Case 4. Treatment with intramuscular gammaglobulin (—) since discovery of IgA deficiency in 1969, and timing of tests for anti-IgA antibodies (arrowed).

after the injections. The patient with anti-IgA antibodies had no side effects.

Discussion

Regular intramuscular administration of gammaglobulin apparently does not stimulate anti-IgA formation in patients with hypogammaglobulinaemia and IgA deficiency despite the presence of small amounts of IgA, which invariably occurs in commercial preparations.¹³ This finding is important, since gammaglobulin is beneficial against recurrent infections in patients with hypogammaglobulinaemia.

Three of our patients had some IgA in their serum as measured with the haemagglutination inhibition assay and enzyme immunoassay and were thus unable to form class-specific antibodies to IgA owing to immunological tolerance. We think that it is essential to use more sensitive methods than immunodiffusion for determining IgA concentrations before a person is considered to be lacking IgA and at risk of forming dangerous antibodies to IgA.

Low serum IgG and IgM concentrations, which we found in five patients, may indicate poor general immune response, which would accord with the inability to form anti-IgA antibodies. The

antibody titre in one of the patients, whose IgG and IgM concentrations were normal, remained at the same level throughout the follow-up period. This is compatible with our earlier experience—namely, that the titre of class-specific anti-IgA antibodies in serum remains relatively constant.

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CONDENSED REPORT

Pupillary signs in diabetic autonomic neuropathy

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Summary and conclusions

Pupillary function was investigated in 36 insulin-dependent diabetics and 36 controls matched for age and sex. About half of the diabetics had evidence of peripheral somatic or autonomic neuropathy, or both. The diabetic patients had abnormally small pupil diameters in the dark and less fluctuation in pupil size (hippus) during continuous illumination than the controls. They also had reduced reflex responses to light flashes of an inten-

sity adjusted for individual retinal sensitivities. The pupillary findings were compared with results of five tests of cardiovascular function and five tests of peripheral sensory and motor nerve function.

Almost all the patients with autonomic neuropathy had pupillary signs, which we therefore conclude are a common manifestation of diabetic autonomic neuropathy.

Introduction

Dysfunctions of the cardiovascular, gastrointestinal, sweating, and genitourinary systems constitute the well-known manifestations of diabetic autonomic neuropathy.¹ The effect on the pupil, however, has not been well defined, and pupillary abnormality has been described as both a rare²⁻³ and a frequent⁴⁻⁵ complication. This abnormality, sometimes called an Argyll Robertson pupil,⁶ has been reported to comprise a reduced diameter at rest and poor, sluggish responses to light. Reduced light reflexes may, however, be the result of diminished afferent input due to retinopathy. In the study reported here pupillary function was investigated in detail and the influence of reduced

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retinal sensitivity excluded. The pupillary findings were compared with other indices of autonomic and somatic nerve function.

Subjects and methods

Thirty-six insulin-treated diabetic patients and 36 age- and sex-matched controls volunteered for the study. The controls were selected from 250 volunteers employed at County Hall, London. The first 17 diabetics investigated were taken at random from the diabetic clinic, but subsequent patients were selected for known autonomic neuropathy, poor control, or long duration of disease. The patients were therefore a selected, not a typical, sample of the diabetic population. All the patients and controls had visual acuity of 6/12 or better, and none took any drug except insulin. The mean duration of diabetes was 13.4 years (range one month to 41 years) and mean daily insulin dose 50 units (range 18 to 108). Investigations were performed on each subject in the following order.

Blood pressure—Systolic and diastolic arterial pressures were recorded from the brachial artery using a sphygmomanometer cuff incorporating an ultrasonic pulse detector (Arteriosonde, Roche). Pressures were measured at one-minute intervals for five minutes with the subject supine, then for five minutes after a slow tilt (2.5 minutes) to a 70° upright posture, and again after return to the horizontal position.

Heart rate—Measurements of the R-R interval over five minutes (or 300 beats maximum) with the subject supine were obtained in lead II and recorded on magnetic tape. Computer analysis was used to provide the mean R-R interval and its standard deviation. Changes in heart rate during deep breathing⁷ and Valsalva's manoeuvre (40 mm Hg pressure for 10 seconds) were obtained from an instantaneous rate-meter, using the same electrocardiographic output. Pulse changes to Valsalva's manoeuvre were expressed as ratios.⁸

Vibration threshold—Thresholds to vibration sense⁹ were determined at the tips of the great toes and thumbs and over the medial malleoli with a Bio-Thesimeter (Bio-medical Instruments Ltd). Results were expressed as means of left and right measurements. These determinations of vibration thresholds were omitted in five controls and nine diabetics owing to unavailability of the equipment.

