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PATTERN OF MALFORMATION IN OFFSPRING OF CHRONIC ALCOHOLIC MOTHERS

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Summary Eight unrelated children of three different ethnic groups, all born to mothers who were chronic alcoholics, have a similar pattern of craniofacial, limb, and cardiovascular defects associated with prenatal-onset growth deficiency and developmental delay. This seems to be the first reported association between maternal alcoholism and aberrant morphogenesis in the offspring.

Introduction

THE purpose of this report is to alert physicians and other health professionals to a pattern of altered morphogenesis and function in eight unrelated children who have in common mothers who were chronic alcoholics during pregnancy. Ulleland [1] has called attention to growth deficiency and developmental delay in such children.

Clinical Findings

Methods of Patient Ascertainment

Eight children born of alcoholic mothers were brought together and evaluated at the same time by the same observers (K. J. and D. W. S.). Four of these children were recognised as having a similar pattern of altered growth and morphogenesis. Thereafter, two other children were ascertained by the abnormal features identified in the first four patients, while the remaining two affected children were ascertained because their mothers were chronically alcoholic.

The mothers of the affected patients all satisfied the criteria for alcoholism as published in 1972 by the Criteria Committee, National Council on Alcoholism.[2] Complications and duration of maternal alcoholism as well as general background information are outlined in table I. All drank excessively throughout the pregnancy, the mothers of patients 1 and 7 to the extent that they were in hospital with delirium tremens. Patient 3 was born while her mother was in an alcoholic stupor. None of the mothers was known to be addicted to any other drug. Features shared by these eight children are summarised in table II and are illustrated in figs. 1 and 2. Further pertinent data and descriptions are found in the case-reports. Palpebral fissure length was measured from medial to lateral canthus and is shown in fig. 3. The growth and performance are presented in figs. 4 and 5 and in table III, and are summarised following the case-reports.

Case-reports

Patient 1, a 1-year-old girl, had asymmetric maxillary hypoplasia. There was lack of full extension at both elbows and bilateral hip dislocations. At birth the 5th fingers overlapped the 4th bilaterally, but they have subsequently come to be in a normal position. A grade 4 out of 6 systolic murmur was repeatedly noted during the first 6 months, but is no longer audible. It was interpreted as representing a ventricular septal defect which had closed. A single upper palmar crease was present on the right hand. Incomplete development of the superior helix of both ears was present bilaterally. There was a 3×3 cm. capillary hæmangioma over the lateral aspect of the right thigh. The labia majora were hypoplastic. Chromosomal study was normal.

Patient 2, a female, was admitted at 11 weeks of age in congestive heart-failure secondary to an atrial septal

TABLE I—GENERAL DATA

—	Patient no. 1	2	3	4	5	6	7	8	All patients (means or proportions)
Maternal history of alcoholism:									
Duration (yr.)	7	3	4	11	2+	10	23	15	9·4
Delirium tremens	+	?	+	+	?	−	+	+	5/6
Cirrhosis	−	?	−	+	?	−	+	−	2/6
Nutritional anæmia	−	?	−	+	?	−	+	−	2/6
Maternal age at birth (yr).	26	34	22	31	32	39	40	30	31·7
Weight change during pregnancy (lb.)	↓1	?	?	↓5	↓15	↓5	↑19	↑30	..
Birth order	5/5	7/7	3/4	6/6	4/7	6/6	4/4	5/5	..
Gestational age (wk.)	40	40	38	36	38	34	44	37	38
Birth-weight (g.)	1850	2500	2500	1600	1673	1550	2345	2250	2034
Birth length (cm.)	45	44·5	47	42	43	38	45·7	43·2	43·6
Breech presentation	+	−	−	−	+	−	+	−	3/8
Apgar score at 1 min. and 5 min.	4/4	9/10	8/9	8/9	5/6	5/8	8/9	4/9	..

+ = present; − = absent; ? = unknown.

