it is believed that the abnormal demands of pregnancy exceed the available supplies of folic acid, and in many cases the defect is purely a dietary inadequacy which could be prevented by improved social conditions and advice on consumption of suitable foods such as fresh fruit and green vegetables and " marmite," which are all rich in folic acid, together with supplementary therapy if necessary. However, in a significant number of cases the defect appears to be one of intestinal malabsorption. In these circumstances large doses of folic acid by mouth may be effective, but often parenteral therapy is required. In certain cases there may be faulty utilization, possibly due to the presence of folic-acid antagonists or some specific metabolic defect peculiar to pregnancy.

Conclusions

In conclusion it is evident that although abruptio placentae occurs only once in every 100 pregnancies the consequences for the mother may be serious and even fatal; in one year alone 94 bottles of donor blood and plasma were administered to patients with abruptio placentae in the hospital from which this series was drawn. Nearly two-thirds of the infants are born dead or die in the neonatal period. Indeed, the perinatal loss is comparable with that due to major deformities of the central nervous system, and is five times that due to haemolytic disease of the newborn or the hazards of breech delivery. In these circumstances comprehensive prophylactic folic-acid therapy during pregnancy requires serious consideration. It is undoubtedly indicated in those patients who have been shown to run a high risk of abruptio placentae—namely, grand multiparae, patients with anaemia, multiple pregnancies, previous unsuccessful pregnancies, and bad obstetric histories, especially when the latter include abruptio placentae. Whenever possible, such patients should have their folic-acid status assessed at frequent intervals throughout pregnancy, even though they may be receiving oral folic acid prophylactically.

By instituting a programme of this nature it is hoped that future surveys will show a significant reduction in the incidence of this distressing and dangerous accident of pregnancy.

Summary

Abruptio placentae occurs in approximately 1% of pregnancies. A study of 320 cases occurring in approximately 27,000 deliveries reveals the following features: (*a*) pre-eclampsia and essential hypertension do not play a major part in the aetiology of abruptio placentae; (*b*) grand multiparity is a predisposing factor in abruptio placentae; (*c*) affected patients have unsatisfactory obstetric careers in relation to their other pregnancies—premature and undersized babies are particularly common; (*d*) abruptio placentae tends to recur in succeeding pregnancies; and (*e*) a constant relationship between abruptio placentae and folic-acid deficiency is demonstrated—megaloblastic erythropoiesis is found in a high proportion of cases.

The significance of these features is discussed in relation to other theoretical and experimental findings.

Possible preventive measures and their limitations are outlined.

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MULTIPLE SCLEROSIS: THERAPEUTIC TRIALS OF CHLOROQUINE, SOLUBLE ASPIRIN, AND GAMMAGLOBULIN

BY

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In a succession of therapeutic trials previously reported from this department a standard procedure has been evolved which was designed to assess any possible effect of a particular therapeutic procedure on the natural history of multiple sclerosis. Groups of patients in the clinically active stage of the disease were allotted to treatment and control groups by a restricted randomization procedure designed to produce groups roughly comparable in all measurable respects at the beginning of treatment. Disability was scored numerically and function graded by a standard method based on that of Alexander *et al.* (1958). The patients were subjected to periodic re-examination and functional assessment by an observer who was unaware whether the patient was in the treatment or the control group. By this method intrathecal tuberculin (Miller *et al.*, 1961c, 1962), prednisolone (Miller *et al.*, 1961a), and tolbutamide (Foster *et al.*, 1961) have been shown to exert no discernible effect on the course of the disease over a period of observation, which varied from a maximum of three years in the first trial to three months in the last.

The present paper reports the results of two separate studies carried out on similar lines. The first describes the respective effects of chloroquine, soluble aspirin, and dummy tablets on the course of multiple sclerosis over a period of 14 months, and the second the effects of repeated injections of gammaglobulin and saline respectively on two small groups of patients over a period of six months. The results of both trials were essentially negative, but they are reported together because they show certain

similarities which illustrate anomalies that may arise in the course of studies which appear extremely simple.

Chloroquine and Soluble Aspirin

The therapeutic trial of chloroquine originated in a suggestion by Keil (1960). In a stimulating presentation of the similarities between multiple sclerosis and the systemic collagenoses such as disseminated lupus erythematosus and rheumatoid arthritis Keil suggested that since chloroquine seemed to favour the resolution of mesodermal proliferative inflammatory changes in these diseases it deserved a trial in multiple sclerosis, in which disease comparable alterations occur in the functionally similar though predominantly ectodermal supporting tissues of the nervous system. In a previous paper (Miller *et al.*, 1961a) reporting the negative results of maintenance treatment of multiple sclerosis with prednisolone we also mentioned a possible though very uncertain effect of soluble aspirin in retarding clinical deterioration in this disease. The analogy of the relations between acute disseminated encephalomyelitis and multiple sclerosis with those between acute rheumatism and rheumatoid arthritis, serum sickness and polyarteritis nodosa, and acute and chronic glomerulonephritis has obvious attractions, and the trial reported below was designed both to test Keil's suggestion about chloroquine and to check our equivocal observations on salicylate by a further trial.

