became deficient or, as seems more likely, the suppression of circulating antibody was a consequence of the increasing tumour mass. The Chester Beatty team have now confirmed that cytotoxic autoantibodies can be provoked in melanoma patients lacking them, by immunization with the irradiated cells of their own excised tumours. The immunization procedure, employing multiple inoculation sites, apparently bypasses the regional immunological unresponsiveness that is already present.

It is disappointing but not really surprising that immunization had no detectable effect on the clinical course of the disease. Circulating cytotoxic antibodies would be expected to be effective only against cells to which there was good physical access—such as those in the bloodstream, which might otherwise cause distant metastases. Moreover, the artificially provoked serum antibody persisted for only one to two weeks, with a tendency toward the longer time in patients with little residual disease. Perhaps antibody was absorbed by the residual tumour, which was itself ineffective in stimulating further antibody formation because of regional immunological insufficiency.

It may now be asked how can immunotherapy provide an effective anti-cancer weapon. Doubtless the rejection of solid tumours will be effected only by specifically sensitized lymphocytes and when the circumstances favour the host—such as minimal tumour mass together with a maximal immunological response. The latter can apparently be influenced by artificial immunization, and there is promise that an effective supplementary weapon will be provided by the extracorporeal culture of immune lymphocytes now going on at Roswell Park Memorial Institute of cancer research. Methods, whether surgical or chemical, of radical reduction of melanoma mass with minimal interference with immunological efficiency should be energetically pursued.

Recurrent Infection and Deficiency of Complement

In laboratory investigations the various components of haemolytic complement have been shown to possess several activities of possible value in the defence against invasion by micro-organisms. These activities include lysis, the generation of a factor chemotactic for polymorphonuclear cells[1], and of another factor rendering micro-organisms susceptible to phagocytosis by these same cells.[2] Despite these activities the actual participation of complement in antimicrobial defence has been extremely difficult to prove. This is partly because of the complexity of complement itself and partly because the recognition of deficiency of the individual components, now known to number at least nine if subcomponents are excluded, has only recently become possible. The simultaneous publication of two cases[3 4] of recurrent infection attributed to two distinct deficiencies of complement may serve to direct attention to the important protective role of complement components.

The first case was a young man with Klinefelter's syndrome who had recurrent pyogenic infections necessitating admission to hospital on 28 occasions between infancy and the age of 25. No deficiency of cellular immunity or of any of the immunoglobulins was detected, and the humoral response to tetanus toxoid was normal. But overall complement activity, as measured by haemolysis of sensitized cells, was only about one-third the normal, though of the first six components only C3 was deficient. As measured immunologically it amounted to only some 4-8% of the normal level apparently because of rapid conversion to the inactive form C3b. Since the full activity of this patient's complement could not be restored by addition of pure C3 but only by whole serum, it was concluded that the underlying fault was the absence of a normal inhibitor of a protease which specifically inactivates C3 by conversion to C3b. The addition of normal serum but not of pure C3 provides the missing inactivator of this protease.

The second patient was a baby girl 4 months old with severe eczematoid dermatitis and repeated infections with Gram-negative bacteria and staphylococci. Unlike the first case there was a familial abnormality in the antimicrobial defences, as shown by the considerable impairment of the normal ability of the serum to enhance the phagocytic activity of polymorphonuclear cells. This defect was a functional abnormality of C5, which could be readily made good by the addition of normal serum, purified C5, or normal mouse serum, but not serum from mice congenitally deficient in C5.

There can be little doubt that similar cases will soon be recognized in increasing numbers and it is important that they should be, since transfusion with fresh serum is a simple and efficient method of treatment.

Folate and Vitamin B_{12} in Epilepsy

Megaloblastic anaemia developing in patients who had been on anticonvulsants was described in 1954.[1 2] C. F. Hawkins and M. J. Meynell[2] found that their first patient failed to respond to vitamin B_{12} but did respond well to folic acid. Later they found confirmatory evidence of this blood change in a series of epileptics in institutions,[3] though frank anaemia was not common.

