THE TREATMENT OF GENERAL PARALYSIS BY MALARIA.

By THOMAS TENNENT, M.B.Glas.

Assistant Medical Officer, Maudsley Hospital.

It has long been regarded that the outlook in general paralysis is most unfavourable, and that it is one of the most fatal diseases affecting the human race. Until recently all efforts to treat this condition proved worthless, and a fatal termination within a few years was the inevitable outcome. Remissions throughout the course of the illness were recognized, but any claim of recovery aroused, in the minds of most, grave doubts as to the diagnosis. Fortunately this state of affairs has changed and remissions may now be induced by prompt and appropriate treatment.

The first clinical account of a case of general paralysis was recorded in 1798 by Haslam, who was then Apothecary of Bethlem Hospital. It was not, however, until 1822 that the condition was recognized, by a French psychiatrist named Bayle, as a disease entirely based upon a known pathology. His description of the pathological changes and of the clinical symptoms holds good in its essentials to-day.

From this time until the discovery of the true nature of general paralysis many factors were elaborated to account for its ætiology, and equally numerous and varied were the remedies suggested. The latter included such diverse methods as venesection, cautery to the head and spine, baths of varying temperature, purgatives and electricity. Iron, potassium bromide, quinine, silver nitrate and digitalis were the more prominent drugs advocated.

These methods of treatment held prominence at various stages and, until a better understanding of the ætiology was obtained, little headway from the therapeutic angle
was made. In 1857 the relationship between general paralysis and syphilis was stressed by Esmarck and Jessen, who reported three cases of syphilis followed by general paralysis. Thereafter there developed a controversy as to the nature of the causation which lasted over fifty years, and was only settled by the researches of Wassermann and Noguchi.

Meantime treatment had progressed chiefly along two channels, the specific and non-specific forms of therapy. It is with the chief variety of the latter that I propose to deal to-day, namely, the treatment by the induction of malarial fever.

The beneficial effect of fever in the psychoses generally had been recognized and observed since the days of Hippocrates and Galen. Many centuries later Pinel elaborated among the conditions tending to produce a "permanency of cure" a quartan fever. Clouston, a little over forty years ago, wrote: "I believe some day we shall hit on a mode of producing a local inflammation or manageable septic blood-poisoning by which we shall cut short or cure attacks of acute mania." This observation then, that the onset of a febrile illness during a psychosis frequently resulted in an improvement in the mental state, suggested to Wagner von Jauregg, in 1887, the possibility of imitating this experiment of nature for the cure of the psychosis. At that time he mentioned malaria as one of the diseases suitable for such experimentation. He did not, however, employ this method then, but began to induce fever by injections of Koch's tuberculin. In many cases, however, sooner or later the disease recurred, and re-inoculation then proved of little value. Consequently he endeavoured to find a means which would produce better and more lasting results, and this led to the employment of typhus and later typhoid vaccine. In the course of these experiments he noted that the most complete and lasting remissions were obtained in patients in whom, during the course of treatment, an infectious disease such as pneumonia had set in, and it suggested to him that treatment might be more effective still if directly produced by infectious disease.

Other two observations were reported meantime bearing on this point and are worthy of note.

(1) Bercovitz pointed out that neurosyphilis was extremely rare in certain areas of China, although syphilis was extremely common; malaria in these districts was endemic.

(2) In 1913 Pilcz and Mattauschek analysed the case histories of over four thousand officers and men of the Austrian army who had become infected with syphilis. They pointed out that those who during their first year after infection had developed an acute febrile illness such as pneumonia or erysipelas did not later develop neurosyphilis. On the other hand, practically without exception, those who developed neurosyphilis had not suffered from an acute febrile illness during the first year after infection by syphilis. Fortified by these observations von Jauregg, in 1917, thirty years after his original suggestions, inoculated his first series of nine cases of general paralysis with malaria, from a soldier who had not been treated with any quinine. Since then several thousands have been so treated.

**Technique.**

The patient may be inoculated by either of two methods, namely, by mosquito bite, or by blood inoculation.

