Fig. 4 shows that there was a definite variation of individual response within the supplemented group. It is interesting to note that the percentage increase in the white blood cell concentration varied from 5% to over 100% for individuals whose initial concentration was between 12·5 and 15 μg./10^8.

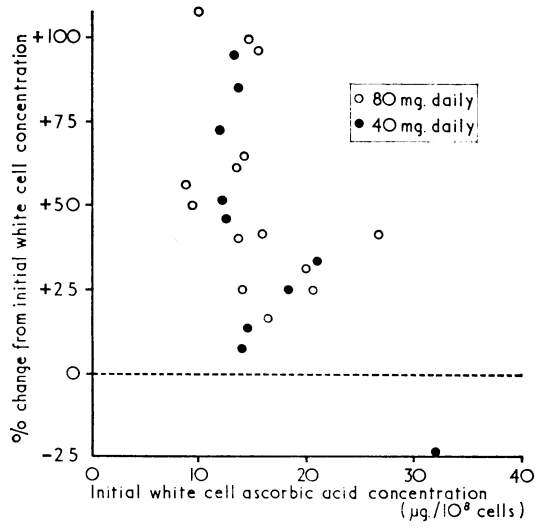

FIG. 4.—Individual response to vitamin C supplement for 17 months.

One might expect that the people most deficient in vitamin C would display the greatest response, but this is not shown here. Individual dietary investigation failed to show any change in personal dietary habits sufficient to account for these considerable individual variations. These latter must be taken into account if recommendations are to be made for any nutritional targets in the elderly. Moreover, as a result of animal studies Williams and Deason (1967) have claimed that there is a substantial individual variation in vitamin C requirements.

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Abnormalities of the Electrocardiogram in Female Carriers of Duchenne Muscular Dystrophy

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Summary: The algebraic sum of the R and S waves (R-S) in the V_1 lead of the electrocardiogram has been found to be significantly greater in female carriers of X-linked Duchenne muscular dystrophy (but not in women with limb-girdle muscular dystrophy) compared with normal women of comparable age. A similar E.C.G. abnormality is found in affected boys, and possibly certain carriers have a latent cardiomyopathy and may even be predisposed to cardiac failure.

Introduction

Duchenne muscular dystrophy is characterized by progressive muscle weakness beginning in early childhood and affecting first the pelvic girdle musculature and later the pectoral girdle musculature. The child becomes confined to a wheelchair by about the age of 10 and dies at about 20, from either respiratory infection or cardiac failure. The condition mainly affects boys, and in most cases is inherited as an X-linked recessive trait, being transmitted by female carriers who are usually healthy but very occasionally may have muscle weakness (Emery and Walton, 1967).

Cardiac muscle as well as skeletal muscle is affected in Duchenne muscular dystrophy as evidenced by the frequent occurrence of arrhythmias and persistent tachycardia, and sudden death from cardiac failure is common. The histological findings in cardiac muscle resemble those found in skeletal muscle (variation in fibre size, hyalinization, fatty infiltration, and connective-tissue proliferation) and have been described

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in patients in whom there were not necessarily any symptoms of heart disease during life (Globus, 1923 ; Bevans, 1945 ; Nothacker and Netsky, 1950 ; Rubin and Buchberg, 1952 ; Storstein, 1962 ; Gilroy *et al.*, 1963 ; Warlamidis and Ludwig, 1966 ; Perloff *et al.*, 1966, 1967 ; Jedrzejowska-Kulakowska *et al.*, 1968 ; Slucka, 1968).

A variety of electrocardiographic (E.C.G.) abnormalities have been reported in patients with Duchenne muscular dystrophy (Lowenstein *et al.*, 1962), but the most frequent and consistent abnormality is the presence of tall R waves in the right precordial leads (Weisenfeld and Messinger, 1952 ; Schott *et al.*, 1955 ; Gailani *et al.*, 1958 ; Manning and Cropp, 1958 ; Gilroy *et al.*, 1963 ; Perloff *et al.*, 1966, 1967 ; Jedrzejowska-Kulakowska *et al.*, 1968 ; Slucka, 1968) resulting in an abnormally high value for the algebraic sum of the R and S waves (R-S) in V_1 (Skyring and McKustick, 1961). This abnormality in the E.C.G. is uncommon in other forms of muscular dystrophy and when present is much less marked (Schott *et al.*, 1955 ; Manning and Cropp, 1958 ; Skyring and McKusick, 1961 ; Emery, 1964 ; Perloff *et al.*, 1966).

