

### PERICONCEPTIONAL SUPPLEMENTATION WITH VITAMINS AND FOLIC ACID TO PREVENT RECURRENCE OF CLEFT LIP

SIR,—There is evidence that a pregnant woman's diet and preconceptional supplementation with folic acid<sup>1,2</sup> of the multivitamin preparation 'Pregnavite Forte F',<sup>3,4</sup> can reduce recurrences of neural tube defects. Neural tube defects, which belong to the "common malformation group", have a multifactorial aetiology: the genetic component renders the fetus susceptible to environmental factors acting on the closing neural tube during the fourth week of development. Vitamin deficiencies (possibly folic acid alone) seem to be a major, but certainly not the only factor, interfering with the orderly formation of the neural tube in early pregnancy in Britain.

Many of the orofacial clefts also belong to the common malformation group. It would therefore not be surprising if vitamin supplementation for pregnancies at increased risk for cleft lip (with or without cleft palate) which certainly has a multifactorial polygenic background<sup>5</sup> was also to reduce the number of recurrences. Indeed, three studies of polyvitamin supplementation periconceptionally or in early pregnancies at risk for orofacial clefts suggest some reduction in the recurrence risk of cleft lip (with or without cleft palate),<sup>6-8</sup> though at least one study demonstrated no effect.<sup>9</sup> There seems to be no effect on isolated cleft palate which is not only less common but is also a more heterogeneous abnormality with differing causes.

Early in 1976 we began a prospective study of pregnancies at increased risk for harelip, giving supplements of a multivitamin preparation ('Sporavit') which contains 2000 IU vitamin A, 1 mg vitamin B<sub>1</sub>, 1 mg vitamin B<sub>2</sub>, 1 mg vitamin B<sub>6</sub>, 50 mg vitamin C, 100 IU vitamin D<sub>3</sub>, 2 mg vitamin E, 10 mg nicotinamide (vitamin PP), and 1 mg calcium pantothenate. Healthy women living mainly in Bohemia who have had one child with a unilateral harelip (with or without cleft palate) and who have no other family history of orofacial clefts, were recommended to take three tablets of sporavit and 10 mg folic acid per day, for at least 3 months before conception and to continue taking these tablets at least until the end of the first trimester of pregnancy.

In 85 pregnancies, fully supplemented, there was just 1 recurrence. Acting as control 212 pregnancies, not supplemented, ended in 15 recurrences (7.4%) (table) ( $p=0.023$ ; Fisher's exact test, one tailed).

The patients were selected from our register of orofacial clefts in Bohemia. Born in 1970-75 were 376 children with unilateral cleft lip with or without cleft palate (without associated anomalies and any other clefts in the pedigree). Multivitamin prophylaxis was offered to all mothers of these children; 84 mothers did not plan to conceive again in a near future. Of the remainder, 80 mothers accepted our suggestion (supplemented group) and 212 mothers did not (controls). No substantial social differences were noted in these groups.

The frequency of clefts found in our control group (7.4%), was higher than the risk calculated from 2487 sibships (4.1% for cleft lip with or without cleft palate unilateral and bilateral) in previous

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### UNILATERAL CLEFT LIP WITH OR WITHOUT CLEFT PALATE

	Outcome of pregnancy			
	Total	Spontaneous abortion	No cleft	Clefts
Supplemented	85 (80)*	1†	83	1
Control	212 (202)*	6‡	191*	15

\*Figures in parentheses show no. of mothers.

†Examined; no cleft. ‡Not examined. §1 hypospadias, 1 with talipes equinovarus.

studies published in *Acta Chir Plast* 1972; 14: 4 and 1975; 17: 3.

These results seem highly suggestive, but further data on a larger number of cases are needed. By analogy with the findings of Laurence<sup>2</sup> it would also be worth studying the effects of folic acid alone.

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### CIMETIDINE AND BRUCellosIS

SIR,—The development of acute brucellosis in a patient taking cimetidine, reported by Dr Cristiano and Dr Paradisi (July 3, p. 45), may not have been due to hypochlorhydria preventing intragastric killing of *Brucella melitensis*. Cimetidine lowers suppressor/cytotoxic T lymphocyte counts.<sup>1</sup> Some patients with latent or chronic brucellosis (*B. abortus*) may have high suppressor/cytotoxic T lymphocyte levels, and reduction of the numbers of these cells by cyclophosphamide and prednisone has resulted in acute exacerbation of brucellosis.<sup>2</sup> Likewise stimulation of the cellular immune system by levamisole, coumarin, or brucellin to overcome suppression in patients with latent or chronic brucellosis usually leads to acute exacerbation.<sup>3</sup> *Brucella*, in common with other intracellular organisms, can apparently lie dormant for years in macrophages, producing symptoms of acute disease only if disturbed. This is the basis of the anamnestic test for latent carriers in cattle described by Cunningham.<sup>4</sup>

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### TREATMENT OF NEUROLEPTIC MALIGNANT SYNDROME WITH DANTROLENE

SIR,—Dr Goekoop and Dr Carbaat (July 3, p. 49) point out, once again, the similarities between malignant hyperthermia and neuroleptic malignant syndrome (NMS). They do not refer to a case of dantrolene treatment in NMS which we described in 1981.<sup>5</sup> We achieved a return to normal temperature by the 72nd hour of oral dantrolene treatment with no other therapy and no cooling with ice. The muscle rigidity responded as quickly as did the fever.

Dantrolene can rapidly produce muscular relaxation and a return to normal temperature in NMS. The fact that dantrolene has no central effect suggests a role for muscular rigidity in the genesis of fever. It is not certain that treatment with ice-packs, chilled water, or ice-baths is completely safe, given the cutaneous vasoconstriction that cooling provokes.

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