If the former method is adopted, then female mosquitoes of the anopheles group are employed and are allowed to feed on the patients. Such mosquitoes are readily obtainable through the Ministry of Health. They are taken to the bedside in a glass container, the top of which is covered with muslin. The glass vessel is inverted over the area of skin selected and the mosquitoes allowed to bite. It may be, however, that the mosquito does not choose to feed at
THE TREATMENT OF GENERAL PARALYSIS BY MALARIA

this moment, and so further attempts may be necessary.

The other method, by blood inoculation, has generally proved to be more advantageous; 2 to 5 c.c. of blood are taken from a patient either immediately before or during a febrile attack. If the inoculation is done in hospital, or in such circumstances that the two patients may be brought together, then the blood may be transferred direct. If, however, the blood has to be transported, then clotting must be prevented. This may be accomplished by adding an equal quantity of 5 per cent. sodium citrate. Successful results are obtained if the blood is simply debrinated. The blood is transferred immediately from the syringe into a sterile test tube, and stirred briskly with a sterile glass rod. It should be stirred continuously for twelve minutes, at the end of which period the fibrin is usually found collected along the rod.

The actual inoculation may be given subcutaneously, intramuscularly or intravenously. The site usually selected for subcutaneous inoculation is that between the scapulae, but it matters little where the blood is injected. It is desirable to move the needle about under the skin prior to withdrawal, thereby injuring some of the superficial vessels. The intramuscular method does not differ materially from the subcutaneous. Either are useful where it is desired to keep the strain of the parasite alive for the maximum period.

The intravenous method is usually adopted where the saving of time is important. The incubation period is frequently shortened, and in my opinion the results of infection are more dependable. Of course, one must take all precautions in such injections against introducing air or blood-clot which would result in embolus formation.

The causes of failure to develop malaria may result from faulty administration, or may rest in the patient himself.

With regard to the administration, it is important to remember that antiseptics may have a deterrent effect on the inoculation. It is therefore advisable to sterilize instruments, &c., by boiling, but such must be cooled prior to use. The exposure of the parasites to the influence of heat is inadvisable. Rudolf found that they were killed if exposed to a temperature of 120° F. for a period of three minutes. Another cause of failure is the delaying of the inoculation after the blood has been withdrawn. If such a delay is necessary the blood should be kept on ice. It should, of course, be remembered that a few people possess an immunity to malaria which may account for the failure, as also may any antimalarial drugs taken just before or at the time of the inoculation.

The incubation period is a variable factor and usually extends from four to twenty-five days. If the patient's condition otherwise is good, there is no necessity to keep him in bed during the day while the fever is developing. The temperature during the first seven days should be recorded at least twice daily, and thereafter every four hours, until the onset of the fever. This is usually preceded by headache, malaise and the complaint by the patient of feeling out of sorts. He then welcomes bed. During the rigor the temperature should be taken every thirty minutes, and it is not unusual to record temperatures over 105° F. No drugs should be administered to control the pyrexia. Tepid sponging of the patient is advocated if the degree of fever exceeds 105° F.

As to the nature of the fever, this depends largely on the strain of parasite used. As the benign tertian variety is that most frequently employed, one expects the patient to have a rigor every second day. With the passage of the infection through various patients and re-inoculation of some of these, a double infection is frequently obtained, the febrile attacks occurring daily. This allows the patient little time to recover from his attacks and is very exhausting. More recently the quartan variety has been employed, and its use is advocated in
debilitated subjects. Here there is an interval of two days between the rigors, most valuable where the general condition is not very good. Attention at this time should be paid to the condition of the bowels and a look-out kept for retention of urine. Cardiac drugs, such as digitalis, strophanthus or caffeine, are given regularly during the fever. Von Jauregg advocates their administration at the beginning of the rigor and again when the fever reaches its highest peak. Blood-films should be examined at daily intervals throughout the pyrexia. The number of parasites found varies greatly in different subjects. Some have few parasites in a field, and yet are more upset clinically by the fever than others who show numerous parasites. Of great value, however, is a rapid increase in the number of parasites seen in each field, and it should be taken as a warning sign.