Nerve conduction velocity—Conduction velocities of the median (motor) and sural (sensory) nerves were measured by previously reported methods^{10,11} using bipolar skin electrodes. Action potentials were recorded with an AA7 amplifier and AV11 6 signal averager (Medelec Ltd). The ambient temperature was 21–23°C, and skin temperature was always above 32°C. Sural-nerve action potentials could not be detected in four normal and six diabetic subjects.

Pupillary measurements—All measurements of pupillary diameter were performed in darkness, to which the subjects had adapted by wearing red goggles for 30 minutes before the test. Vertical pupillary diameters were measured with a Whittaker Corporation Series 1800 binocular infrared television pupillometer¹² with the subject focusing on infinity. Light flashes of duration 0.5 s were directed at the left eye with the light beam focused to a diameter of 1.8 mm in the plane of the pupil. Light stimulation was thus "open loop" in that the beam was too small to be diminished in size by a constricting pupil. The intensity of light was adjusted by inserting Wratten neutral filters of different densities between the source and the focusing lens system. In order to control for individual variation in retinal sensitivity each subject's threshold of visual perception was measured.¹³ Ten light flashes, of intensity 10⁶ times greater than the perception threshold, were given at 8-sec intervals and the resulting light reflex responses recorded on magnetic tape for subsequent averaging by computer analysis. This analysis gave the following parameters: resting diameter at the foot of the reflex, reflex amplitude and latency, and maximum rates of constriction and dilatation. In 10 selected patients and their controls we determined the amount of hippus (pupillary oscillations that occur during continuous stimulation with a bright light⁶). The diabetics showed abnormal results to at least two of the cardiovascular and neurological tests in the study. The intensity of the light (about 10⁹ times greater than the mean perception threshold) was the same for each subject. After the initial constriction the pupil diameter was recorded on tape and the oscillations subjected to Fourier frequency analysis by computer. Pupil measurements were omitted in one diabetic patient with aphakia.

Statistical analysis—Differences between diabetics and controls were assessed with paired *t* tests. Each variable was also assessed for dependence on age, sex, and other selected independent variables by multiple regression analysis using standard techniques. Abnormal

results were defined as those falling outside the 95% confidence limits of variation in the normal subjects, derived from the regression analysis when appropriate.¹⁴ Possible influences of smoking habit were assessed by χ^2 tests.

Results

PUPILLARY FINDINGS

Analysis of the normal data showed that resting darkness diameter correlated strongly with age ($r = -0.75$, $P < 0.001$). Comparing the two groups showed that the diabetics had smaller pupils than their matched controls ($P < 0.001$). Fourteen diabetics had pupil diameters below the normal range, and none had a diameter larger than normal (fig 1).

The normal light reflex (fig 2) had a latency of about 0.3 s and reached a mean peak constriction of 1.63 mm approximately 1 s after the beginning of the stimulus. Light reflexes in diabetics were reduced in amplitude ($P < 0.001$), 12 out of 34 falling below the normal range, and appeared to be slow in onset and time course. There was,

FIG 1—Relation between resting pupillary diameter and age in 35 diabetic subjects. Normal range is indicated by the regression (solid) line and the 95% confidence limits (dotted lines) from the data on 36 normal subjects matched for age and sex.

FIG 2—Pupillometer recordings from a matched pair of subjects (normal woman aged 40 and diabetic woman aged 42) showing reflex responses to light stimuli of duration 0.5 s given when indicated.

however, a strong correlation between the maximum velocities of constriction and dilatation and the size of the reflex, which was maintained in the diabetics despite the reduced amplitudes of their reflexes (fig 3). Similarly, in diabetics with small reflexes the latencies were prolonged but were still normal for the reflex size, since analysis of the normal data showed that latency varied inversely with amplitude. In normal subjects the amplitude of the light reflex was independent of the resting diameter. In diabetics, however, there was a significant regression of amplitude on diameter ($r=0.65$, $P<0.001$).

The 10 diabetics selected because of suspected neuropathy had a reduced amount of hippus ($P<0.02$)—that is, their pupillary diameters oscillated less than normal in response to continuous bright light. Most of the oscillations elicited were slow (0.0–2 Hz), and the distribution of oscillations across the frequency range analysed (0.0–2.0 Hz) was the same in diabetic and normal subjects.

The results given above refer only to the directly stimulated (left) eye. Both pupils were measured, however, and comparison of the binocular data shows that diabetic and normal subjects had the same degree of resting anisocoria. In contrast, the difference in diameters between left and right eyes at the peak of the reflex constriction was greater in the diabetics than the controls ($P<0.02$).

FIG 3—Dependence of maximum velocities of pupillary constriction and dilatation on amplitude of light reflex in normal (●) and diabetic (○) subjects.