Method

Fifty-seven patients with established multiple sclerosis were admitted to the trial. All were selected from a concurrent epidemiological study in North-eastern England. Patients belonged to the functional grades II—IV described by Miller *et al.* (1961a). We used 250-mg. tablets of chloroquine, together with dummy tablets of identical size and shape, and tablets of soluble calcium aspirin ("solprin"). The daily dosage of chloroquine was 250 mg., a larger dose being considered inadvisable in view of the reported cases of corneal opacity and retinal degeneration following its prolonged use (Hobbs *et al.*, 1959). One dummy tablet a day was taken by each patient in the control group, and the patients allocated to the aspirin group took three tablets three times a day—nine tablets (54 gr.; 3.5 g.) a day.

Nineteen patients were allocated to each of three groups, using a scheme of randomization which guaranteed approximately equal numbers of each age and sex and also allowed for the severity of the disease. Seven patients withdrew from treatment during the course of the trial; a further patient died from unrelated disease. Of the seven, three were already unavailable for assessment after six months. One had abandoned medication because of a skin rash, one had moved from the area, and a third had been subjected to thalamotomy for relief of severe intention tremor. After 14 months there remained 49 patients; these were re-examined by the same observer, who had no knowledge of the patients' treatment group.

Table I outlines the composition of the three groups with regard to mean age, mean duration of disease, and average severity (Alexander *et al.*, 1958). No patient was admitted to the trial who had been included in previous therapeutic observations or whose previous treatment had been more than symptomatic. Each patient was assessed at successive examinations according to a modification of the numerical scoring system of Alexander *et al.* (1958).

After six months one of the chloroquine and two of the solprin cases were not available for examination. At the end of the trial, after 14 months' treatment, the remaining patients were re-examined, and the final assessment was carried out on 16 patients on dummy tablets, 17 on solprin, and all of the 16 on chloroquine.

TABLE I.—*Comparison of Groups Before Treatment* (52 *Patients*)

	Treatment Group		
	Dummy	Solprin	Chloroquine
No. of patients	18	18	16
Males	7	9	6
Females	11	9	10
Mean age (years)	40·2	42·2	43·2
,, ,, at onset	28·1	33·8	34·7
Average severity (Alexander)	185	202	192
Functional grade: I	2	0	0
Functional grade: II	2	7	3
Functional grade: III	8	8	10
Functional grade: IV	6	3	3

Results

The average changes in Alexander score are given in Table II. It will be seen that, except for the 14-months assessment of the chloroquine group, the general trend during this period had been towards slight clinical improvement.

TABLE II.—*Comparison of Groups After Treatment*

	Treatment Group		
	Dummy	Solprin	Chloroquine
Average change in Alexander score:			
From onset to 6 months	−24·6	−15·1	−6·4
,, ,, ,, 14 ,,	−12·6	−3·1	+13·3

A negative difference indicates an improvement.

After six months the patients on dummy tablets had improved by an average of 25 points, solprin patients by 15 points, and those on chloroquine by 6 points. Analysis of variance shows that there is no significant difference between these three means ($F=0.90$, d.f.$=2, 44$, $P>50\%$).

At 14 months the results were slightly worse than at six months for each of the treatments. Patients on dummy tablets were then only 13 points better than originally, on solprin 3 points better, and on chloroquine 13 points worse. Again, analysis of variance shows no significant difference between the three ($F=1.93$, d.f.$=2,46$, $P=15\%$).

The individual figures in Table II may also be considered in their own right. On this basis, the dummy and solprin patients had improved significantly at six months, and the chloroquine patients had deteriorated significantly by 14 months.

From these results it appears that chloroquine in the dose administered had not exerted any favourable influence on the course of established multiple sclerosis and that soluble aspirin was similarly without effect.

The importance of using stringent methods of control in therapeutic observations on multiple sclerosis is underlined by the record of one patient who had been receiving dummy tablets: his Alexander score improved from 199 initially to seven on re-examination after six and 14 months of "treatment."

