pupillary unrest was

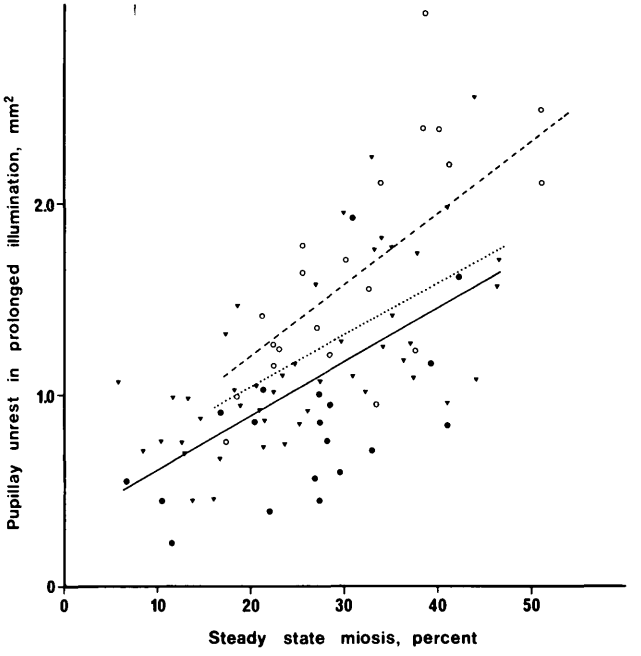

FIG. 3. Relationship between pupillary unrest and miosis during prolonged illumination with 512-μlm continuous light in control (○) and diabetic (●, pupil size in darkness below normal range; ▼, pupil size in darkness within normal range) subjects. Regression lines are shown for all diabetic subjects (*solid line*), diabetic subects with miosis and pupil size in darkness above lowest values of control subjects (*dotted line*), and control subjects (*dashed line*).

21% less in diabetic subjects than in controls, and during prolonged and brief illumination the difference between diabetic and control subjects was 35 and 37%, respectively. Both diabetic and control subjects had greater unrest during continuous illumination than in darkness: during prolonged illumination, the difference was 50 ($2P < 10^{-6}$) and 59% ($2P < 10^{-6}$), respectively; during brief illumination, 60 ($2P < 10^{-6}$) and 70% ($2P < 10^{-4}$), respectively. Pupillary unrest during brief illumination was greater than the unrest during prolonged illumination in the diabetic and the control groups, respectively [24% ($2P$ = .00032) and 27% ($2P$ = .046)]. There was no significant correlation between age and pupillary unrest or any demonstrable differences in pupillary unrest between the sexes in either group.

Fractional reduction in pupil size (relative miosis) was 19% less during prolonged illumination in diabetic subjects than in controls (Table 2), but during brief illumination the difference of 10% was not statistically significant. Pupillary unrest and the fractional reduction in pupil size during prolonged illumination were found to be rather closely correlated in both groups, i.e., the greater the degree of relative miosis obtained, the higher unrest (diabetic subjects: r = .61, $2P <$

TABLE 2
Pupillary measures in diabetic and control subjects

	Darkness		Prolonged illumination (512 μlm)		Brief illumination (512 μlm)	
	Pupil size (mm²)	Pupillary unrest (mm²)	Relative miosis (%)	Pupillary unrest (mm²)	Relative miosis (%)	Pupillary unrest (mm²)
Diabetic	28.2 ± 8.6	0.55 ± 0.25	26.2 ± 10.5	1.10 ± 0.49	44.5 ± 14.2	1.44 ± 0.49
Control	34.9 ± 6.1	0.70 ± 0.25	32.5 ± 10.6	1.69 ± 0.59	49.4 ± 10.1	2.30 ± 0.94
2*P*	.00035	.0077	.017	.000012	NS	.0063

TABLE 3
Dependencies between pupillary unrest and pupil size and parameters of diabetes and its long-term manifestations

Dependent variable	Independent variable	Subjects*	*n*	*r*	2*P*
Pupillary unrest in darkness	Pupil area in darkness	Diabetic	80	.36	.00098
		Control	26		NS
Pupillary unrest in prolonged light	Pupil area in darkness	Diabetic	66	.38	.0016
		Control	21		NS
Pupillary unrest in brief illumination	Pupil area in darkness	Diabetic	52	.50	.00014
		Control	13	.70	.0079
Unrest in prolonged light	Duration of diabetes	Diabetic	66	−.25	.046
	Vibratory perception	Diabetic	66	−.38	.0016
Unrest in brief light	Duration of diabetes	Diabetic	52	−.35	.010
Unrest in darkness	Vibratory perception	Diabetic	79	−.43	10^{-5}

