

## CORRESPONDENCE

## Correspondents are asked to be brief

<b>Immunodiagnosis of Cancer</b>	<b>Aetiology of Varicosity</b>	<b>Diagnosis of Sarcoidosis by Labial Gland Biopsy</b>
E. J. Field, F.R.C.P., and others..... 641	R. S. Lawson, M.S., F.R.C.S..... 645	T. Bates, F.R.C.S..... 646
<b>Ultrasound and Calcified Cardiac Valves</b>	<b>Effects of Dietary Fibre</b>	<b>Malathion-resistant Pediculosis Capitis</b>
D. Gordon, M.B., D.M.R.D..... 642	Surgeon Captain T. L. Cleave, M.R.C.P.... 645	N. H. Silverton, F.R.C.G.P..... 646
<b>Growing Pains</b>	<b>Chloramphenicol Resistance in Typhoid</b>	<b>Sexual Freedom</b>
J. C. Hawksley, F.R.C.P.; J. A. Ford, M.R.C.P., and M. G. Dunnigan, F.R.C.P.ED..... 642	J. F. Calder, M.B..... 645	L. H. Cane, M.B..... 647
<b>Pulmonary Oedema of Mountains</b>	<b>Transmission of Malaria</b>	<b>People with Epilepsy</b>
A. Pines, F.R.C.P.ED..... 642	G. O. Barber, M.B..... 645	J. E. S. Jarrett, M.A..... 647
<b>College of Anaesthetists</b>	<b>E.N.T. Advances</b>	<b>Treatment of Early Breast Cancer</b>
E. B. Lewis, F.F.A. R.C.S..... 643	J. C. Ballantyne, F.R.C.S..... 645	Sir Hedley Atkins, F.R.C.S..... 647
<b>Pimozide</b>	<b>Hands off Postgraduate Centres</b>	<b>Trapped Nerves</b>
E. A. Burkitt, D.P.M., and M. H. Faulkner, M.B..... 643	P. S. Byrne, F.R.C.G.P..... 645	J. D. Sidey, F.R.C.S.; M. D. Mehta, F.F.A. R.C.S. .... 647
<b>Misleading Prospectuses</b>	<b>Influence of pH on Radioimmunoassay of Angiotensin I</b>	<b>Occupational Health Service</b>
W. S. B. Loosmore, F.R.C.S.ED..... 643	B. Bagni and others..... 646	P. L. Pelmeur, D.P.H..... 647
<b>Overpopulation</b>	<b>Brodrick Report</b>	<b>Conditions of Residence</b>
J. Guillebaud, F.R.C.S.ED..... 643	G. Behr, F.R.C.P..... 646	J. Winter, M.D..... 648
<b>Detecting Sickle Haemoglobin</b>	<b>Sulphonamide Crystalluria with Acetazolamide</b>	<b>New Consultant Contract</b>
J. E. Bowman, M.D..... 644	R. T. Orchard, M.R.C.P., and others..... 646	D. P. Degenhardt, F.R.C.P..... 648
<b>Dental Caries: An Alternative to Water Fluoridation</b>	<b>Ergocryptine</b>	<b>Income of G.P.s</b>
C. F. J. Baron, M.R.C.S..... 644	J. S. Pryor, M.R.C.P..... 646	J. Egerton, M.R.C.G.P..... 648
<b>Asian Immigrants</b>	<b>Cot Deaths and Hypokalaemia</b>	<b>Junior Members Forum</b>
C. R. Salkeld, F.R.C.S.ED..... 644	J. A. Fraiss, M.R.C.S..... 646	R. E. W. Fisher, D.P.H..... 648
		<b>Cold Drink and Syncope</b>
		S. C. C. Parry, D.P.H..... 648

## Immunodiagnosis of Cancer

SIR,—There is general agreement that early diagnosis of cancer is a prerequisite for successful management, and this theme was again brought out at the Paris cancer symposium referred to in your leading article (5 August, p. 308). But what is early? It is widely held among pathologists and radiotherapists (largely on the basis of extrapolation from growth rate regression curves) that malignant tumours may be present for years before they impinge on the patient's or the doctor's attention.