TABLE II—PATTERN OF ANOMALIES

—	Patient no. and ethnic group								Total
	Native American (American Indian)			Black			White		
	1	2	3	4	5	6	7	8	
Growth features and performance:									
Developmental delay	+	+	+	+	+	+	+	+	8/8
Microcephaly	+	+	+	+	+	+	+	−	7/8
Prenatal growth deficiency	+	+	+	+	+	+	+	+	8/8
Postnatal growth deficiency	+	+	+	+	+	+	+	+	8/8
Craniofacial:									
Short palpebral fissures	+	+	+	+	+	+	+	+	8/8
Maxillary hypoplasia with relative prognathism	+	+	+	−	+	+	+	+	7/8
Epicanthal folds	+	−	−	−	+	−	+	+	4/8
Limbs:									
Joint anomalies *	+	−	−	+	+	−	+	+	5/8
Altered palmar crease pattern	+	−	+	+	+	−	+	+	6/8
Other:									
Cardiac anomaly	+	+	+	+	−	−	−	+	5/8

+ = present; − = absent.

* Limitation of motion at elbow, interphalangeal and metacarpal-phalangeal joints, and hip dislocation (see text).

defect, confirmed by cardiac catheterisation. Incomplete development of the superior helix of the ears was present bilaterally. A 1 × 2 cm. capillary hæmangioma was present over the area of the left scapula.

Patient 3, a girl aged 4 years 3 months, had a grade 3 out of 6 systolic murmur heard before but not after 10 months of age. This was thought to represent a ventricular septal defect which had closed. There was aberrant alignment of the upper palmar crease and a rudimentary mid-palmar crease bilaterally. The superior helix of the right ear was incompletely developed.

Patient 4, a girl aged 3 years 9 months, had esotropia of the left eye and bilateral asymmetric ptosis. She has worn glasses since 2 years of age for bilateral myopia. There was 15 degrees of limitation in extension at both elbows and inability to fully supinate or pronate the forearms. She had a patent ductus arteriosus, diagnosed by clinical evaluation, for which surgery was planned. The upper palmar crease formed an unusually deep furrow between the 2nd and 3rd fingers bilaterally.

Patient 5, a 17-month-old boy, had mild strabismus. He had mild camptodactyly of the 5th fingers bilaterally and clinodactyly of the 2nd, 3rd, and 4th toes on the left and the 2nd and 3rd toes on the right. He had a single upper palmar crease on the left hand and aberrant alignment of the upper palmar crease with a rudimentary mid-palmar crease on the right. A moderate diastasis recti was present.

Patient 6, a boy aged 3 years 3 months, had hypoplastic 2nd and 5th toenails bilaterally.

Patient 7, a girl aged 3 years 9 months, had bilateral camptodactyly, with absent distal interphalangeal creases of the 3rd, 4th, and 5th fingers. She also had bilateral hip dislocations. Aberrant alignment of the upper palmar crease with a rudimentary mid-palmar crease was present bilaterally. There was a capillary hæmangioma over the upper back. A pectus excavatum was present. The labia majora were hypoplastic. Chromosome study was normal.

Patient 8, a boy aged 2 years 6 months, had limited flexion at all metacarpal-phalangeal joints. There was a grade 2 out of 6 systolic murmur noted until 1 year of age, which was thought to represent a ventricular septal defect that had closed. A single upper palmar crease was present bilaterally. A rudimentary extra nipple was present on each side. There was a pectus excavatum.

