Many children have now been treated from early infancy and followed up to school age. The published data [5–12] show that with few exceptions these children have I.Q.s above 70 and attend ordinary schools. The fact that in these series of early treated patients there have been only isolated instances of mental retardation is probably the best evidence for the efficacy of the diet. Guthrie [14] rightly points out that the evidence is strengthened by the inclusion in these series of many patients with severely retarded siblings. However, even such a comparison does not allow a quantitative assessment of the influence of early treatment on ultimate intelligence, because the index cases are selected as a result of mental retardation. With certain reservations, which have been discussed, our method of comparing the second siblings of group I and group II enables one to make a valid comparison and reveals the overwhelming influence of early treatment on ultimate intelligence in phenylketonuria.

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"It looks suspiciously as if couples in the United States, at least, are well aware of the opportunity cost of having children, and trade off the wife's job satisfaction and earning power against the satisfaction of having a family. . . . As for children, they perform a different function for families in developing countries from families in the United States. They help with farm work and provide their parents with some prospect of security in their old age. . . . In nineteenth-century Britain the birth rate started to accelerate at the beginning of the century. . . . Then it began to slow down. Why? Nobody knows for sure, but the acceleration coincides strikingly with the Industrial Revolution, its first dip comes suspiciously soon after the passing of the first Factory Act limiting the employment of children, and the more lasting fall came in the wake of compulsory education. When children could work in factories, it cost less to raise them than when they could only be employed on a small-holding. When they had to go to school, they began to be a luxury. There are plenty of morals here for the Third World. Raise the school leaving age, stop children working, introduce a pension scheme and, above all, educate women—and the birth rate may well begin to decline."—FRANCES CAIRNCROSS, *Guardian*, Aug. 27.

ASCORBIC ACID SUPPLEMENTATION IN THE TREATMENT OF PRESSURE-SORES

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Summary In a prospective double-blind controlled trial the effect of large doses of ascorbic acid on the healing of pressure-sores has been assessed. 20 surgical patients were studied, the pressure areas being assessed by serial photography and ulcer tracings. The mean ascorbic-acid levels in treated and non-treated groups one month after the start of treatment were 65·6 and 25·8 μg. per 10^8 white blood-cells. In the group treated with ascorbic acid there was a mean reduction in pressure-sore area of 84% after one month compared with 42·7% in the placebo group. These findings are statistically significant ($P<0.005$) and suggest that ascorbic acid may accelerate the healing of pressure-sores.

Introduction

IT is well established that in scurvy wound healing is delayed [1,2] and that the healing process may fail completely.[3] Ascorbic-acid stores may be reduced in paraplegic patients with pressure-sores,[4] and ascorbic-acid therapy may increase collagen formation in these sores.[4]

In view of the possible role of ascorbic-acid deficiency in the development or delayed healing of pressure-sores, we decided to assess the effect of therapeutic supplementation with ascorbic acid in the management of these patients.

Patients and Methods

Conduct of Trial

20 surgical patients, each with a pressure-sore, were admitted to the trial. The clinical diagnoses are given in table I. The mean hæmoglobin concentration of the patients at the outset of the trial was 11·1 g. per 100 ml. and the erythrocyte-sedimentation rate was raised in all except 4 patients. No blood transfusions were given during the period of study. 3 patients had an indwelling urethral catheter and 4 had a mild urinary-tract infection. All patients had standard hospital beds and mattresses, the same basic hospital diet, and similar local therapy to the pressure areas. There were 8 males and 12 females in the study, aged 54–88 years with an average age of 74·5 years.

TABLE I—CLINICAL DIAGNOSIS IN THE TWENTY PATIENTS INCLUDED IN THE TRIAL

Diagnosis	No.
Fractured neck of femur	9
Rheumatoid arthritis	2
Cerebrovascular accident	2
Fractured pelvis	1
Peripheral vascular disease	1
Paraplegia	1
Gastric ulcer	1
Benign prostatic hypertrophy	1
Diverticular disease	1
Aortic aneurysm	1

Identical white tablets, A and B, were dispensed con-

taining either 500 mg. of ascorbic acid (E. Merck Ltd) or an inert placebo. Each patient was given one tablet twice daily throughout the duration of the trial, and patients were allocated to the treatment groups A or B according to their year of birth. The age and sex distribution, hæmoglobin concentration, and underlying pathological diagnoses were similar in the two groups. The series was consecutive, there being no exclusion clauses.

In 18 patients twice-weekly ascorbic-acid estimations were carried out by the method of Denson and Bowers,[5] the lower limit of normal in our laboratory being 18 μg. per 10^8 white blood-cells.