It has also been known for many years that some epileptics, children in particular, who require prolonged and sometimes heavy dosage with anticonvulsant drugs may show a steady deterioration of mental performance. While this may start in a child whose brain is already damaged, it may also occur in children previously of good intelligence. It is by no means uncommon in hospitals caring for the chronic epileptic. The importance of a low serum folate in these patients was shown by J. S. Malpas and his colleagues,[4] and their mental state could be improved by treatment with folic acid.[5] Unfortunately this resulted in an increase in fits, and at the same time the vitamin B_{12} level in the serum fell. Giving vitamin B_{12} then diminished the fits, and F. B. Gibberd confirmed[6] that if folic acid and vitamin B_{12} were given together to these patients the fits did not increase. Why anticonvulsants act in this way is not clear.[7]

[1] Ward, P. A., Cochrane, C. G. and Müller-Eberhard, H. G., *Immunology* 1966, **11**, 141.
[2] Johnston, R. B., jun., Klempere, M. R., Alper, C. A., and Rosen, F. S., *Journal of Experimental Medicine*, 1969, **129**, 1275.
[3] Alper, C. A., Abramson, N., Johnston, R. B., jun., Jandl, J. H., and Rosen, F. S., *New England Journal of Medicine*, 1970, **282**, 349.
[4] Miller, M. E., and Nilsson, U. R., *New England Journal of Medicine*, 1970, **282**, 354.
[1] Badenoch, J., *Proceedings of the Royal Society of Medicine*, 1954, **47**, 426.
[2] Hawkins, C. F., and Meynell, M. J., *Lancet*, 1954, **2**, 737.
[3] Hawkins, C. F., and Meynell, M. J., *Quarterly Journal of Medicine*, 1958, **27**, 45.
[4] Malpas, J. S., Spray, G. H., and Witts, L. J., *British Medical Journal*, 1966, **1**, 955.
[5] Reynolds, E. H., *Lancet*, 1967, **1**, 1086.
[6] Gibberd, F. B., *British Medical Journal*, 1969, **4**, 281.
[7] Baugh, C. M., and Krumdieck, C. L., *Lancet*, 1969, **2**, 519.

The level of cerebrospinal-fluid folate is normally three times that of the blood and probably more closely reflects the level in the nervous system; if it falls below blood level then retardation and dementia may become severe.

Dr. C. Neubauer has now studied the problem in 50 epileptic children, all of whom had been on anticonvulsants for a long time, and his findings are published at page 000 of this issue of the *B.M.J.* They confirm the previous workers' results and suggest that combinations of drugs are worse than single drug treatment; perhaps patients on primidone and phenobarbitone are slightly more liable to show these changes than others. Treatment with folic acid and vitamin B_{12} together can have a very beneficial effect on mental state without increasing the number of fits. On 10-15 mg. of folic acid daily at first (with the folate levels being watched) it required 4-6 weeks for these patients' levels to return to normal, and they could then be maintained by 5 mg. weekly. The dosage of vitamin B_{12} varied from 1,000 microgrammes weekly to a maintenance dose of 250 microgrammes monthly, according to the serum levels. Thirty-one of the children showed encouraging improvement, in view of the fact that many were severely retarded to begin with, and incontinence became controlled, while 20 had a reduction in their fits.

These investigations were carried out in a special community, and it is always difficult to decide whether a chronic epileptic's mental deterioration, if it occurs, is due to the continued epileptic activity, pre-existing cerebral disease, or the treatment. This study emphasizes, like those carried out earlier, the need for reliable estimations of folate and vitamin B_{12} in patients on prolonged anticonvulsant therapy to detect any ill-effects of treatment. If a grossly defective child can be made more manageable, one who was able to attend a normal school but whose performance was showing signs of falling off might be improved sufficiently to maintain him at that school, which after all should be one of the primary aims of the management of an epileptic child. It is clear that both folic acid and vitamin B_{12} need to be administered, and that dosage should not be determined on an empirical basis but be governed by a careful study of the blood levels of these substances.

The mechanism of the antagonism that exists between vitamin B_{12} and folic acid has been a matter of interest since folic acid first came to be used and it was found that a patient with pernicious anaemia could be precipitated into subacute combined degeneration by its use alone. It is of particular interest that in so different a disorder as epilepsy this antagonism is still of great importance.

