Vitamin C and the Common Cold

SIR,—An article appeared in the *Sunday Times* of 14 February in which Dr. Linus Pauling's book *Vitamin C and the Common Cold*[1] was discussed. During the past six years a programme of research has been carried out in this department on various aspects of the metabolism and action of vitamin C, and several papers have now been published describing the results.[2-7] Included in this programme has been a study on the relationship between the administration of supplementary vitamin C and the occurrence of symptoms of the common cold. Dr. Pauling referred to the results of these investigations in his book.

Any discussion about vitamin C and the common cold must take into account the human requirements for exogenous vitamin C. The United Kingdom Panel on Recommended Allowances of Nutrients points out that there are two theories about the human requirements for vitamin C.[8] One specifies that humans require only sufficient exogenous vitamin C to prevent them from degenerating into a scorbutic state. The other theory proposes that human beings should, ideally, be saturated with vitamin C. They would then physiologically resemble other animals which can make sufficient vitamin C to keep themselves continuously saturated. The official British attitude is to support the former theory. The Americans and Russians incline to support the latter theory. Accordingly they specify larger daily human requirements for vitamin C.

It was stated in the *Sunday Times* article that many trials have been carried out in an attempt to investigate the relationship between administration of supplementary vitamin C and control of the common cold. The results of these trials have been reviewed in *Nutrition Reviews*[9] and more recently by Regnier.[10 11] Examination of the results of these trials makes two points evident. The first is that all the trials have measured the relationship between the appearance and severity of symptoms of the common cold and the administration of various doses of supplementary vitamin C for varying periods of time to different population samples. In addition, Dr. D. A. J. Tyrrell's trial[12] attempted to evaluate the relationship between viruses associated with the appearance of common cold symptoms and administration of supplementary vitamin C. In the latter trial, however, production of cold symptoms in subjects inoculated with common cold viruses had a success rate of only 38%. No information was provided about the sex, age, or vitamin C status of the treated or control volunteer subjects.[13] There is considerable evidence that the first two factors affect ascorbic acid metabolism in different individuals, and that the third factor influences tissue integrity and normal function.[14] Nothing can therefore be concluded about the relationship of ascorbic acid metabolism and the appearance of cold symptoms in the different experimental groups from the results of this trial. In the *Sunday Times* it was stated that this trial, carried out at the Common Cold Research Unit, was probably the best conducted up to the present date. It may successfully have demonstrated the relationship between the common cold viruses and development of symptoms of the common cold, but by modern standards of clinical trial methodology it could not be classified as a well conducted clinical trial on the relationship between development of the clinical features of the common cold and the administration of supplementary vitamin C.

The second point which is apparent from all the clinical trials on vitamin C and the common cold is that no investigations, apart from those carried out in Dublin,[15] have examined the vitamin C tissue status of individuals who have colds. Development of symptoms of the common cold is dependent upon a particular virus-host relationship being attained. Dr. Tyrrell has demonstrated that infection of a host with a suitable virus must be achieved before a cold can develop.[16] However, it is equally necessary for the host's tissues to be in a susceptible state for attack by the virus. As yet no evidence has been published which demonstrates whether this susceptible state is associated with an abnormality of vitamin C metabolism in the host at the time of attack by the virus. It has already been demonstrated that a significant elevation of tissue levels of vitamin C occurs in subjects susceptible to attack by common cold viruses when they are given supplementary vitamin C during the winter months,[15 17] and that this supplementary ascorbic acid significantly reduces the duration, severity, and incidence of common cold symptoms in adolescent subjects.[16] However the final proof of the efficacy of supplementary vitamin C in reducing the severity of common cold symptoms requires critical interpretation of the state of ascorbic acid metabolism in the infected subjects during their colds. Such interpretation is dependent upon accurate knowledge of the relationship between their plasma and leucocyte ascorbic acid values, and the state of their ascorbic acid stores.[18 19]

Dr. Pauling did not provide this critical evidence necessary for support of his hypothesis about the relationship between the administration of supplementary vitamin C and reduction of the symptoms of the common cold.—I am, etc.,

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Histology of Burkitt's Lymphoma

SIR,—To those of us who have diagnosed dozens of Burkitt's lymphomata in a routine laboratory the findings of Drs. A. Z. Bluming and A. C. Templeton (9 January, p. 89) are not unusual. In fact, when I see the occasional case that looks like the beautiful pictures in the W.H.O. monograph, I am surprised and delighted. All too many of our biopsies are squeezed by surgeons on removal, squeezed into small bottles by attendants, travel for days in a dash of formalin, and arrive in the laboratory to be handled by partly trained staff. The result is a slide that the pathologist can barely recognize as a lymphoma, never mind a Burkitt's. Even in well processed tissues the characteristic picture of Burkitt's lymphoma may not be present in all parts of the tumour. Obviously, then, in a small biopsy the diagnosis can be missed. When there is no clinical information with the specimen we try to follow up but often without result. So, many Burkitt's tumours go unreported as such.