In view of the findings in boys with Duchenne muscular dystrophy an attempt was made to determine whether similar E.C.G. changes are present in adult female carriers of this disease. Some preliminary observations (Emery, 1964) in 20 carriers suggested that the value of R-S in V_1 was greater than normal in some carriers. In order to substantiate this the investigation was extended and a further 30 carriers were examined. The present communication concerns the E.C.G. findings in these 50 carriers, and the results have been compared with those in 107 healthy women and 12 women with limb girdle musclar dystrophy.

Patients and Methods

Controls.—The controls, aged 20 to 56 (mean 37·6 ; S.D. 6·8), were 107 healthy women with no clinical evidence of cardiovascular disease (including hypertension) or muscle disease.

Carriers.—All the carriers were examined clinically. They were divided into three groups:

(1) Definite carriers, 25 women each with at least one affected son or proved carrier daughter and an affected brother or maternal male relative. They were aged 23 to 58 (mean 38·8 ; S.D. 10·2).

(2) Probable carriers, 18 women each with at least two affected sons. They were aged 29 to 49 (mean 37·5 ; S.D. 5·1). Probable carriers have been distinguished from definite carriers, because the family history could be compatible with autosomal recessive inheritance. However, since all the boys in these families were severely affected, and since the autosomal recessive form is much less common and less severe than the X-linked form of Duchenne muscular dystrophy, it is highly probable that all these women are heterozygous for the X-linked gene (Thompson *et al.*, 1967).

(3) Possible carriers, seven women each either having one affected son or being a sister or daughter of a known carrier. They were aged 21 to 40 (mean 25·7 ; S.D. 7·5) and were chosen because they had significantly raised levels of serum creatine kinase and are therefore presumably heterozygous (Emery, 1967).

The average age of all the carriers (mean 36·5 ; S.D. 9·3) did not differ significantly from that of the controls.

Limb Girdle Muscular Dystrophy.—Twelve women aged 24 to 57 (mean 39·9 ; S.D. 13·7) with limb girdle muscular dystrophy were studied. All had muscle biopsies, the histology in each case being consistent with that of muscular dystrophy, and the clinical features agreed with the accepted criteria for this type of muscular dystrophy (Walton, 1964). None of these cases was familial.

E.C.G. Records.—Conventional 12-lead E.C.G.s (leads I, II, III, aVR, aVL, aVF, and V_{1-6}) were carried out on all the controls, carriers, and women with limb girdle muscular dystrophy. With regard to the controls all the records appeared normal by conventional criteria. The R and S waves were measured to the nearest 0·5 mm. and the average of several readings was recorded for each individual. All records were read twice, on the second occasion without knowledge of the individual's identity. There was close agreement in the results obtained on the two occasions.

Results

Clinical Findings in Carriers

There was evidence of thyroid pathology in four carriers: one had a non-toxic enlargement of the thyroid gland, two had undergone thyroidectomy, one for thyrotoxicosis and one for a thyroid adenoma (no details are available), and a fourth is believed to have had an " overactive thyroid " in adolescence. All these women had normal serum levels of protein-bound iodine at the time of examination. One carrier had pernicious anaemia.

Six carriers had definite muscle weakness ; clinical details of five have been reported previously (Emery, 1963, 1967). Three carriers were referred because they had weakness. The remainder were unselected. The weakness in all cases was proximal, with pelvic girdle musculature being mainly affected. In four other carriers there was a suggestion of some weakness on hip flexion.

With regard to the cardiovascular system, two carriers had blood pressures of 155/90 and 160/90 mm. Hg. The remainder were normotensive and there was no evidence of any cardiac abnormalities on clinical examination.

E.C.G. Findings

In one carrier there were occasional ventricular extrasystoles, and in another the T waves from V_2 to V_6 were of low voltage. In only one carrier (aged 42) were the R waves in the right precordial leads clearly abnormally tall (R-S in V_1 = 11·0–8·0 mm.). This woman did not have any muscle weakness. Otherwise all the records on inspection appeared normal, and in particular none showed changes which by conventional criteria would be clearly indicative of right ventricular hypertrophy, and there was no obvious notching or slurring of the R and S waves.

In the carriers the R waves were significantly greater than in the controls (controls: mean 1·85, S.D. 1·26 ; carriers: mean 3·23, S.D. 2·01) and the S waves were decreased, though not significantly (controls: mean 8·54, S.D. 3·21 ; carriers: mean 7·60, S.D. 3·10).

Compared with the controls, the value of R-S in V_1 was significantly greater in the carriers, whether considered in separate groups or combined together (see Table). Four of the 50 carriers had values which exceeded the normal 99 percentile of −0·22 mm. in the controls. The values in women with limb girdle muscular dystrophy, however, did not differ significantly from the controls.