10^{-6}; controls: r = .69, $2P$ = .00043; Fig. 3). The same relationship was also obtained during brief illumination in diabetic subjects (data not shown) but was not significant in controls. The regression line for diabetic subjects within the same range of fractional reduction in pupil size as the controls was parallel to but significantly displaced below that of the controls ($2P$ = .00043), which means that for a given miosis the diabetic subjects still had a smaller unrest than the controls. Also, as shown in Fig. 3, the regression line for the diabetic subjects who had both pupil size and relative miosis within the normal range is parallel to but significantly displaced below that of the controls ($2P$ = .0090).

The size of the pupil in darkness was 19% smaller in diabetic subjects than in controls (Table 2). Pupil size in darkness was positively correlated to pupillary unrest in darkness and during prolonged illumination (Table 3), whereas there was no indication of such a relationship in the controls. Pupil size in darkness was also correlated to unrest during brief illumination, and this relationship was significant for both groups. There was no correlation between pupil size in darkness and relative miosis during prolonged or brief illumination in either diabetic or control subjects.

Pupillary unrest during prolonged and brief illumination was inversely correlated to the duration of diabetes (Table 3). The same tendency was shown for unrest in darkness, but the relationship did not reach the level of statistical significance. There was no correlation between the degree of miosis during prolonged or brief illumination and the duration of diabetes. As expected, the diabetic subjects had a vibratory perception threshold that was higher than that of the controls: 18.1 ± 10.3 vs. 9.5 ± 3.0 V (mean ± SD; $2P < 10^{-6}$). In the diabetic subjects there was an inverse correlation between vibratory perception threshold and the pupillary unrest both in darkness and during prolonged illumination (Table 3).

Table 4 shows the relationship between pupillary unrest in darkness and manifestations of microangiopathy in long-term diabetes (duration ≥15 yr). There was a significant inverse correlation to the severity of retinopathy (τ = −.54, $2P < 10^{-5}$) and to the presence of nephropathy (τ = −.38, $2P$ = .0046) but no indication of correlation to biomicroscopic changes in the iris. Also, pupillary unrest during prolonged illumination was inversely correlated to the severity of retinopathy (τ = −.30, $2P$ = .040) but not significantly so to nephropathy or iridopathy.

Data were available for estimating the long-range mean annual blood glucose in 40 of the 46 long-term diabetic subjects. There was an inverse relationship between mean annual blood glucose and pupillary unrest both in darkness (r = −.46, $2P$ = .0026; Fig. 4) and during prolonged illumination (r = −.34, $2P$ = .05). There was no correlation between the degree of miosis during illumination and mean annual blood glucose. None of the pupillary parameters showed correlation to the actual blood glucose value obtained at the time of the study.

DISCUSSION

There is a tradition in clinical medicine of examining the pupil of the eye for obtaining information about the state of the autonomic nervous system, e.g., looking for the Argyl-Robertson phenomenon. With modern techniques an exact quantitation of both the stimulus applied to the pupil and of the pupil's movements or responses has become possible. In this study the fluctuations in the size of the pupil—pupillary unrest—have been monitored and quantitated by means of infrared television pupillography and computerized calcu-

TABLE 4
Relationship between pupillary unrest in darkness and grades of retinopathy, iridopathy, and nephropathy in long-term diabetes (duration ≥15 yr)

		Retinopathy (n = 47)*				Persistent proteinuria (n = 47)†		Iridopathy (n = 38)‡		
Pupillary unrest in darkness	*n*	No change	Red dots	Hemorrhage and/or exudates	Neovascularization	Absent	Present	No change	Pigment defects	Rubeosis iridis
>0.610	17	10	5	2	0	15	2	10	2	0
0.480–0.610	8	5	1	1	1	7	1	5	1	1
0.365–0.480	11	1	2	4	4	8	3	9	1	0
<0.365	11	1	0	4	6	4	7	7	2	0

*$2P < 10^{-5}$, †$2P$ = .0046, ‡NS.

