septicaemia in these patients. Bacteraemia occurring commonly in malnourished children with impaired mucosal immunity would stimulate systemic lymphoid tissues with resultant hyperimmunoglobulinaemia, a common finding in such patients.

Poor secretory antibody response with good humoral response may predispose to severe reactions when subjects are exposed to the virus again. Administration of inactivated measles vaccine, which elicits a poor antibody activity in nasopharyngeal secretions, when followed by natural infection or administration of live attenuated vaccine has resulted in severe local and systemic reactions.¹⁸ It has been postulated that antigenaemia in the presence of high titres of serum antibody would induce immune-complex formation. This may occur locally at the site of the injection of vaccine or the lungs in the case of natural infection or systemically. Some malnourished children who have fulminant fatal measles may have had a subclinical episode earlier, which may have predisposed them to a severe illness via the above pathogenetic mechanism. This may also be true of other infections.

There is a high frequency of serum antibodies to common food proteins in malnourished children.¹⁹ Several factors may contribute to the genesis of such food antibodies: malnutrition is associated with a gross atrophy of the gut wall, the villous height is reduced, and there is inflammatory cell infiltration in the lamina propria; the permeability of the gut wall is increased; and the pancreatic and other digestive enzymes are impaired. These factors, together with reduced secretory antibody response, may allow free passage of food proteins intact or partially digested. The impaired function of the hepatic reticulo-endothelial system would allow such antigens absorbed through the portal circulation to bypass the phagocytic filter of the liver and thus reach systemic lymphoid structures, which are stimulated to form antibodies.

Immunodeficiency, especially IgA deficiency, is associated with a high frequency of autoimmune disease and atopy. Impaired exclusion of antigens at the mucosal level may possibly lead to overstimulation of IgE-producing cells. In the offspring of reaginic parents transient IgA deficiency is associated with atopic disease in the child within one year of birth.^{20 21} Adults positive on skin tests to *Dermatophagoides farinae* and Timothy grass pollen had more IgE antibody and less IgA antibody to the respective allergens compared with controls negative on the skin test.²² It remains to be investigated whether children who are malnourished early in life, including

those with low birth weights,^{23 24} and have poor secretory IgA response are more susceptible to atopic and autoimmune diseases, though the design of such a study which would have to control many other variables is obviously formidable.

Finally, our observations are relevant to the effectiveness of immunoprophylaxis programmes. In underprivileged populations with high incidence of malnutrition protection may be inadequate. It remains to be seen whether malnourished children given measles vaccine have any reactions when they encounter natural virus later.

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Cardiovascular Control in Diabetes Mellitus

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Summary

Heart rate variability and the changes in heart rate and blood pressure which occur on standing were measured in 21 diabetics. These simple measures distinguished four groups of patients, with loss of parasympathetic activity being commoner than loss of sympathetic activity.

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Introduction

The integrity of the autonomic control of the cardiovascular system in diabetics can be studied by observing the heart rate variability¹ and the effects of standing on heart rate and arterial blood pressure.² In early accounts of diabetic autonomic neuropathy patients showed falls in systolic arterial blood pressure accompanied by dramatic tachycardia.³ Since then postural hypotension with variable degrees of tachycardia⁴⁻⁶ or postural hypotension with no change in heart rate⁷ have been described.

No study of diabetics has related postural changes in blood pressure to changes in heart rate over a period of time or described variability in heart rate at rest and changes of heart rate and systolic blood pressure induced by standing. We report here our observations in diabetic patients, which help to clarify some of the apparently contradictory earlier reports.

Patients and Methods

Twenty-one diabetic outpatients (11 men, 10 women) were studied. They ranged in age from 11 to 71 years (mean 44.9 years), and the time since diagnosis ranged from six months to 45 years. All but five patients had one or more of the following features: retinopathy (10 patients), peripheral neuropathy (14), impotence (10), diarrhoea (7), peripheral vascular disease (4), and disordered sweating (4). All except two patients were dependent on insulin, and none were being treated with drugs known to interfere with autonomic nervous function.

PHYSIOLOGICAL PRINCIPLES OF INVESTIGATIONS

Heart Rate Variability.—The variation in heart rate from beat to beat during respiration (sinus arrhythmia) is enhanced by deep breathing.¹ The variation is not seen in all patients,⁸ and tends to be smaller in older than in younger people.¹ Sinus arrhythmia seems to depend on the vagal (parasympathetic) innervation of the heart with no involvement of the cardiac sympathetics. Thus, absence of sinus arrhythmia may be due to loss of cardiac parasympathetic function.¹

Blood Pressure and Heart Rate on Standing.—On standing blood tends to pool in the legs. In normal people there is little or no fall in arterial pressure at heart level since baroreceptors reflexly activate the sympathetic vasoconstrictor supply to resistance and capacitance vessels and the heart rate is increased.² Abnormal responses to standing may thus be due to impaired vasoconstrictor or cardioaccelerator mechanisms or both.