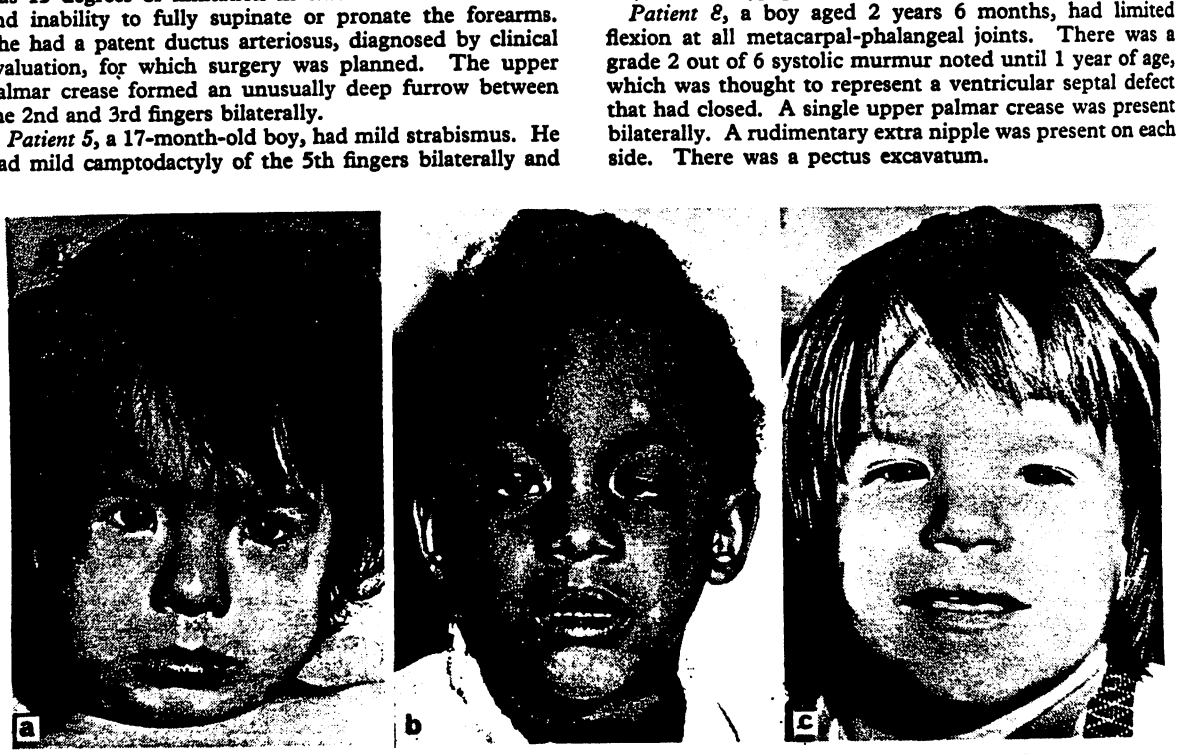

Fig. 1—Patient 1 (a), 4 (b), and 8 (c) at 1 year, 3 years 9 months, and 2 years 6 months, respectively. Note the short palpebral fissures in all patients and the strabismus and asymmetric ptosis in patient 4.

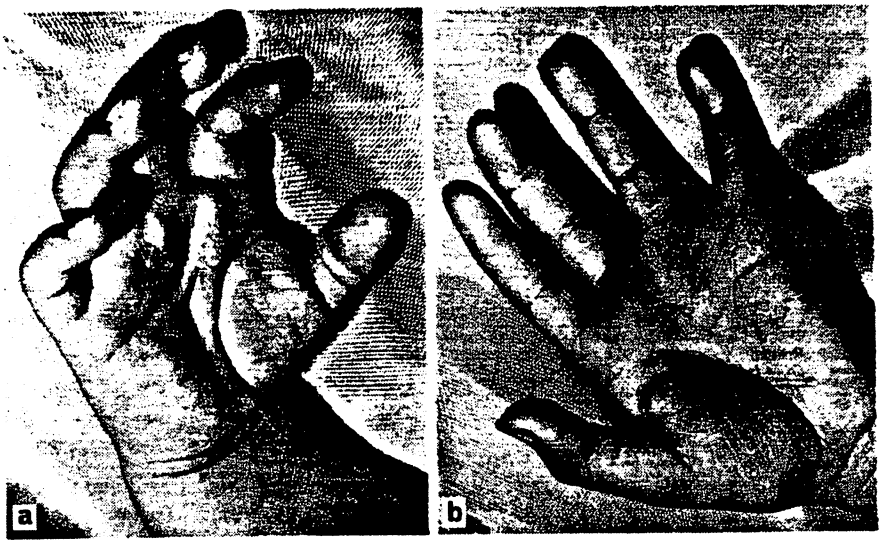

Fig. 2—Aberrant palmar crease patterns in patients 1 (a) and 4 (b).

Growth

All patients had prenatal and postnatal growth deficiency. Though the mean gestational age was 38 weeks, the mean birth length and weight were at the 50th percentile for gestation ages of 33 weeks and 34 weeks, respectively. Thus the degree of linear growth deficiency was more severe than the deficit of weight at birth. Since birth, none of the patients has shown catch-up growth either during hospital admission for "failure to thrive" in six children, during which time adequate caloric intake was recorded, or during foster-care placement in three children. The growth pattern for seven of the eight children is depicted in fig. 4. After 1 year of age the average linear growth-rate was 65% of normal and the average rate of weight gain was only 38% of normal. The mean daily weight increment for the eight patients was 9 g., as contrasted to 26·6 g. for upper-middle-class Seattle children and 24·4 g. for high-risk children followed in the maternal and infant care programme in this city.[8]

Head circumference, depicted in fig. 5, was below the 3rd percentile for gestational age in seven of the eight children at birth. By 1 year of age it had dropped below the 3rd percentile for height age as well as for chronological age in five of the six patients for whom these data were available.