The authors did not mention one interesting pitfall that may be found in patients surviving past the initial disease. in Kenya, several years ago, I saw biopsies from two children with a diagnosis of recurrent Burkitt's lymphoma. They had been free of symptoms for at least three years after cytotoxic drug treatment. The original biopsies were reviewed and the diagnosis confirmed by several experienced pathologists. The recurrences, which I was the first to see, and which I gave without data to my colleagues, were diagnosed as anaplastic nasopharyngeal carcinoma, which is relatively common in Kenya. Nobody suspected Burkitt's lymphoma. An alternative diagnosis was reticulum cell sarcoma. From chromosome studies it appeared that the cells of these tumours were polyploid, thus accounting for the bizarre appearances. Assuming that the tumours were true recurrences and not entirely new diseases (which would be a most extraordinary coincidence) this has led me to wonder if, in fact, the histological appearances we see are diagnostic for one special disease. When recurrent Burkitt's lymphoma looks like nasopharyngeal carcinoma why do we insist that these are two different diseases? Could they be manifestations of the same virus? After all the E.B. virus has been found in both.

At the risk of doing myself out of a job I sometimes wonder if all this separating off of various categories of tumours is valid. Perhaps, like doing a Rorschach test, we read into our slides much that is not there.—I am, etc.,

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Jejunal pH and Folic Acid

SIR,—We read with interest the article of Dr. Ann Benn and others (16 January, p. 148). These workers attribute folate deficiency in epileptics taking phenytoin to

alkalization of the upper small intestine by the drug with consequent malabsorption of folic acid (pteroylmonoglutamic acid). They present evidence that feeding either sodium bicarbonate or phenytoin to a normal subject depresses the rise in serum folate after an oral dose of 5 mg of folic acid. They also found that feeding 10 g of sodium bicarbonate to two normal subjects caused a rise in jejunal intraluminal pH from about pH 6·8 to pH 7·8 within five minutes. They emphasize that proprietary preparations of phenytoin are strongly alkaline in solution and infer that phenytoin depresses the folate absorption curve by raising the intraluminal pH in the upper small intestine and that this effect is mimicked by feeding sodium bicarbonate.

This seemed to us unlikely since, though both compounds are alkaline, their relative buffering capacities are very different. We have found that the amount of acid needed to bring a suspension of 100 mg of sodium phenytoin to pH 6·0 is 400 times less than that required to achieve the same pH with a 10-g suspension of sodium bicarbonate. As little as 0·3 ml of IN hydrochloric acid is needed to titrate 100 mg phenytoin in solution to pH 6·0. Dr. Benn and colleagues measured the intestinal pH of five epileptics who had received long-term phenytoin therapy with an in vivo pH electrode and found generally higher pH values than normal, both in the stomach and in the upper small intestine. However, these subjects had not received anticonvulsants on the day of investigation. Thus, they have no measure of the direct effect of phenytoin on intraluminal pH comparable to their measurements immediately after bicarbonate feeding.

We determined by the same method as Dr. Benn and colleagues the immediate effect of giving a suspension of 100 mg of phenytoin on the intraluminal pH of the third part of the duodenum in two fasting epileptics receiving long-term therapy with phenytoin, one of whom had been folate deficient. No alteration from the resting pH of 6·5 was observed over a 45-minute period. However, 10 g of sodium bicarbonate fed after this period caused the pH to rise to over 8·0 within five minutes.