Gammaglobulin

Blood transfusion has been employed as a form of treatment in multiple sclerosis by a number of European and some American physicians (Alexander *et al.*, 1961). Various hypotheses have been put forward to explain the

apparent benefit conferred by this method in certain hands. These hypotheses have included the transfer of passive immunity against an unspecified infective agent; the correction of a putative enzymatic deficiency; and "filling of the vascular tree" to improve blood-supply to those poorly vascularized regions of the nervous system where the lesions of multiple sclerosis are often to be found.

Alexander *et al.* (1961) have made valiant efforts to measure the effect of transfusion on the clinical course of the disease as against that observed in matched controls. These authors have no doubt about the benefit yielded by transfusion, which they find especially valuable in patients who have failed to make the recovery anticipated after a severe acute exacerbation. Unfortunately their observations are something short of impeccable. The complexity with which their cases are grouped puts a great weight of calculation and interpretation on a modest amount of clinical material. Their report affords no information on the way in which cases were allotted to treatment and control groups, nor about the actual management employed in control cases. They do not make clear whether or not the assessor knew if the patient examined was in the treatment or the control group. We ourselves must admit to considerable reservations concerning the evidence for any specific effect of blood transfusion on the clinical course of multiple sclerosis. When we have employed it, sporadically and usually in desperation, we have observed benefit only in patients debilitated and discouraged by chronic disablement, and we have not been impressed by any significant change in physical signs or objective disability.

It was partly a reluctance to embark on a controlled therapeutic trial of blood transfusion in multiple sclerosis which led us to consider the possibility of treating the disease with pooled human gammaglobulin. If transfusion indeed exercised a beneficial effect on the course of the disease it would seem most likely to do so by stimulating the patient's immunity to a hypothetical infective factor. There is nothing inherently improbable in the hypothesis that the disease may be due to the recrudescent activity of a ubiquitous virus, possibly coupled with a failure of the normal immune responses which might prevent the unaffected majority of the population from developing the clinical disease. If this were so, normal blood might contain such antibodies in effective amounts and in all probability they would be present in the gammaglobulin fraction of the serum. Unfortunately gammaglobulin was in short supply and our trial was necessarily limited both in numbers and in duration.

Method

Twenty-one female patients were admitted to this trial. These were allocated to gammaglobulin or dummy groups by a restricted randomization procedure designed to produce groups roughly comparable in age and Alexander score at the beginning of treatment. In the gammaglobulin cases 5 ml. (500 mg.) of pooled human gammaglobulin was injected into the buttock at fortnightly intervals, and similar injections of normal sterile saline were administered to patients in the control group. Three patients failed to complete the course—one in the gammaglobulin and two in the control group. Two defected after six and seven injections respectively because they failed to observe any improvement, and one because of the onset of pregnancy at a similarly early stage in treatment.

Table III shows the status of the two groups of nine patients who completed the course of treatment. These are shown to be very similar in age, duration of symptoms, and severity of the disease as measured by the Alexander score.

TABLE III.—*Comparison of Groups Before Treatment* (18 *Patients*)

		Gammaglobulin	Dummy
Age (years):	Average	39·0	40·4
	20–29	—	1
	30–39	5	3
	40–49	3	4
	50–59	1	1
Duration of symptoms (years):	Average	7·9	8·2
	0–4	1	2
	5–9	5	5
	10 and over	3	2
Alexander score:	Average	271	260
	100–199	4	2
	200–299	4	4
	300+	1	3

Results

The Alexander scores at the termination of treatment are shown in Table IV. The gammaglobulin patients had improved by an average of 19 Alexander points and those on saline injections by 16. The difference is of neither statistical nor clinical importance. The gammaglobulin series included one patient who improved by 198 points (from 278 to 80) during the six months' trial, but such isolated instances are quite commonly encountered in patients on dummy treatment. If this patient is excluded from the statistical assessment the remaining eight patients on gammaglobulin showed an average deterioration of 4 points, which again would not be significantly different from the control figure.

TABLE IV.—*Comparison of Groups After Treatment*

Alexander Score	Gammaglobulin	Dummy
Average score	252	244
Change from initial score after six months' treatment	−19±28·0	−16±8·8
Difference in favour of gammaglobulin	3±29·4	

A negative difference indicates an improvement.

In view of the unpredictable clinical course of multiple sclerosis and the small size and duration of the trial, a difference in the mean Alexander scores in the two groups of about 60 points would have been necessary to demonstrate a significant influence of the therapeutic substance on the natural course of the disease. All that can be said of this present small series is that five of the nine patients on gammaglobulin showed some (small and probably insignificant) improvement during the trial, but so did seven of the nine controls.

Discussion

Each of these trials was designed to measure any possible effect of the therapeutic substance concerned on the spontaneous deterioration which is the anticipated clinical course of untreated multiple sclerosis during an adequate period of observation. Since in each instance no significant deterioration was observed in the control group of patients during the period of the trial—and since in fact there was even some degree of improvement—the initial aim of the trials has not been fulfilled.