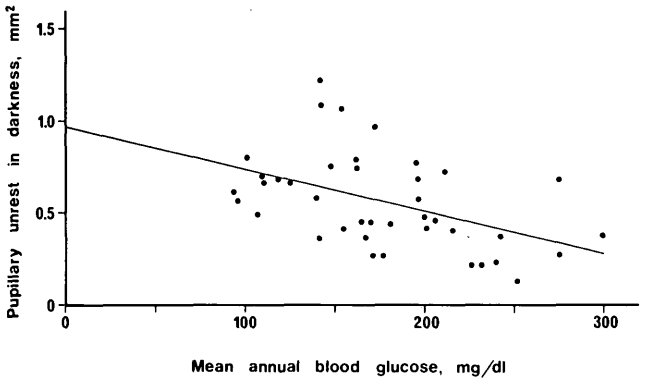

FIG. 4. Relationship between pupillary unrest in darkness and mean annual blood glucose in long-term diabetic subjects (duration ≥15 yr).

lations. Known quantitative stimuli, which increase the unrest, have been applied, and an attempt has been made to further ensure equality of the stimulus by injecting the light in an open-loop fashion to an ophthalmoscopically normal or near-normal area of the retina.

The phenomenon of pupillary unrest is well known, but its cause is less well known. The evidence is that the unrest originates in the central nervous system; the fluctuations are identical and synchronous in both eyes (15), and in cats, neurons that fire synchronously with the unrest have been identified in the midbrain (20). It is also known that the magnitude of the unrest is closely related to the size of the pupil; i.e., the smaller or more stimulated the pupil becomes, the greater the unrest, at least to a certain extent (15). Also, drowsiness normally leads to both a reduction in pupil size and an increased unrest of the pupil (21).

In this evaluation of pupillary unrest there are several factors worth noting. The greater the relative reduction in pupil size during continuous illumination, the greater the unrest; this is true for both diabetic and the control subjects (Fig. 3). The time of illumination is also important, as evidenced from the fact that miosis and unrest become less pronounced when the light stimulus is prolonged (Table 2). When the pupillary unrest of diabetic subjects with the same degree of miosis in light as the controls is compared with that of the controls, they still have a less pronounced unrest than the controls despite a normal fractional reduction in size. This result may indicate that in diabetic subjects there is damage to the nervous system in the area in which the unrest is generated apart from the damage that reduces the ability to maintain miosis. This means that the reduced unrest in diabetic subjects, although closely correlated to the other two abnormalities, also occurs independently of the small size and the reduced ability to maintain miosis in light. These findings also seem to rule out damage to the efferent nerves and retina as the sole cause of reduction in light-induced unrest.

Long-term diabetic patients with small pupils have a less pronounced pupillary unrest and miosis than the control subjects. Within the normal range there is no relation between the resting pupil size in darkness and pupillary unrest, and, as mentioned previously, a smaller pupil generally tends to be associated with an increased unrest. Therefore, it seems that the reduced unrest in diabetes and the reduced pupil size are both caused by a defect in the autonomic nervous system.

A reduced function of the retina or the optic nerve could theoretically be the cause of the reduction in light-induced unrest and degree of miosis in diabetic subjects. Also, it is difficult to exclude an enhanced retinal adaptation to light in diabetic subjects. However, it has been shown that the sensitivity of the retina and, indeed, the whole system involved in the pupil's light reflex is not reduced in these patients (11,22). The same evidence speaks rather strongly against an intrinsic stiffness of the iris as the reason for the demonstrated abnormalities. Furthermore, in this study there was no indication of a correlation between a reduced pupillary unrest and biomicroscopic changes in the iris.

In particular, the reduced pupillary unrest seems to be a part of the long-term diabetic syndrome (9); there is a fairly good correlation to the presence of other long-term diabetic manifestations and to the duration of diabetes. Note that poor metabolic control throughout the years means a more pronounced reduction in the pupillary unrest. In addition to being a long-term diabetic manifestation, reduction in pupillary unrest is the only autonomic nervous system abnormality studied that can be provoked and reversed in a short time by marked, acute changes in the diabetic metabolic state (8). However, within the much more moderate range of metabolic states encountered in this study of ordinary outpatient clinic diabetic subjects, there is no demonstrable relationship between the actual metabolic state and hippus or miosis.

In conclusion, the following abnormalities of the pupil in long-term diabetic subjects stand out: *1*) a reduction in pupil size in darkness; *2*) a reduction in the pupil's ability to maintain miosis in continuous light; and *3*) a reduction in pupillary unrest, both in darkness and in light, not necessarily dependent on the above two abnormalities.

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