Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Tabo-paresis

SIR,—Some senior and experienced psychiatrists have recently had cause to give considerable thought to the topic of tabo-paresis. One British psychiatrist recently found that there was concern in responsible circles in America on the same topic. When the time-lag between primary infection with syphilis and the onset of tabo-paresis is considered, it appears possible that the recent virtual disappearance of tabo-paresis is due to the efficiency of arsenical treatment in the years before the large-scale employment of antibiotics.

It may be that cases treated in the early years of the antibiotic era have yet to develop tabo-paresis. The time factor suggests that the next few years may be particularly important in this respect. Recently a senior psychiatrist with considerable experience of neurosyphilis had four cases referred to him within a very short period—more cases than he had seen for a very long time previously. Two of these cases could easily have been missed by a more junior man with little practical experience of tabo-paresis. Moreover, some of the old, characteristic physical signs seem to be changing somewhat.

It may be hoped that fears of a reappearance of tabo-paresis on a considerable scale may prove groundless, but there appears to be reason for clinicians to be very alert on this topic, so that if an increase in the number of cases should occur the sufferers from it may be diagnosed early and therefore successfully treated.—I am, etc.,

NOEL G. HARRIS,

London, W.1

Chairman, Public Relations Committee,
Royal Medico-Psychological Association.

Neurological Complications of Pertussis Immunization

SIR,—Drs. D. C. Thursby-Pelham and C. Giles's letter (*Journal*, July 26, p. 246) is of great interest. It is remarkable that Dr. Thursby-Pelham has seen six patients in the space of 10 years with neurological reactions following pertussis immunization, in view of the fact that only seven such cases have been recorded in Great Britain (see my paper, *Journal*, July 5, p. 24). One of these seven is Case 2 in their series. It may be, as Drs. Thursby-Pelham and Giles state, that the dangers of whooping-cough immunization are greater than is commonly thought, but this can only be established if the possibility of reactions to immunization are borne in mind and reported when they occur. One would like to make a plea, therefore, that this should be done.

It is possible that the relatively large number of cases of neurological complications of pertussis immunization reported from the United States, as opposed to other countries, including Britain, is due to a greater awareness of, and interest in, the problem in America. If further cases are reported, as Drs. Thursby-Pelham and Giles have now done, it may be that the commonly held view, that the dangers from whooping-cough itself are much greater than those from immunizing against it, will require modification.—I am, etc.,

London, S.W.17.

J. M. BERG.

SIR,—Further to the article by Dr. J. M. Berg (*Journal*, July 5, p. 24) and the letter from Dr. D. C. Thursby-Pelham and Dr. C. Giles (*Journal*, July 26, p. 246), I have given many thousands of injections of both combined diphtheria-pertussis and triple antigen vaccines, and in two instances only have I known convulsions to follow, in sisters.

Case No. 1.—A female infant, first child of a Rhesus-negative mother. Became jaundiced three days after birth. Was admitted to hospital but replacement transfusion unnecessary. At 6 months of age she had a severe convulsion which occurred four hours after her first injection of triple antigen. She was un-

conscious for 10 minutes and made a full recovery within 24 hours. One month later she had a similar convulsion following her second injection. The third dose was not given and one year later she was seen and is quite normal.

Case No. 2.—Sister of Case No. 1. Female infant. Second child of a Rhesus-negative mother. Labour was induced at 38 weeks. At birth, the infant was severely affected by haemolytic disease and replacement transfusion was carried out. At 4 months of age the first injection of triple antigen was given. Three hours later a minor convulsion occurred. Recovery was complete within a short while. In view of her sister's reaction after her second injection, and after reading the article by Dr. Berg, no further injections were attempted.

The fact that these two cases were sisters both suffering at birth from haemolytic disease and both born of a Rhesus-negative mother makes me wonder if the aetiology of this dangerous reaction to pertussis vaccine may not in some way be connected with the Rhesus factor.—I am, etc.,

Tetbury, Glos.

JOHN N. H. ANDREWS.

Dummy Tablets

SIR,—Dr. E. C. Atkinson (*Journal*, June 21, p. 1478) makes out a case for having "some control tablets of inert substances" or "a genuine placebo" included in the *British National Formulary* to help doctors with their investigation of "the relative values of the mass of proprietary drugs" which appear on the market. Dr. W. N. Leak (*Journal*, June 28, p. 1546) points to the difficulty which may arise for a doctor prescribing dummy tablets, when he has to choose between honesty with his patient and impersonal science; and concludes "regretfully, that it would be wrong for the *B.N.F.* to include a dummy tablet. . . ." May I set out in detail some of the considerations which should guide a family doctor in his choice of controls for any therapeutic research which he intends to pursue?