What these trials have shown is that chloroquine, soluble aspirin, and gammaglobulin given in the dosages and under the conditions described and over the respective periods involved exerted no significant effect on the course of the disease as compared with dummy treatment. Had any of these remedies possessed any positive therapeutic value in multiple sclerosis the tests would probably have revealed it. From the statistician's point of view the

comparisons between the treatments are unbiased and independent of any general trend in scores, which applies to all treatment groups during the trial. From the clinician's viewpoint the results are bound to be regarded as somewhat less satisfactory.

It is obvious that, taken as a whole, the anticipated clinical course of multiple sclerosis is not one of clinical improvement, and from this point of view the standard of measurement we have employed in these trials has failed us. In seeking the reasons for these anomalous results the short duration of the gammaglobulin trial imposed on us by the limited availability of the substance should be noted. The tonic effect of any new form of treatment in a chronic disease is notorious, and six months might well not be long enough for such a non-specific psychological effect to be dissipated by subsequent disappointment.

The clinical examinations in the two trials were carried out by two different observers, but the observer was the same throughout each trial, and it is improbable that the mean improvement observed in treated and control patients in each trial was due to an overall simultaneous change in the standard of scoring of both observers. Again, a placebo effect seems to be the likeliest explanation: in a chronic and fluctuating disease, where the subjective component of the patient's disablement represents a variable moiety of the total incapacity, the detailed interest and attention shown and the rituals attendant on taking part in such a trial often have a striking effect on the patient's attitude towards his disability. Such a patient not infrequently carried out activities previously thought to be quite beyond his capacity. We believe that such factors probably account for the results described above.

Most of our previous trials have covered longer periods of time, when the inexorable progression of the organic process inevitably comes to outweigh the subjective effects of early optimism. In one such trial (Miller *et al.*, 1961a) re-examination after six months did fail to reveal any significant deterioration in both control and treated cases, though we have not previously encountered the slight clinical improvement observed here. It should also be mentioned that the doctors and nurses engaged in treating and examining the patients in the present study were an entirely different group from those concerned in previous trials and may well have exuded more optimism. The therapeutic effect of suggestive measures in chronic disease is the basis of a great deal of unorthodox treatment in these disorders, and it is unfortunate that our observations could be used to furnish ammunition for the view that at the present time—possibly with the solitary exception of corticotrophin in acute episodes of the disease (Miller *et al.*, 1961b)—treatment with inert substances accompanied by suggestion has at least as much to offer as any of the more rational lines of therapy which we have tried during the past few years.

Summary

Two separate controlled therapeutic trials are reported. The first, employing 57 patients, was designed to measure the effects of dosage with chloroquine (250 mg. daily) and also with soluble calcium aspirin (54 g. (3.5 g.) daily) on the clinical course of multiple sclerosis over a period of 14 months. The second, employing 21 female patients, was designed to measure the effect of 500 mg. of gammaglobulin, given intramuscularly at fortnightly intervals, on the course of the disease during a six-months period. Disability was scored numerically and clinical examinations were carried out by an observer unaware of the patient's treatment group. In the dosages and over the respective periods involved none of these three substances could be shown to influence the clinical course of the disease. The only patients who showed assessable deterioration during these two observations were those on chloroquine, who deteriorated by 13.3 points over a 14-months period.

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MINERAL METABOLISM IN MELANCHOLIA

BY

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This paper describes changes in the distribution of sodium between cells and the extracellular space in depressive illness. The work is a sequel to our previous investigations, which suggested that there may be important electrolyte abnormalities in this condition.

Physiological research has established the fundamental importance of electrolytes in the functioning of the cell. According to the ionic hypothesis the generation and propagation of impulses in neurones and other excitable tissues is dependent on the distribution of sodium, potassium, and other ions between the cell and its surrounding medium. The availability of radioactive isotopes of these ions has given an added impetus to research in this field, and great interest has been focused on sodium and its transport across cell membranes. These vital processes can be studied *in vivo* by applying radioisotope techniques to clinical investigations.

Aspects of sodium metabolism have been studied by measuring the mass of sodium in the body ("exchangeable sodium") which will mix or "exchange" with a tracer dose of radioactive sodium. An increasing amount of body sodium exchanges with the isotope over several days, and measurements are usually taken 24 hours after giving the isotope ("24-hour exchangeable sodium") or after allowing full equilibration of the isotope ("total exchangeable sodium"). The total exchangeable sodium is about 20% less than the body content of sodium and about 10% more than the 24-hour exchangeable sodium in normal