Performance

Performance testing, except for patient 5, was done by one of us (A. P. S.). As indicated in table III,

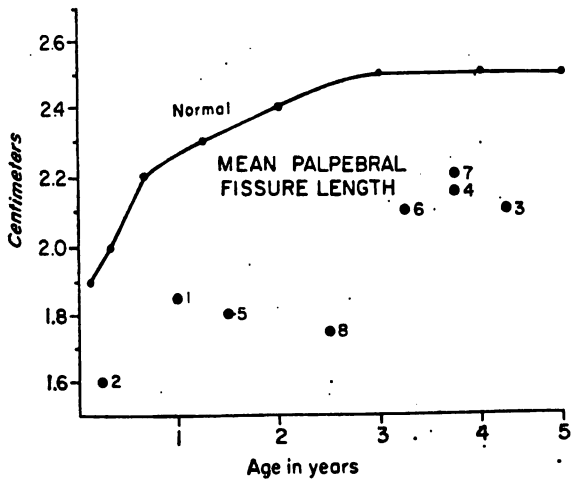

Fig. 3—Palpebral fissure length for patients 1–8.
The normal curve represents the mean for White males and females derived from Chouke.[9]

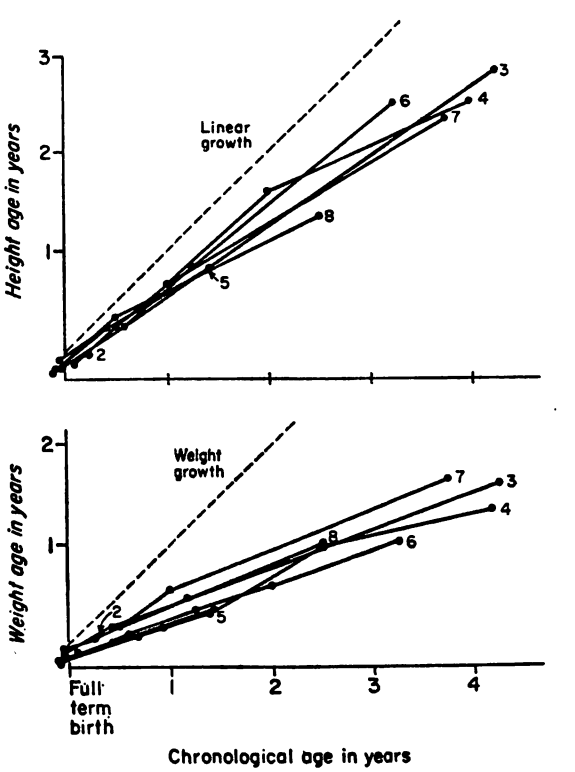

Fig. 4—Growth-rates for patients 2–8.
The dashed lines represent the normal growth-rates, derived from the 50th percentile of the Stuart growth charts.

TABLE III—MENTAL, MOTOR, AND SOCIAL DEVELOPMENT

—	Patient no.							
	1	2	3	4	5	6	7	8
Chronological age* (mo.)	14	3	57	46	18	40	48	34
Motor age estimate† (mo.)	..	2	31	30	..	30	27	21
Mental age‡ (mo.)	10	2+	44	26	11	32	34	19
I.Q. or M.D.I.‡	59	83	75	57	..	79	70	<50
Social quotient§ (mo.)	..	..	..	30	..	36	35	23

* Age at time of testing.
† Bayley scales of infant motor development used where appropriate. This is an estimate only, owing to low ceiling on test relative to age of children. Patient 1 is in hip brace, so motor age could not be estimated.
‡ Stanford-Binet intelligence scale, form L-M (yielding a mental age and I.Q.), used for patients 3, 4 (without glasses), 6, and 7. Bayley scales of infant mental development (yielding a mental age and mental development index) used for patients 1, 2, 4, and 8. Denver developmental scale used for patient 5.
§ Vineland social maturity scale administered to one or both parents.

none of the children were performing within the normal range. In all cases, the children's social and motor performance was more in accord with mental age than chronological age. Fine motor dysfunction, including tremulousness, weak grasp, and/or poor eye/hand coordination was present in five out of the six patients tested, and most of them were delayed in gross motor performance. Five of the children were observed or reported to engage in some type of repetitive self-stimulating behaviour such as head rolling, head banging, or rocking.