It is not primarily the task of a family doctor to test the pharmacological effects of unknown or untested substances on those who seek his advice about their treatment. Logically a doctor could only advise a patient to take such an unknown substance if there was no accredited or orthodox treatment for the condition from which he was suffering. The medicaments prescribed by a general practitioner should be those which he uses in good faith and on the basis of knowledge which he has obtained of their composition and action from different sources. Where the progress of a disease invariably follows a predictable and well-established course, then the past experience of accumulated medical knowledge supplies the control for any therapeutic trial of a possibly beneficial drug, and no other may be needed. The most obvious examples are those diseases in which death is the invariable or predictable result. If, on the grounds of a reasonable hypothesis, the first therapeutic trial of a new substance for the treatment of such a disease were being planned—for example, streptomycin in tuberculous meningitis—it could be argued that it would be unethical to withhold this test substance from any patient in the trial. A proper structure of this first trial might well be to test the action of the new substance in a continuous series of cases until the question was beyond doubt, either that it had no action or that the predictable course of the disease was undoubtedly altered by the use of the test substance. In general practice, however, such trials are rare.

Therapeutic research in general practice falls broadly into six categories. The first, and perhaps a neglected field, is a fresh assessment of the action of time-honoured remedies in common diseases—for example, the use of potassium iodide or tincture of stramonium in asthma. Second comes the controlled trial of new drugs for old and familiar diseases, such as the prophylactic use of sulphonamides for the complications of measles. Third come trials designed to reveal new uses of familiar drugs, such as aspirin in diabetes. Fourth, and we hope rarely in general practice, comes the administration of new and unfamiliar drugs to patients with diseases for which a standard treatment already exists. The fifth comprises those trials where the family doctor is in ignorance of the precise nature of the

substance which he personally prescribes or dispenses for any particular patient—for example, “blind” trials—and, lastly, there is the experimental use of drugs in volunteers who may be either sick or healthy.

In planning a therapeutic trial of any of the first three types, if a control is necessary, what kind should be selected in general practice? There are four possibilities: (i) the action of the drug in question may be compared with that of one or more other accredited remedies already in common use for that particular disability (e.g., potassium iodide or tincture of stramonium in asthma; sulpha drugs or penicillin in measles); (ii) the action of the test substance may be compared with that of one or more *innocuous* substances or mixtures, whose accepted use in general practice lies as much in their psychological as in their chemical value, in so far as they have been found to allay any apprehension by the patient that nothing could be done for his condition (placebo); (iii) the action of the test substance may be compared with that of one or more “inert” substances; strictly speaking these should have been proved already to have absolutely no positive or negative action on the course of the disability for which they are given, but more commonly the phrase is used to include substances which are *expected to be inert* but whose action in this disability has never been put to a critical therapeutic trial. Where an “inert” substance is made to resemble in presentation the form of the test substance, the use of the phrase “dummy” tablet (mixture, capsule, etc.) is not only justified but more explicit, since it draws attention to the purpose of the counterfeit, which is to deceive the patient and often also the doctor taking part. (iv) The action of giving the test substance may be compared with that of withholding it. In fact this is what is done in both (ii) and (iii) above, and the reasons for choosing either (ii) or (iii) rather than (iv), or for choosing (iii) rather than (ii) needs to be examined closely.

In trials of the fourth, fifth, and sixth types mentioned above—namely, with unfamiliar drugs—if the general practitioner is working “blind” or where the consent of the patient is sought, legal and ethical as well as statistical difficulties may arise for the investigator. For example, it is the duty of a doctor to act only in what he considers to be the best interest of each individual patient. He ought not, in relation to any particular patient, to regulate his treatment according to any other consideration unless with the express knowledge and approval of his patient. An “infant” cannot and his parents may not give consent for any treatment not directed towards his own benefit; he may not be experimented on for the sake of others. Furthermore, it is dangerous to rely merely on the knowledge and approval of the patient, because he does not have the necessary medical knowledge to enable him to appreciate in full the considerations involved; the doctor would have to be quite sure that the patient really had a full appreciation of the position. This is particularly important when the toxicity of the trial substance is uncertain or known not to be negligible. Failure to act in accordance with the principles set out above might expose the doctor to risk of legal proceedings, based on a breach of contract or duty, or on assault.