Assessment of Pressure Areas

The areas of the pressure sores were assessed weekly in three ways: (1) subjectively by one of us (T. V. T.) on a purely clinical basis; (2) by pressure-area tracings performed independently by the department of physiotherapy; (3) by weekly photographic assessment. The photographic assessment was made by taking a 35 mm. colour photograph from a point perpendicular to the plane of the lesion, with a centimetre scale placed adjacent to the pressure area. On each occasion a card with the patient's trial number and the week of the trial was included in the photograph for subsequent identification. The data were subsequently analysed by an independent observer (S. R.), the slides being projected on to graph paper and a line being drawn around the periphery of the pressure-sore so that the area could be measured. This method proved to be the most reliable assessment of pressure-sore area and has been used in the analysis of the results.

TABLE II—LEUCOCYTE ASCORBIC-ACID LEVELS (μg. PER 10^8 WHITE BLOOD-CELLS) IN PATIENTS STUDIED BEFORE AND ONE MONTH AFTER COMMENCING SUPPLEMENTS

Group A (placebo)		Group B (ascorbic acid)	
Pre-trial	After one month	Pre-trial	After one month
40	7	5	56
40	10	14	57
35	13	20	60
30	45	20	60
20	25	20	65
20	15	31	90
16	45	45	75
11	50	21	61
4	22		
Mean 24·0	25·8	22·0	65·5

TABLE III—REDUCTION (%) IN AREA OF PRESSURE-SORES IN INDIVIDUAL PATIENTS AFTER ONE MONTH

Group A (placebo)	Group B (ascorbic acid)
50	81
54	72
4	87
60	87
22	21
39	90
45	100
14	100
60	100
80	100
Mean 42·7	84

$0{\cdot}001 < P < 0{\cdot}005$.

Results

Leucocyte ascorbic-acid levels.—In group A (placebo) the mean pre-treatment ascorbic-acid level was 24·0 μg. per 10^8 white blood-cells, and in group B (ascorbic acid) it was 22·0 μg. per 10^8 white blood-cells. After one month of treatment the mean level in group B was 65·5 μg. per 10^8 white blood-cells (table II). The comparative levels are shown in fig. 1; after two weeks' treatment the levels of all the patients in group B had risen substantially and were greater than those of the patients in group A. These increased levels in group B were, in general, maintained throughout the duration of the trial.

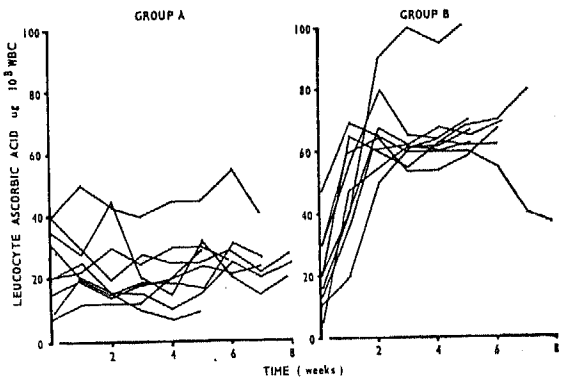

Fig. 1—Serial measurements of leucocyte ascorbic-acid levels in placebo-treated patients (group A) and in those receiving ascorbic acid (group B).

Changes in pressure-sores.—The percentage reductions in area of the pressure-sores after one month are shown in table III. In group A (placebo) the mean percentage reduction in area at one month was 42·7% (S.E.=7·41), whereas in group B (ascorbic acid) the mean reduction was 84% (S.E.=7·60). These changes differ significantly ($0{\cdot}001 < P < 0{\cdot}005$). In fig. 2 the pressure-sore areas are shown graphically, illustrating that six of the pressure-sores in the treatment group healed completely compared with three in those in the placebo group. The mean rates of healing were 2·47 sq. cm. per week and 1·45 sq. cm. per week in the treated and untreated groups respectively.