We used four other tests of cardiovascular reflexes though the detailed results will be described elsewhere.

Breath-holding and Immersion of Face in Water.—In normal people apnoeic face immersion causes bradycardia and peripheral vasoconstriction,⁹ which are triggered by receptors in the facial area.¹⁰ The bradycardia seems to be due to increase in vagal tone while the vasoconstriction is sympathetic.⁹

The Valsalva Manoeuvre.—During the Valsalva manoeuvre intrathoracic pressure increases, venous return decreases, and hence cardiac output and systemic arterial blood pressure fall.² Peripheral vasoconstriction occurs, and on release of the intrathoracic pressure blood is ejected into a constricted vascular bed and the pressure rises. This rise is detected by baroreceptors which reflexly initiate a vagal (parasympathetic) bradycardia.²

Response to Phenylephrine.—Phenylephrine injected intravenously has a direct vasoconstrictor action. The resulting rise in arterial blood pressure reflexly elicits a vagal bradycardia. The rise in arterial pressure and the slowing of the heart are linearly related.¹¹

Response to Mental Stress.—Mental stress causes tachycardia which is due to sympathetic mechanisms.¹² Performance of a mental task under mild harassment is sufficient to activate this system.²

MEASUREMENT OF HEART RATE AND HEART RATE VARIABILITY

The electrocardiogram (E.C.G.) was recorded from bipolar chest leads in positions V₁ and V₄. The E.C.G. was fed into a Nielson ratemeter

(Devices), which converted R-R intervals into instantaneous heart rates (beats/min); the output from the ratemeter was monitored on an ultraviolet recorder (S.E. Labs).

The patient was monitored when supine for 10 minutes, standing for five minutes, and supine for a further five minutes. Then the patient breathed in and out as deeply as possible for 30 seconds to enhance sinus arrhythmia.¹ Heart rates were measured directly from the ultraviolet recording. Heart rate variability was taken as the mean difference between the lowest and highest heart rates during deep breathing.⁸ Systolic and diastolic arterial pressures were recorded from the brachial artery using a sphygmomanometer cuff incorporating an ultrasonic pulse detector (Arteriosonde, Roche). Pressures were recorded during supine rest and 15 seconds, one minute, and five minutes after standing.

Results

There was no relation between high resting heart rates and low heart rate variability (fig. 1) or between heart rate variability and age. Except in two patients (cases 9 and 10) low heart rate variability correlated with the results of other tests indicating vagal loss or impairment (see table).

FIG. 1—Resting heart rates (●) and lowest and highest heart rates achieved during deep breathing in 21 diabetics. Division into patients with functional and defective vagi is based on this and other tests (table). Division into normal and abnormal adaptation to standing is based on findings shown in figs. 2 and 3.

Measurement of systolic arterial blood pressure on standing showed that the patients fell into two groups (fig. 2). Cases 1-13 showed little or no fall in systolic arterial pressure. Each patient had a raised heart rate on standing (fig. 3 a). Three patients (cases 11-13) seemed to have impaired cardiac vagal control, but their responses to standing were no different from those of patients with normal vagal function. Cases 14-21 showed a definite fall in systolic arterial blood pressure on standing (fig. 2; P<0.05); all had defective cardiac vagal control. In two patients (cases 14 and 15) blood pressure gradually returned to

Responses of 21 Diabetic Patients to Various Tests of Cardiovascular Reflexes

Case No.:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Sympathetic Effects																					
Orthostatic adaptation	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	A.
Tachycardia with mental stress	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Vasoconstriction with face immersion	+	+	+	+	+	+	A.	A.	A.	+	+	+	+	A.	A.	A.	A.	A.	A.	A.	A.
Pressure overshoot after Valsalva	+	+	+	N.D.	+	+	+	+	A.	N.D.	+	+	+	+	+	A.	A.	A.	A.	N.D.	N.D.
Parasympathetic Effects																					
Bradycardia: After Valsalva	+	+	+	N.D.	+	+	+	+	N.P.O.	N.D.	-	-	A.	A.	A.	N.P.O.	N.P.O.	N.P.O.	N.P.O.	N.D.	N.D.
After phenylephrine	+	+	+	N.D.	+	+	+	+	+	N.D.	-	-	-	-	-	A.	-	-	-	N.D.	N.D.
With face immersion	+	+	+	+	+	+	+	+	+	+	A.	A.	A.	A.	A.	A.	A.	A.	A.	A.	A.
Heart rate variability	+	+	+	+	+	+	+	+	-	-	-	-	A.	-	-	A.	A.	A.	A.	A.	A.