Discussion

Past evidence from animal experiments and human experience has not given clear indication of an association between maternal alcoholism and aberrant morphogenesis in the offspring.[4] This report points strongly to such an association. Eight unrelated children of three different ethnic groups, all raised in the fetal environment provided by an alcoholic mother, had a similar pattern of craniofacial, limb, and cardiovascular defects with prenatal-onset growth deficiency and developmental delay. The similarity in the pattern of malformation among these eight children suggests a singular mode of ætiology, most likely environmentally determined by some as yet unknown effect of the maternal alcoholism. Direct ethanol toxicity is the most obvious possibility. There is good evidence in man and other animals that ethanol freely crosses the placental barrier.[5] Animal studies have shown it to be distributed in the amniotic fluid and in multiple fetal tissues, at least during mid or late gestation.[6] Other direct toxic possibilities include one of the breakdown products of ethanol such as acetaldehyde or an unknown toxic agent in the alcoholic beverages which these mothers were consuming. The adverse effect on morphogenesis could also be the indirect consequence of general maternal undernutrition or the deficiency of a specific nutrient or vitamin. However, this degree of prenatal growth deficiency and the pattern of malformation have not been previously recognised in offspring of undernourished women who were not alcoholics.[7]

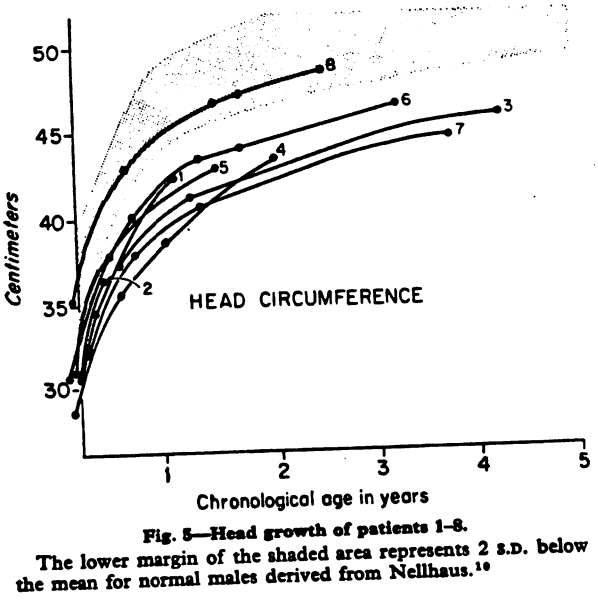

Fig. 5—Head growth of patients 1–8.
The lower margin of the shaded area represents 2 S.D. below the mean for normal males derived from Nellhaus.[10]

The following comments and interpretations relate to the specific anomalies of this syndrome. The short palpebral fissures were interpreted as being secondary to deficient growth of the eyes. A prenatal onset of this implied ocular growth deficiency was indicated for at least patients 1 and 7, who were noted in the records as having "microphthalmia" at the time of birth. The hypoplasia of the maxilla, most evident in its anterior-posterior dimension, resulted in relative prognathism at an age when this is unusual. The variable alterations in joint mobility and positioning in hands, elbows, hips, and feet could be the consequence of limited movement and/or aberrant position during early fetal life. This is further implied by the altered palmar flexional crease patterns, which are normally determined by 11 weeks.[8] In terms of severity, the hand positioning in patient 1, which has improved in time, was at first similar to that found in babies with the 18 trisomy syndrome. None of the patients have had any serious functional joint disability except for the problem of hip dislocation in patients 1 and 7. Of the five patients with evidence of a cardiac anomaly, three were considered to have had a ventricular septal defect which closed before 1 year of age.

The prenatal growth deficiency was more profound in terms of linear growth than for weight growth. This is in contrast to studies of generalised maternal undernutrition in which the newborn is usually underweight for length,[9] and hence suggests that a factor other than nutritional deprivation alone was adversely affecting prenatal growth in these children. Whatever

the cause of growth deficiency in fetal life, the insult to growth-rate has continued during early childhood. The lack of catch-up growth in the face of adequate nutritional intake during hospital admission and/or foster-care placement implies that the postnatal growth deficiency is not secondary to environmental deprivation per se.