We conclude that phenytoin has no immediate effect on the intraluminal pH of the third part of the duodenum in chronic epileptics. Whether or not the higher fasting intraluminal pHs observed by Dr. Benn and her colleagues in chronic epileptics are attributable to a secondary, delayed action of phenytoin or are unrelated to phenytoin therapy remains undecided.—We are, etc.,

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Trimethoprim-sulphamethoxazole in Typhoid

SIR,—Your leading article (8 August, p. 297) on trimethoprim-sulphamethoxazole in typhoid is interesting. I would, however, like to draw attention to an important omission of a drug, furazolidone, a nitrofuran derivative which has been widely and successfully tried in the treatment of enteric fevers in India,[1 2] Egypt,[3 4] and Pakistan.[5 6] All the studies published have equally confirmed the efficacy of furazolidone in the treatment of enteric fevers. The relapse rate has been extremely low, and no serious toxic reactions have been reported in patients with typhoid fever treated with furazolidone. Its success had earlier been reported in the salmonella carrier state.[7 8]

Typhoid fever is primarily a disease of developing countries. In general practice, as in the hospitals, treatment is normally instituted immediately upon clinical diagnosis of typhoid fever. Serological and blood culture facilities are not widely available in the countries where typhoid is most prevalent, and where available they are expensive and time-consuming. Under these circumstances, furazolidone, which is not only effective and relatively free from toxic reactions but at the same time is a highly economical drug, deserves mention.—I am, etc.,

M. A. BEG

Karachi, Pakistan — Medical Adviser and Head of the Department of Research and Development, Smith Kline and French of Pakistan Ltd.

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Restless Legs and Pulmonary Disease

SIR,—In your leading article "Restless Legs" (26 December, p. 758) you comment on Dr. J. D. Spillane's paper in the same issue (p. 796), on restless legs syndrome in chronic pulmonary disease, stating that the author gave reasons for preferring to consider restless legs a nervous manifestation of the patients' invalidism rather than a metabolic consequence of respiratory failure.

Certainly, in all of Dr. Spillane's 8 cases the respiratory disease had started years in advance of the symptoms of restless legs. In this connexion I would like to mention that I have myself been a sufferer from restless legs for about 10 years, during which time I have scarcely had a whole night's sound sleep. The last three years I have also been a victim of bronchial asthma, which has necessitated daily medication with corticosteroids for the last 2 years. Thus the symptoms of restless legs preceded the pulmonary disease by about seven years.

It does not necessarily follow, therefore, that the restless legs syndrome in a patient suffering from chronic pulmonary disease is a result of the pulmonary ailment. Perhaps there might yet be a causal relationship between some chronic pulmonary diseases and restless legs?

As to the difficulty of describing the discomfort of restless legs, I think that the nearest to what I experience was expressed by a patient who once told me "It feels as if my marrow bones are freezing."—I am, etc.,

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Naming the Compound

SIR,—There is still a tendency for papers to be published concerning oral contraceptives and their side effects without the authors stating the drugs involved.[1]

The various types and combinations of oral contraceptives available should be well enough known to make specific reference to the drugs involved possible. This information would be of value to those seeking rational definition of the side effects of oral contraceptives. If I were to submit a paper on, say, hypertensive drugs and their side effects, and omitted to mention even the types of drugs involved, I would hope that clarification would be requested.—I am, etc.,

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Treatment of Narcolepsy

SIR,—I would like to report a patient with narcolepsy with cataplexy, who is being successfully treated with imipramine.

My patient is a Barnardo boy, aged 25, of mixed race who knows nothing of his parentage. He works as a builder's labourer. Narcolepsy with cataplexy was first diagnosed at St. Catherine's Hospital, Birkenhead in 1965 when he was 19. He complained then that from his schooldays onward he would suddenly fall asleep—in class at school, driving a tractor, at dances, etc. Also, when excited, he would lose the muscular power in his limbs. He was a nervous young man, who suffered from nocturnal enuresis.

Clinical examination and E.E.G. were negative and no organic cause for the attacks was found. He was treated initially with ephedrine building up to a dose of 60 mg two or three times a day. This was successful in controlling his narcoleptic attacks; but, after moving to my practice area in 1966, he claimed that the tablets were losing their effect. He was then put on amphetamine sulphate. By the summer of 1970 he had worked up to a dose of 30 mg a day. He was getting side effects in the form of nervous twitches and neurotic excoriations on the forehead.

Since the beginning of last September he has been taking imipramine 25 mg three times a day. He says that the drug has been quite as effective as either of the others in controlling the narcolepsy, and it has also completely stopped the attacks of cataplexy, which neither the ephedrine nor the amphetamine touched ("I can now throw a double top at darts and still remain standing"). His nervous symptoms quickly cleared. The only fly in the ointment has been a weight gain of over a stone (6·5 kg.).—I am, etc.,

J. L. BOURDILLON

Dyserth, Flints