+ = Normal. - = Abnormal. A. = Absent. N.P.O. = No pressure overshoot after Valsalva. N.D. = Not done.

FIG. 2—Systolic arterial blood pressures measured during supine rest (L) and 15 seconds after standing (S).

normal and this recovery seemed to be largely unrelated to changes in heart rate (fig. 3 b). These two patients were the only ones in this group who showed an arterial pressure overshoot after Valsalva's manoeuvre, indicating the persistence of a vasoconstrictor response to decreased systolic pressure.² In the other patients in this group a recovery of systolic blood pressure was associated with a persistent rise in heart rate (fig. 3 c), which suggested that vasoconstrictor mechanisms were defective in this group (see table). One patient's (case 21) circulation adapted particularly poorly to standing (fig. 3 d), and after one minute symptoms from his hypotension forced him to sit down.

There were no systematic differences in the rate of increase of heart rate on standing—that is, cardioacceleration—between the two groups.

FIG. 3—Mean changes ($\pm$ S.E. of mean) in heart rate (●) and systolic blood pressure (□) measured 15 seconds, one minute, and five minutes after standing in (a) 13 patients (cases 1-13) with normal pattern of change in heart rate and systolic blood pressure on standing; (b) two patients (cases 14 and 15) with initial fall in systolic blood pressure on standing and recovery without further increase in heart rate; (c) five patients (cases 16-20) with marked systolic hypotension and tachycardia on standing ($P < 0.001$); and (d) one subject (case 21) with profound hypotension accompanied by only mild tachycardia.

Discussion

Our results show that measurement of heart rate variability and changes in heart rate and systolic blood pressure in response to standing can distinguish different categories of cardiovascular reflex defects in diabetics. The larger group of patients showed little or no change in systolic blood pressure on standing with a moderate, but significant, tachycardia; similar changes are seen in normal people.² Some patients in this group showed abnormal

vasomotor responses to other tests. People showing abnormal responses to Valsalva's manoeuvre but normal responses to postural changes have been described.¹³ Three patients who showed normal circulatory adaptation to postural change had impaired or absent vagal cardiac reflexes. Thus our results do not support the contention that postural hypotension in diabetes is due to vagal dysfunction.¹⁴ Since vagal defects alone did not seem to impair the cardiac responses to standing the tachycardia observed must have been due to sympathetic drive. The cardioacceleration is not likely to be due to circulating catecholamines since catecholamine levels in diabetics with neuropathy change little on standing.¹⁵ The patients who showed a fall in systolic arterial pressure on standing had all lost their cardiac vagal reflexes but were judged to have vasoconstrictor defects also.

From our results it seems that diabetics may fall into the following categories: (a) those with normal responses to standing (little or no change in systolic arterial pressure and mild tachycardia; the mean tachycardia after 5 minutes' standing was 11 beats/min, which compares with a mean value of 13 beats/min in normal people).¹⁶ These patients may have no autonomic neuropathy or a slight vasoconstrictor impairment and no, some, or complete loss of vagal cardiac reflexes; (b) those who show an initial fall in systolic arterial pressure and a more sustained tachycardia on standing. The recovery of pressure indicates that vasoconstrictor loss is not complete, but we found an absence of vagal reflexes in such patients; (c) those who show a definite fall in systolic arterial pressure and dramatic tachycardia on standing. The tachycardia is probably due to sympathetic drive to the heart since vagal reflexes seem to be absent in these people. The absence of hypotensive symptoms in this group seems to be due to their ability to maintain an adequate arterial pressure by cardioacceleration alone, since they have lost their vasoconstrictor mechanisms; (d) those who show a definite fall in systolic arterial pressure on standing but no appreciable tachycardia. The failure of the heart to increase its rate adequately seems to be due to an impaired sympathetic drive, which permits the symptoms of postural hypotension to appear.

Since we studied each patient only once it is not yet clear how diabetic autonomic neuropathy progresses. Nevertheless, loss of parasympathetic activity seems to be more common than loss of sympathetic activity. A long-term follow-up programme is now being set up to determine whether diabetic patients do develop parasympathetic lesions before sympathetic lesions, whether autonomic neuropathy progresses through the categories described above, and whether treatment of the diabetes affects the progress of autonomic neuropathy.

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