You underline the need for better ways of assessing a patient's immunological status. With the macrophage electrophoretic migration (M.E.M.) method of measuring cellular sensitization described by Field and Caspary<sup>1</sup> and set out with additional material and full experimental protocol in the *B.M.J.*<sup>2</sup> it is possible to make an early diagnosis of cancer (for example, cervical cancer *in situ*) with confidence. This depends on the very precocious development of lymphocyte sensitization to encephalitogenic factor (E.F.) and, in somewhat greater degree, to a cancer basic protein (Ca.B.P.) extractable from a variety of human tumours.<sup>3,4</sup> Independent confirmation of our preliminary results with E.F. has recently been made by Pritchard and co-workers (submitted for publication).

The M.E.M. technique has now been used to study the length of time for which a cancer may have been present before attracting attention. We started from our observation<sup>3</sup> that special lymphocyte sensitization which a mother possesses during gestation is handed on to her newborn child, so that the latter's lymphocytes react to the same antigens. In particular, if the mother has had a cancer and therefore carries lymphocytes sensitized to Ca.B.P. the newborn

child does so too. The question arises: For how long do such "marker lymphocytes" persist? From study of families in which mothers have had children at intervals subsequent to developing malignant disease it is clear that the cells "injected" as it were, at birth are detectable up to about 12 years.

We went on to study families in which children had been born at intervals before the mother developed malignant disease. Such children would be carrying Ca.B.P. marker lymphocytes from birth, and we set out to establish how long before a mother's cancer a child could be born and still show such Ca.B.P. sensitized lymphocytes (knowing that they would have died away in periods greater than about 12 years). We started with papillary cancer of the thyroid—a growth thought to have a long natural history—and found that a child born nine years before the mother presented did indeed have lymphocytes sensitized to Ca.B.P. Of course, the mother's cells may have been sensitized much longer (we have found sensitization to persist 24 years after carcinoma *linguae*), but because of the natural decline outlined above this is the limit to which our test can be stretched. From study of families in which the mother has developed cancer of the breast it is clear that she may have carried the tumour for at least seven years before presenting to her doctor. Further studies are in progress and a full report will be published elsewhere. Meanwhile, it is already clear that the earliest surgical diagnosis is already relatively late.

Three other points are relevant to your leading article.

(1) Mathé's striking results<sup>5</sup> are generally attributed to non-specific stimulation of immune response—no doubt because of the asso-

ciation of mycobacteria with Freund's adjuvant. Indeed, you report Professor Benacerraf as drawing attention to the usefulness of crude preparations of mycobacteria and *Corynebacterium parvum* in this respect. However, work we recently published<sup>6</sup> opens the possibility that beneficial results from mycobacterial adjuvants may not be as non-specific as is (on a *prima facie* case) so easily supposed. It has long been known that encephalitogenic factor (E.F.) shares antigenic determinant(s) with P.P.D. of tubercle<sup>7</sup> and this is true also of Ca.B.P.<sup>8</sup> It is possible, therefore, that some at least of the effect of mycobacteria may be due to their sharing antigen(s) with Ca.B.P. In other words, Mathé may have been using a cancer antigen—albeit not the most efficient which could be employed. This theme is developed in some detail by Field and Caspary.<sup>6</sup>

(2) We know that molecule for molecule Ca.B.P. is at least 10<sup>4</sup>-times more antigenically active than is E.F. (Dickinson, Caspary, and Field, unpublished). This makes sound teleological sense since the emergence of even a very few molecules will be enough to trigger off an "early warning system" to lymphocytes engaged in immunosurveillance.<sup>9</sup> Indeed, we have found that cancer antigen derived from as few as 10<sup>3</sup> malignant cells is enough to give a positive result. It is indeed this together with the operation of lymphokines<sup>10</sup> which makes the M.E.M. test so sensitive.

(3) With the advanced diagnostic techniques (mammography, thermography, etc.) currently available it not uncommonly happens that specialist diagnosis precedes therapeutic intervention by two years or more. This is especially so in relation to cancer of the breast. At a recent symposium organized by the Marie Curie Foundation Professor E. Samuel demonstrated two cases of very early breast cancer diagnosed two years before convincing clinical signs set active treatment in motion. So long as doctors wait for classical signs of cancer—a palpable lump, obstruction of a tube, or bleeding—valuable years will be lost. We may speculate that well before the turn of the century immunodiagnosis of cancer will be standard practice

and immunotherapy (an attempt to assist natural defence) will be instituted without necessarily predicting the site and nature of the malignant growth.