Discussion

There have been numerous reports of reduced ascorbic-acid levels in geriatric-hospital patients,[6-8]

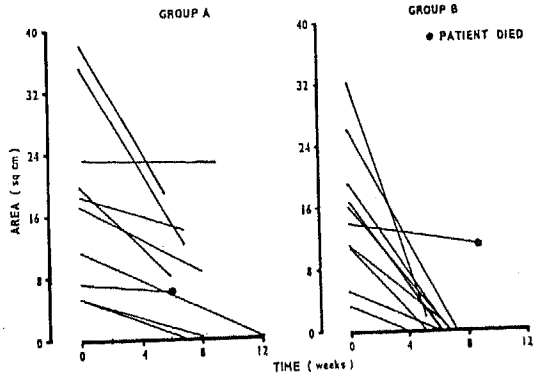

Fig. 2—Comparison of pressure-sore areas before treatment and at completion of the trial in the placebo-treated patients (group A) and in those receiving ascorbic acid (group B).

and in one study similarly reduced stores were recorded in healthy old people living at home.[9] One of the striking features of this study has been the dramatic rise in ascorbic-acid levels during therapeutic supplementation. Griffiths[10] and Andrews et al.[11] were able to show similar biochemical improvement in geriatric patients following ascorbic-acid supplementation, whilst Brocklehurst et al.[12] and Dymock and Brocklehurst[13] found both clinical and biochemical improvement following therapy with a multivitamin preparation.

Ham and Elliott[14] have shown that ascorbic acid is an important factor for the normal synthesis and maintenance of collagen in the repair of tissues, so that when ascorbic acid is deficient the hydroxylation of the aminoacids proline and lysine in the protocollagen molecule is inhibited.[15] In addition, Dunphy and Udupa[16] have reported delay in wound healing with protein deficiency, and that this delay can be reversed by administering methionine. However, in guineapigs with both protein and ascorbic-acid deficiency ascorbic acid as well as methionine is necessary for normal collagen synthesis. Although we have no direct evidence that our patients were protein-depleted our results do show that some had subnormal ascorbic-acid levels. The patients in this study had a mean pre-treatment ascorbic-acid level of 23 μg. per 10^8 white blood-cells, which is only slightly above the lower limits of our normal range of 18 μg. per 10^8 white blood-cells. Ascorbic acid therapy increased these levels as has been reported previously.[9,10] As the rates of healing were significantly improved ($p<0.005$) in the ascorbic-acid-treated group, we would postulate that ascorbic acid is of value in the treatment of pressure-sores. However, correction of protein deficiency, prolonged direct pressure, anæmia, ischæmia, and incontinence must also be regarded as important factors in the treatment of pressure areas. It remains to be determined whether ascorbic-acid supplementation may have a role in the prevention of pressure-sores.

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VAGAL CONTROL OF GLUCAGON RELEASE IN MAN

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Summary A significant fall in fasting plasma-pancreatic-glucagon was produced by injection of atropine. After arginine infusion atropine reduced the normal rise of glucagon by 33% and glucose by 40%. Eleven patients studied during insulin hypoglycæmia after a selective vagotomy showed a peak rise in plasma-glucagon of 173 pg. per ml., which was not significantly different from the glucagon rise in ten preoperatve controls (168 pg. per ml.). The glucagon response to insulin hypoglycæmia (81 pg. per ml.) in a matched group of ten patients with truncal vagotomy was significantly less than after selective vagotomy. This evidence of parasympathetic control of the alpha cell accords with morphological and laboratory-animal findings. Maintenance of normal glucagon release after selective vagotomy favours the use of this operation rather than the cruder truncal vagotomy.

Introduction

Langerhans in 1869[1] observed that autonomic-nerve fibres were closely associated with the pancreatic islets, and many histologists have since confirmed this finding.[2,3] Electron-microscopy has demonstrated cholinergic nerve terminals applied to the surface of the alpha cell.[4] In 1973 Iverson demonstrated, in the isolated perfused dog pancreas, that the addition of acetylcholine to the perfusion medium caused an immediate large release of glucagon.[5] Later, direct stimulation of the peripheral end of the thoracic vagus nerve in the anæsthetised calf was shown to produce a rapid rise of plasma-glucagon.[6] In the conscious calf atropine lowered the fasting plasma-pancreatic-glucagon and substantially delayed the glucagon response to insulin hypoglycæmia. The importance of the parasympathetic innervation in the calf was shown even more clearly by division of the splanchnic sympathetic nerves, thus removing the very sensitive sympathetic control mechanism.[7] Sympathetic division alone did not significantly alter the glucose or glucagon response to insulin hypoglycæmia, but the additional administration of atropine almost totally abolished the expected glucagon rise and caused a much greater glucose fall with development of hypoglycæmic convulsions.

The role of the parasympathetic innervation in the control of circulating glucagon concentration has both a physiological interest and a practical importance. Vagotomy for the treatment of duodenal ulceration is popular, but there is argument concerning the merits of a selective vagotomy, in which the vagal innervation of the pancreas is preserved, versus the simpler and easier operation of truncal vagotomy. We have tried to establish the importance of this parasympathetic pancreatic innervation in glucagon control in man.