NEUROLOGICAL TESTS

Vibration thresholds were higher in diabetics than normal subjects (see table). The toe and ankle tests elicited more abnormalities among the diabetics than did the thumb test—for example, 11 out of 27 diabetics had ankle vibration thresholds above the normal range. These thresholds increased with age (ankle, $r=0.68$, $P<0.001$; toe, $r=0.69$, $P<0.001$; thumb, $r=0.47$, $P<0.01$).

Conduction velocities in the median motor and sural sensory nerves, which were not age-dependent, were slower in diabetics than controls. Ten out of 32 diabetics had sural-nerve conduction velocities below the normal range.

CARDIOVASCULAR TESTS

Analysis of the data for the normal subjects showed a decrease with age of beat-to-beat variation ($r=-0.43$, $P<0.005$), pulse change on

deep breathing ($r=-0.51$, $P<0.01$), and Valsalva ratio ($r=-0.42$, $P<0.02$). In addition, women had a shorter mean R-R interval than men ($P<0.01$), and there was a positive correlation between the standard deviation and the length of the R-R interval ($r=0.45$, $P<0.005$). All five cardiovascular variables differed significantly between the diabetic and normal groups (see table).

COINCIDENCE OF PUPILLARY SIGNS AND OTHER ABNORMALITIES

The table summarises the results of the 12 tests of pupillary, cardiovascular, and neurological function that were significantly different between the normal and diabetic groups. Nineteen diabetics (and one control) had pupillary diameters or reflex amplitudes, or both, below the 95% confidence limits of normal. Fourteen of these had at least one and ten had at least four other abnormalities. Most of the patients with evidence of cardiovascular autonomic or peripheral somatic neuropathy also showed pupillary signs. Ten out of 11 patients with cardiovascular abnormalities, nine out of 12 with raised vibration thresholds, and nine out of 11 with slow conduction velocities also had abnormal pupils. We found that the diabetics smoked significantly more than their matched controls ($P<0.05$). Smoking was not, however, related to the incidence of abnormalities in any of the tests performed.

The incidence of abnormalities was not obviously related to either the duration of diabetes or its control as assessed by the mean of the three previous clinic estimations of blood glucose concentrations.

Discussion

Half of the patients studied had evidence of neuropathy in that they responded abnormally in at least one of the 10 tests of cardiovascular and peripheral somatic nerve functions. Of these patients, almost all with autonomic neuropathy of the cardiovascular system had pupillary signs, which suggests that these are a common manifestation of diabetic autonomic neuropathy. The diabetic patients had smaller pupils in the dark, reduced or absent light reflexes, and less hippus than their age- and sex-matched controls, which confirms other reports.¹⁵ Elderly non-diabetic subjects also have small resting pupillary diameters, and possibly the age-related degenerative process that reduces pupil size is accelerated in diabetics.

Earlier reports^{4,5} that the amplitude of the light reflex is reduced in diabetes are difficult to interpret because no account was taken of reductions in retinal sensitivity due to diabetic retinopathy. This study, in which the intensity of the light stimulus was related to thresholds of visual perception, shows that the efferent side of the arc is indeed affected by the neuropathy. It could be argued that the small reflexes are merely a result of the physical limitation imposed by the small resting pupil, and the significant regression found between reflex size and pupil diameter in diabetics appears to support this view. On the other hand, there was no correlation between reflex size and diameter in the controls, and, moreover, the two abnormalities occurred independently in 11 diabetic patients. Therefore a significant regression was probably found in diabetics because of the coincidence in seven patients of a small reflex and a small resting pupil diameter rather than because of an intrinsic relation between the two parameters.

Several authors have reported that the light reflex in diabetics appeared sluggish and delayed in onset.^{3,4,16} This impression was confirmed in the present study using computer analysis to obtain precise quantitative information about the latency and velocities of constriction and dilatation. Nevertheless, the speed (see fig 3) and time course of the reflex were normal for its size; therefore the reflex is sluggish because it is small.

The pupillary abnormalities reported here cannot be ascribed solely to neuropathy, since pathological changes occur in the iris muscles of diabetics.⁵ Furthermore, the reduction in reflex size is not necessarily the result of the pathological process, be it neurological or muscular, that underlies the small diameter at rest. In our patients binocular discrepancies occurred in reflex amplitudes but not in darkness resting diameters, a finding that

Clinical details and pupillary, cardiovascular, and neurological findings in 36 diabetic patients grouped according to duration of disease. (0 = Finding within 95% confidence limits of results in normal subjects. + = Finding above upper 95% confidence limit. - = Finding below lower 95% confidence limit)