Any general practitioner taking part in the National Health Service has a further duty to carry out his terms of service conscientiously and to the best of his ability. In selecting an inert substance as the only treatment of a patient seeking medical advice, the legal requirements of the terms of service under the N.H.S. would seldom, if ever, be met.

In dealing with new drugs a clear distinction should be drawn between a general practitioner's use of an unfamiliar drug on the advice of a consultant, as the appropriate and necessary remedy for a particular patient, and his use (either alone or with others) of a drug with which he is unfamiliar or uncertain, as part of a clinical trial on patients, whether volunteers or not. It is one thing to use a familiar drug as a new line of treatment in some particular condition; it is quite another to experiment with new drugs on our patients as though they were guinea-pigs.

Finally a word about “blind trials,” in which the person observing the response to treatment is intentionally kept in ignorance of whether a particular patient is receiving the trial drug or a control. Such an observer is really acting

as an assistant to those who planned the trial. A family doctor who is in general practice as a principal could ethically be in some difficulties about taking part in such a trial, unless he had a share in its design, since he is personally responsible to his patients for the treatment which he prescribes for them. An assistant, however, can act as observer for his principal, and a single-handed practitioner can plan his own “blind” trials, if he in turn seeks help from a nurse or relative as observers, or in appropriate cases from the patient himself. This applies particularly to trials in which treatment is given for the relief of symptoms, such as pain, sleeplessness, worry, or anxiety, rather than for the alteration of physical signs which the doctor himself can observe. For all these reasons I agree with Dr. Leak, without regret, “that it would be wrong for the B.N.F. to include a dummy tablet. . . .”—I am, etc.,

Peaslake.

G. I. WATSON.

Congenital Dislocation of the Hip

SIR,—In your annotation on congenital dislocation of the hip (*Journal*, July 5, p. 38), you say that most cases of the disease in this country are diagnosed at the age of 1 or 2 years. A recent answer in “Any Questions?” referred to asymmetry of the skin creases as a useful sign.¹ Much earlier diagnosis could and should be made. Professor Marino Ortolani,² director of the Instituto Provinciale per l'Infanzia, Ferrar, has described a sign which can be elicited in newborn babies which is obviously not sufficiently well known in this country. First the thigh is flexed on the abdomen; then pressure is exerted along the long axis of the femur. The femur is then abducted. As the head of the femur rolls over the rim of the acetabulum there is a click, which may be felt or even heard.

From now on all newborn babies should be subjected to this manoeuvre at their first examination. In this way cases will be detected early, and much suffering prevented.—I am, etc.,

Bath.

H. R. E. WALLIS.

REFERENCES

- ¹ *Brit. med. J.*, 1958, 1, 1432.
- ² *Pediatrics (Napoli)*, 1937, 45, 129.

Aetiology of Cancer

SIR,—The highly interesting lecture on the aetiology of cancer by Dr. Ludwik Gross (*Journal*, July 5, p. 1) prompts me to draw some conclusions from the viewpoint of a clinician. The principle of “vertical transmission of potentially pathogenic agents” remaining harmless to their hosts often for generations and activated into cancer-producing pathogens only occasionally by “obscure reasons,” “intrinsic or extrinsic stimuli,” necessitates the following unavoidable logical conclusion as to human cancer aetiology. The latent harmless pathogenic agent must be ubiquitous in humans, since there is hardly any human family without a case of malignancy in the last four or more generations. In other words, every human being would be potentially susceptible to malignancy and the real enigma of cancer aetiology would remain unsolved because “the obscure reasons” for activation of the cancerogenic virus would be completely unknown in the great majority of human cancers.

We must taken exception to Dr. Gross's statement that genetic factors as contrasted with “vertical transmission” are “transmitted in an orderly and foreseeable manner.” This is not the case where polygenic (multifactorial) heredity is involved.¹ As to inheritability of predisposition to malignancy, it can be foreseen as little as physical resemblance of a child *in statu nascendi* to any of his ancestors. Thus the genetic concept of cancer aetiology does not seem to me to be overthrown by the concept of “vertical transmission” of a virus. The question of similarity of a gene with a virus, however, is another matter.—I am, etc.,

Los Angeles, Calif.

JULIUS BAUER.

REFERENCE

- ¹ Bauer, J., *The Person Behind the Disease*, 1956. Grune and Stratton, New York.