Further work in this laboratory has not induced us to relinquish our tentative conclusion<sup>2</sup> that there may well be a common antigen appearing in all human malignant neoplasms. If this is indeed so we may be optimistic that an effective treatment of cancer (whatever its primary cause(s) may be) is a problem essentially soluble with methodology already developed.—We are, etc.,

E. J. FIELD  
E. A. CASPARY  
R. T. H. SHEPHERD

Newcastle General Hospital,  
Newcastle upon Tyne

- 1 Field, E. J., and Caspary, E. A., *Lancet*, 1970, 2, 1337.
- 2 Caspary, E. A., and Field, E. J., *British Medical Journal*, 1971, 2, 613.
- 3 Field, E. J., and Caspary, E. A., *Lancet*, 1971, 2, 337.
- 4 Carnegie, P. R., Caspary, E. A., and Field, E. J., *Biochemical Journal*, 1972, 126, 5.
- 5 Mathé, G. et al., *Lancet*, 1969, 1, 697.
- 6 Field, E. J., and Caspary, E. A., *British Journal of Cancer*, 1972, 26, 164.
- 7 Field, E. J., Caspary, E. A., and Ball, E. J., *Lancet*, 1963, 1, 11.
- 8 Field, E. J., Caspary, E. A., and Carnegie, P. R., *Nature*, 1971, 233, 284.
- 9 Burnett, F. McF., *Immunological Surveillance*. Oxford, Pergamon Press, 1970.
- 10 Dumonde, D. C., and Maini, R. N., *Clinical Allergy*, 1971, 1, 123.

#### Ultrasound and Calcified Cardiac Valves

SIR,—Readers of the paper of Mr. A. Hedley Brown and Mr. Peter G. H. Davies, (29 July, p. 274) on the ultrasonic decalcification of calcified heart valves and annuli may be deterred from adopting this technique because they have read the work of Reeves and colleagues.<sup>1</sup> These workers, in Portland, Oregon, use a generator and transducer of my design to produce mitral stenosis artificially and have also produced atrial fibrillation. This provides an excellent means of research into the treatment of these conditions.

Such sequelae are obviously objectionable in cardiac surgery but it is possible to reassure those concerned. In Portland a collimated beam of ultrasound is transmitted through saline directly to the leaflet at an intensity of about 20 watts or more per cm<sup>2</sup> at 1 MHz. This is a true effect of ultrasound. The dental scaling machines operate at 25 to 40 kHz, and function more like a miniature pneumatic drill. The cutting edge is in contact for only about 10% of each cycle and hardly any energy passes into the tissues. Because the wavelength is long in relation to the area of contact, the energy dissipates in all directions very rapidly.

Professor M. Arslan, of Padua, who introduced the ultrasonic surgery of the labyrinth in the treatment of Ménière's disease also used a low frequency transducer of the dental scaler type in the removal of the footplate of the stapes.<sup>2</sup> Arslan stresses that it is possible to remove the bone without any damage to the adjacent structures.—I am, etc.,

DOUGLAS GORDON

Harrow,  
Middlesex

- 1 Reeves, M. M., Dick H. L. H., and McCawley, E. L., *Medical Research Engineering*, 1969, 8, 16.
- 2 Arslan, M. Personal communication.

#### Growing Pains

SIR,—The leading article on growing pains (12 August, p. 365) is of interest in raising as well as settling a number of points.

The study of the subject between 1920 and 1939 was important because rheumatic heart disease with cardiac involvement was rife and a number of clinicians, believing that "growing pains" could be a manifestation of rheumatic fever, were condemning children to long periods of rest to no purpose while others, misdiagnosing mild rheumatic fever as growing pains, were allowing children to go their ways with incipient or active heart disease. The credit for pointing this out goes to Sir Wilfrid Sheldon.<sup>1</sup> Rheumatic fever is now a rare disease in Britain. Naish and Apley<sup>2</sup> gave 4.2% as the incidence of growing pains which, in spite of their stricter clinical definition, is still far below the 33.6% of 505 children examined in 1928<sup>3</sup> and diagnosed on history taken from the mother, description of the site, severity, and nature, by the child, and a clinical examination.