Patients			Pupil		Cardiovascular findings					Neurological findings				
Sex	Age in years	Blood glucose concentration (mmol/l)*	Resting diameter	Reflex amplitude	Mean R-R interval	SD _{RR}	Pulse change on deep breathing	Valsalva ratio	Fall in diastolic BP on tilting	Vibration threshold			Conduction velocity	
										Toe	Ankle	Thumb	Median motor nerve	Sural nerve
Duration of diabetes ≤5 years														
M	27	12.0	0	0	0	0	0	0	0				0	0
M	63	22.0	-	-	-	-	-	-	-				0	-
M	65	-	-	0	0	0	0	0	0				0	
F	21	13.0	0	0	0	0	0	0	0	0	0	0	0	0
F	49	7.0	0	0	0	0	0	0	0	0	0	0	0	0
F	18	21.0	-	-	-	-	-	-	-	+	+	+	-	-
M	53	-	0	0	0	0	0	0	0	0	0	0	-	-
M	46	10.0	0	-	0	0	0	0	+	+	+	0		-
Duration of diabetes 6-10 years														
F	56	-	0	0	0	0	0	0	0				0	0
F	19	15.0	0	0	0	0	0	0	0	0	0	0	0	0
M	43	4.0	-	0	0	0	0	0	0	0	0	0	0	0
M	40	7.0	-	0	0	0	0	0	0	0	0	0	0	0
F	34	19.0	-	-	0	-	-	-	+	+	+	0	-	0
F	19	14.0	-	0	0	0	0	0	0	0	0	0	0	0
Duration of diabetes 11-20 years														
F	59	-	0	0	0	0	0	0	0	+	+	+	0	0
M	62	9.0	0	0	0	0	0	0	0	+	+	+	0	0
M	39	10.0	0	0	0	0	0	0	0	0	0	0	0	0
F	25	5.0	-	0	0	0	0	0	0	+	0	0	0	0
F	41	18.0	0	0	0	0	0	0	0	0	0	0	0	0
F	39	11.0	-	-	0	0	-	-	0	+	+	+	-	0
F	20	15.0	0	-	0	0	0	0	0	0	0	0	0	0
F	26	-	-	-	-	-	-	-	+	+	0	0	0	0
F	44	11.0	0	-	0	0	0	0	0	0	0	+	0	0
M	69	9.0	0	-	0	0	0	0	0	+	+	0	-	-
F	31	18.0	0	0	0	0	0	0	+	0	0	0	0	-
Duration of diabetes ≥21 years														
M	45	12.0	-	-	0	-	-	-	0				0	-
F	31	8.0	0	0	0	0	0	0	0				0	0
M	56	-	0	0	0	0	0	0	0				0	0
M	59	14.0	0	0	0	0	0	0	0				0	0
M	39	4.0	0	0	0	0	0	0	0	0	+	0	0	0
F	42	13.0	-	-	0	-	-	-	+	+	+	+	-	0
M	49	10.0	-	-	0	0	-	-	+	0	0	0	0	0
M	38	-	-	0	0	0	0	0	0	0	0	0	0	0
F	43	13.0	0	0	0	0	0	-	0	0	+	+	0	0
F	31	12.0	-	-	-	-	-	-	0	+	+	+	-	-
F	65	17.0	0	-	0	0	0	0	+	+	+	+	0	-
Probability†			<0.001	<0.001	<0.005	<0.005	<0.005	<0.01	<0.05	<0.001	<0.01	<0.01	<0.001	<0.001
Correlations in controls			Decreased with age	Nil	Decreased in women	Decreased with age; increased with R-R interval	Decreased with age	Decreased with age	Nil	Increased with age	Increased with age	Increased with age	Nil	Nil

SD_{RR} = Standard deviation of R-R interval. *Mean of three previous estimates. †Paired t test, controls v diabetics. Conversion: SI to traditional units—Blood glucose: 1 mmol/l ≈ 18 mg/100 ml.

might indicate a patchy defect in the light reflex pathways. This, together with the fact that signs of neuropathy elsewhere were associated more commonly with abnormal light reflexes than with abnormally small resting diameters, suggests that reflex size may be the more specific indicator of neuropathy.

The frequency of symptoms in diabetic peripheral neuropathy suggests that sensory nerves, particularly in the leg, may be more sensitive to damage than motor nerves. Correspondingly, measurement of sural sensory conduction velocity is particularly relevant, and the present study shows that it may be measured conveniently with surface electrodes. In addition, measurement of impaired vibration sense, which is found more frequently in the toe and ankle than the thumb, is inexpensive and easily performed and is thus well suited to routine clinical examinations.

Since pupillary abnormalities occurred more frequently than cardiovascular signs it would be useful to incorporate such tests of pupillary function into routine examinations, and measurements of, for example, resting pupil size could be performed conveniently using Polaroid photography. More work is needed to determine whether the changes described here are due to neuropathy or myopathy of the iris and to assess whether they may be reversed by improving diabetic control by methods such as the recently introduced home monitoring of blood glucose concentration.¹⁷

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Full details of pupillary reflex amplitudes and hippus, ankle vibration thresholds, and sural-nerve conduction velocities are available on request.

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