Values of R–S in V_1 in Healthy Women, Carriers of Duchenne Muscular Dystrophy, and Women with Limb Girdle Muscular Dystrophy

	No.	R-S in V_1		Significance of Difference from Controls
		Mean	S.D.	
Controls	107	−6·80	2·83	
Carriers:				
Definite	25	−4·36	3·73	P < 0·01
Probable	18	−3·83	2·74	P < 0·001
Possible	7	−4·79	2·10	P < 0·02
Total	50	−4·23	3·18	P < 0·001
Limb girdle muscular dystrophy	12	−6·42	3·07	N.S.

In a larger series of 158 healthy women from the Edinburgh region (E.C.G. measurements kindly made available by Drs. R. W. D. Turner and W. H. Price) aged 20 to 60 (mean 34·0, S.D. 11.2), the values for R-S in V_1 were calculated (mean −6·83, S.D. 3·87). No significant difference was found between these values and those in the controls, and the levels of significance of the differences from the various groups of carriers were the same as for the controls.

There do not appear to be any published figures for R-S in V_1 in a large series of normal women. However, mean values and standard deviations for the R and S waves in V_1 for various age groups are given by Simonson (1961) for 311 healthy women, and from these data an approximate mean value of −5·84 (S.D. 3·91) was derived. This differs significantly from the values in both the controls and the Edinburgh series, possibly due to differences in the selection of subjects with perhaps different body measurements. Nevertheless, this value is still significantly less than the value for the carriers as a whole ($P<0·01$).

There was a small but significant ($P<0·02$) regression of −0·10 mm. per year of age for R-S in V_1 in the controls ($Y= -2·84-0·10X$) but not in either the Edinburgh series or the carriers.

There was a correlation of +0·15 between the value of R-S in V_1 and the serum level of creatine kinase in the carriers, but this was not significant. Of the six carriers with definite muscle weakness, two had values for R-S in V_1 which were at the upper limit of normal (0·0 and −0·5 mm.), but since none of the women with limb girdle muscular dystrophy had abnormal values it is unlikely that proximal muscle weakness alone could account for this E.C.G. abnormality.

Discussion

The existence of tall R waves in the right precordial leads of the E.C.G. in patients with Duchenne muscular dystrophy has been variously attributed by different authors to thoracic deformity, including changes in the anteroposterior chest dimension, pulmonary hypertension, conduction defect due to myocardial dystrophy, and ventricular septal hypertrophy. The clinical, pathological, electrocardiographic, and haemodynamic evidence for and against these various possibilities has been extensively reviewed by Perloff *et al.* (1966), who concluded that none of these explanations is entirely satisfactory. In two boys with Duchenne muscular dystrophy whose cardiovascular state had been extensively investigated (including catheterization studies) during life, Perloff *et al.* (1967) observed marked diffuse interstitial fibrosis in the basal portion of the left ventricle in both boys. They suggested that these pathological changes are the most likely explanation for the anterior shift of the QRS complex in Duchenne muscular dystrophy. However, if this is so the problem remains of why this portion of the myocardium is so selectively involved in this form of dystrophy.

Hausmanowa-Petrusewicz *et al.* (1966) noted E.C.G. abnormalities in a proportion of their female relatives of patients with Duchenne muscular dystrophy, and more recently they have reported that 6 out of 34 definite carriers had E.C.G.s which they considered resembled those found in affected boys, though no details were given (Hausmanowa-Petrusewicz *et al.*, 1968). Mann *et al.* (1968) reported that out of 18 carriers of Duchenne muscular dystrophy two had E.C.G.s which on inspection resembled those found in affected boys with tall R waves in the right precordial leads but only 13 of these carriers were adults, one of whom had an abnormal record. In the present study only one carrier (aged 42) had an E.C.G. in which the R waves in V_1 appeared abnormally high on inspection. Careful measurement of the R and S waves in V_1, however, has shown that the algebraic sum of these waves was significantly greater in carriers than in normal women. It therefore seems that not only may female carriers of Duchenne muscular dystrophy occasionally have muscle weakness (reviewed by Emery and Walton, 1967) but that a proportion have E.C.G. changes similar to those found in affected boys. Since these E.C.G. changes have not been found in women with limb girdle muscular dystrophy, electrocardiography might prove to be useful in distinguishing a manifesting carrier of X-linked Duchenne muscular dystrophy from a woman with limb girdle muscular dystrophy.

This paper has been concerned only with showing that there is a significant difference between the E.C.G.s of carriers and of normal women and not with the pathogenesis of these changes. The precise meaning of this difference will require more detailed investigation. Clinical data on the cardiac state of carriers in later life and serial E.C.G.s over a period of time would be of great interest in this regard. It is not known, for example, what is the incidence of cardiac failure among carriers. It may be that some have a latent dystrophic cardiomyopathy and are predisposed to cardiac failure. If true this would have important implications, since these women often have to lift and carry their affected sons.

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