The criterion "severe enough to interrupt normal activities" begs the question at what point a child's activities cease to be normal. If the activity is unwelcome, such as going to school, children are not above cashing in on pains in the legs in order to stay at home. At the age of 11 I escaped the unwelcome activity of compulsory association football for a whole season with the self-made diagnosis of "bad cold in the head, Sir." This observation (I must have been a psychopath), substituting coryza for growing pains, is in accord with Apley's consideration that growing pains are associated with emotional disturbance.<sup>4</sup> Neustatter<sup>5</sup> saw a link of this nature 35 years ago. Other associations with growing pains have been noted, such as allergic disorders by Bray.<sup>6</sup>

"Growing pains" is still a hunting ground for clinical investigation; those whom you have quoted have added considerably to its solution. This letter is based on rereading my article in the *B.M.J.* in 1939.<sup>3</sup>—I am, etc.,

J. C. HAWKLEY

Marlborough,  
Wilts

- 1 Sheldon, W., *Diseases of Infancy and Childhood*. London, Blakiston, 1936.
- 2 Naish, J. M., and Apley, J., *Archives of Diseases in Childhood*, 1951, 26, 134.
- 3 Hawksley, J. C., *British Medical Journal*, 1939, 1, 155.
- 4 Apley, J., *Proceedings of the Royal Society of Medicine*, 1953, 51, 1023.
- 5 Neustatter, W. L., *Guy's Hospital Reports*, 1937, 87, 8.
- 6 Bray, G. W., *Recent Advances in Allergy*. London, Churchill, 1931.

SIR,—In your recent interesting leading article (12 August, p. 365) it is proposed that when considering the practical problems of the differential diagnosis of growing pains the number of possibilities is reduced by restricting the term to "intermittent limb pains recurring over a period and not specifically located to the joints." In addition, you emphasize the imprecision of the term subacute rheumatism. That the clinical use of these terms is likely to lead to diagnostic error has been made apparent to us in our recent experience with rachitic immigrant children.

During our survey (17 June, p. 677) we found that several of the subjects who had rickets had attended their general practi-

tioners complaining of pain in the lower limbs. Characteristically this was localized to the knee or ankle joints, varied in intensity, was produced or worsened by exercise, and resulted in considerable curtailment of physical activity. As the patients were well nourished and, with two exceptions, had no rachitic deformities, the diagnosis of growing pains or rheumatism was commonly made. The former term presumably seemed acceptable in view of the age group (8-16) of the patients, while the latter was probably made to appear somehow appropriate when considering an Asian suffering the vicissitudes of our damp and sun-starved climate. In addition, the readiness with which such misdiagnosis occurs is influenced, as you mention, by traditional misconceptions and, in these particular cases, by a lack of clinical awareness of the prevalence of rickets in Asian immigrant children when considering the differential diagnosis. However, in no case was biochemical investigation performed and simple analgesics were prescribed resulting in the patients having continued pain. This was in marked contrast to the dramatic amelioration of symptoms obtained by administering vitamin D and calcium supplements.

We trust that this account of our clinical experience will serve both to underline the urgent need for the restrictive definition of growing pains as given above and for a more critical approach when considering the differential diagnosis. In addition, we would concur that the term subacute rheumatism in children lends only to diagnostic confusion and should be discarded.—We are, etc.,

J. A. FORD  
M. G. DUNNIGAN

Stobhill General Hospital,  
Glasgow 2

#### Pulmonary Oedema of Mountains

SIR,—Your leading article (8 July, p. 65) rightly stresses that the true mechanism of this illness—met with in increasing frequency and often fatal—is still unknown. You do not mention the role of the kidney, and recent experience of mine supports the contention<sup>1</sup> that this may be a prime factor in causation.

I recently spent 14 days at a constant altitude of between 16,500 and 18,500 feet (5,016-5,624 m) in the Kulu area of the Central Himalayas. My companions were one European and four "Sherpas." Only the latter had been to such heights before. Our fluid intake, including food, was kept at approximately three litres daily. Within 1-2 days of ascending we all experienced the well known diuresis of high altitudes.<sup>1</sup> Measurements of specific gravity on many daily specimens showed that it remained between 1.002 and 1.005 during the first week and over each 24 hours. The specific gravity varied little with rest, strenuous climbing, or at night, nor was it altered by great heat, by the cold of intense blizzards, nor by water deprivation for 18 hours—though the amount of diuresis varied, naturally. Traces of albumin were sometimes found and occasionally of blood and glucose (Labstix), especially on climbing days. During the second week the diuresis tended to lessen and the specific gravity increased slightly, earlier in the Sherpas. On