Muscular Dystrophy in Young Girls

Duchenne type muscular dystrophy, being inherited as an x-linked or sex-linked recessive factor, is characteristically a condition limited to the male sex. Nevertheless, there have been persistent reports over the past 20 years that a condition clinically identical with, or at least very similar to, typical muscular dystrophy of this variety may occasionally affect girls.[1-5] Most authors are, however, agreed that when muscular dystrophy does occur in young girls the clinical pattern usually shows certain striking differences from that of the typical disorder in males, and the fact that sibships have been described including both affected male and female individuals has supported the suggestion that there may be an uncommon form of muscular dystrophy inherited by an autosomal recessive mechanism which resembles the Duchenne type and which occasionally affects girls.[4-8] Typical Duchenne dystrophy may occur in chromatin-negative individuals of female morphology who have an XO chromosome constitution, but only two such cases have yet been reported in the world literature.[9 10] It has also been suggested[11] that manifestations resembling those of Duchenne dystrophy may occur in the female heterozygote or carrier, but when there are any clinical abnormalities in such carrier females the evidence of muscular weakness is relatively mild.[12 13]

In an attempt to clarify this question, A. S. Penn, R. P. Lisak, and L. P. Rowland[14] have recently carried out a careful study of 76 cases of Duchenne type muscular dystrophy seen between 1957 and 1967, all of which were fully investigated by modern techniques. During this same period they saw five girls who for one reason or another might have been considered to be suffering from the same disease. On analysis, however, each of the girls differed in some essential respect; either the age of onset was late, the rate of progression was slower than that of typical Duchenne dystrophy, the serum enzyme pattern was not characteristic, or there was conflicting electromyographic and histological evidence. They also analysed all previous reports of Duchenne type dystrophy occurring in girls. The clinical manifestations in 85 of the reported cases differed from those typically seen in boys with the disease in characteristic form, and there were only 19 in which the clinical manifestations of the disease were essentially similar. In none of the latter cases, however, were there adequate laboratory tests to exclude other possible diagnoses such as spinal muscular atrophy, polymyositis, or chromosomal abnormality. They found no case on record in which an affected girl with all of the features of Duchenne type muscular dystrophy had typically affected male sibs. As they point out, it has become particularly apparent in recent years that pseudomyopathic spinal muscular atrophy (the so-called Kugelberg-Welander syndrome)[15] may be clinically indistinguishable from muscular dystrophy, particularly in the early stages, and can only be identified by modern investigative techniques.

Hence while it is apparent that reports continue to appear of muscular dystrophy, closely resembling the Duchenne type, affecting young girls, the evidence on this matter remains inconclusive. There is no definite evidence that typical severe Duchenne type dystrophy, as seen in boys, has ever yet been confirmed as occurring in the female sex. Thus when a clinical syndrome resembling muscular dystrophy does occur in severe form in a young female patient, it is essential that full investigations, including serum enzyme studies, electromyography, and muscle biopsy should be carried out in

1 Walton, J. N., and Nattrass, F. J., *Brain*, 1954, **77**, 169.
2 Dubowitz, V., *Brain*, 1960, **83**, 432.
3 Walton, J. N., in *Muscular Dystrophy in Man and Animals*, ed. G. H. Bourne and M. N. Golarz, p. 263. Basel, Karger, 1963.
4 Jackson, C. E., and Carey, J. H., *Pediatrics*, 1961, **28**, 77.
5 Johnston, H. A., *Journal of Medical Genetics*, 1964, **1**, 79.
6 Lamy, M., and de Grouchy, J., *Journal de Génétique Humaine*, 1954, **3**, 219.
7 Kloepfer, H. W., and Talley, C., *Annals of Human Genetics*, 1958, **22**, 138.
8 Blyth, H., and Pugh, R. J., *Annals of Human Genetics*, 1959, **23**, 127.
9 Walton, J. N., *Annals of Human Genetics*, 1956, **21**, 40.
10 Ferrier, P., Bamatter, F., and Klein, D., *Journal of Medical Genetics*, 1965, **2**, 38.
11 Murphy, E. G., Thompson, M. W., Corey, P. N. J., and Conen, P. E., in *Muscle*, ed. W. M. Paul, E. E. Daniel, C. M. Kay and G. Monckton, p. 529. Oxford, Pergamon Press, 1965.
12 Emery, A. E. H., *Lancet*, 1963, **1**, 1126.
13 Walton, J. N., *British Medical Journal*, 1964, **1**, 1271.
14 Penn, A. S., Lisak, R. P., and Rowland, L. P., *Neurology (Minneapolis)*, 1970, **20**, 147.
15 Gardner-Medwin, D., Hudgson, P., and Walton, J. N., *Journal of Neurological Sciences*, 1967, **5**, 121.