The prenatal onset in growth deficiency of the brain, as evidenced by mild neonatal microcephaly in seven of the eight patients, has shown no significant tendency to catch up in early childhood. Thus it is tempting to ascribe the deficient and often aberrant intellectual, motor, and behavioural performance to a problem of early brain morphogenesis, secondary to the maternal alcoholism. It is difficult to determine the extent to which the socioeconomic situation or factors related to continued maternal alcoholism may have adversely affected developmental progress. Although all families are living on welfare, these children come from diverse backgrounds, the extent of education of the biological parents ranging from 8th grade to college and the occupational level from unskilled to professional. The performance in patient 1, who was raised from birth in a foster home, and that of patient 3, who was in a foster home from 2 to 4 years of age, do not provide evidence for better performance in a more stable environment. In addition, the impaired fine and gross motor function manifested by most of these children can scarcely be attributed to home experience.

Experience with other environmental causes of altered morphogenesis would lead one to anticipate variable severity of the syndrome in infants born to alcoholic mothers. Two of the children have partially affected siblings who were also born while their mothers were alcoholic. Others have siblings who are alleged to be normal, some born before and some after the mothers had become alcoholic. Our purpose is to set forth the pattern of malformation in the more severely affected offspring of alcoholic mothers, and we have purposely not included possible mildly affected cases. We feel the data are sufficient to establish that maternal alcoholism can cause serious aberrant fetal development. Further studies are warranted relative to the more specific cause and prevention of this tragic disorder.

We are especially grateful to Nurse Gertrude D. Paxton, whose efforts and understanding of the problems of chronic alcoholic mothers made possible the accumulation of much of these data. We thank Dr Shirley Anderson, who initially arranged for the evaluation of some of these patients, and Dr Nathan J. Smith and Dr Richard P. Wennberg, who were involved in the early studies of some of these patients. Dr Thomas Carlson, Akron Children's Hospital, kindly supplied information on patient 5, who was personally evaluated by one of us (D. W. S.). We acknowledge the contributions of Mrs Lyle Harrah, research librarian, Bradley Gong for photography, and Mrs Mary Pearlman and Mrs Mary Ann Harvey for secretarial assistance. This work was supported by Maternal and Child Health Services, Health Services and Mental Administration, Department of Health, Education and Welfare project 913; by National Institutes of Health grant HD 05961; and by the National Foundation-March of Dimes.

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HYPERCALCÆMIA AFTER ORAL CALCIUM-CARBONATE THERAPY IN PATIENTS ON CHRONIC HÆMODIALYSIS

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Summary Oral calcium carbonate is widely used in chronic renal failure as a phosphate-binding antacid. Unexpectedly, severe hypercalcæmia developed in three out of ten hæmodialysis patients treated with 3·2–6·4 g. calcium carbonate per day for 4–8 weeks. In one patient the serum-calcium reached 15·8 mg. per 100 ml., and he had nausea, vomiting, muscular weakness, personality changes, and subconjunctival calcifications. Two other patients were symptom-free with serum-calcium levels of 13·2 and 12·7 mg. per 100 ml. Hyperparathyroidism, raised dialysate calcium concentrations, and vitamin-D intoxication were excluded as causes of this complication. When calcium carbonate was discontinued, serum-calcium promptly returned to normal, and in the first patient all signs and symptoms disappeared. It is concluded that the hypercalcæmia resulted from intestinal absorption of calcium, probably by passive diffusion not dependent upon vitamin D. Calcium carbonate should be used with caution in patients maintained on chronic hæmodialysis.

Introduction

PATIENTS with chronic renal failure who are maintained on chronic hæmodialysis still face several metabolic problems, including acidosis, disorders of mineral metabolism, and peptic-ulcer disease. Phosphate retention, an important factor in the ætiology of renal osteodystrophy,[1] is both common and difficult to manage. Oral phosphate-binding agents must be used, but the most popular of these, aluminium hydroxide and aluminium carbonate, are unpalatable to many patients. Makoff et al.[2] recommended the use of calcium carbonate in chronic uræmic patients. Since these metabolic disorders potentially respond to treatment with calcium carbonate, which is in addition well tolerated, we substituted this agent for aluminium compounds in ten chronic hæmodialysis patients. Unexpectedly, moderate to severe hypercalcæmia developed in three of these patients while they were receiving calcium-carbonate therapy.

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