If the general condition remains satisfactory the fever is allowed to continue until the patient has had ten rigors. Thereafter it is discontinued by the administration of quinine sulphate or hydrochloride, 10 gr. being given three times a day for a few days. The effect is rapid, the fever subsides and the parasites disappear from the blood.

Attached to this form of treatment there are certain dangers which must be fully appreciated, and for these one must be constantly on the look-out, prepared to abort the fever. A most important indication for stopping the fever is a sudden drop in strength, characterized by apathy and listlessness in the interval between the paroxysms. Cardiac weakness is the frequent cause of death, and shows itself as an irregularity or weakness of the pulse, weakened heart sounds, oedema and pulmonary congestion. An increase in the pulse-rate of over 160 beats a minute, or in the respiratory rate of over 60 a minute should be taken as danger signals. A small quantity of albumin is found in the urine during the fever and need not be regarded seriously unless the amount increases, when it is of great importance. The appearance of jaundice is also an indication for delaying the next paroxysm.

If it is desired to curtail the fever then it may be accomplished by the administration of a small dose of quinine, 3 or 4 gr. of quinine sulphate. This will temporarily arrest the fever. There is no further pyrexia as a rule for at least seven days, and if the patient’s general condition improves during that period the fever may be allowed to continue again. If such is considered inadvisable, further doses of quinine may be administered and the fever stopped altogether.

It should be borne in mind, however, that the best results are usually obtained following a series of ten to twelve pyrexial attacks.

Re-inoculation with malaria is possible in many cases and a further course of fever may be given if no improvement follows the original fever. In some, however, it is impossible to re-inoculate with malaria; immunity develops after one attack. Only rarely are patients immune to the original inoculation, and, as a rule, such patients have been resident in tropical countries during some period of their life. It is claimed for quartan fever that inoculation by this strain is frequently possible after an initial course of fever of the tertian variety.

Recurrence of the fever is rare following upon blood inoculation. It is more frequent after inoculation by mosquito bite and may occur several months after the original fever.

Effect of the Fever.

It is important to remember that mental phenomena may be exhibited during the fever attributable to the malaria. Most frequently this is a state of confusion with hallucinations, usually auditory in type. Delusions, persecutory in nature, sometimes occur and the patient may become restless and excited. As a rule the confused state clears when the fever is discontinued. The more marked physical effects are a marked
anaemia and a distinct loss of weight. The degree of anaemia may be profound. Colonel James has stated that in primary attacks of the naturally acquired disease the loss of red cells may be from 250,000 to over 1 million during a single febrile paroxysm. Improvement in this respect is usually rapid during convalescence, when tonics of iron and arsenic are valuable. With regard to loss of weight, this is as a rule also rapidly gained. This regain of weight is sometimes of prognostic value. It has frequently been found that those who do not regain all or part of the weight lost do not show a marked improvement in their mental state.

The assessment of results obtained following this treatment is complicated by the fact that spontaneous remissions have long been known to occur in the course of the illness. Patients improved and were well enough to be discharged from hospital. Some resumed work and appeared to their friends to have recovered. Their improvement was invariably ascribed to whatever treatment had been given. As a rule, however, their remission was only of short duration, necessitating their re-admission to hospital.

A study of the literature shows that spontaneous remissions occurred in about 10 per cent. of general paralytics. Some record figures slightly above this, others below. The duration of such remissions lasted as a rule a matter of months, and only in a very few cases did they extend into a few years. Meagher has recently made a detailed study of the cases of general paralysis admitted to the English County and Borough Mental Hospitals in 1923 and 1924, and his results are very interesting. He investigated the subsequent histories of all certified cases of general paralysis admitted to these hospitals in that period who had not been treated with malaria. The number of cases so investigated was 1,173. He found that of those there had been discharged from hospital a total of sixty-six patients, or 6 2 per cent. Of these only seventeen were discharged as recovered, forty as relieved and nine as not improved.

Twenty-six of these, between 1924 and 1927, had either died at home or had been re-admitted to hospital, so that only forty patients were alive and not under care in a mental hospital three or four years after they originally came under certificate. Of the total number 1,173, only 157 or 14 per cent. were alive in 1927, and 1,016 were dead. These figures show that long-lasting spontaneous remissions in general paralysis are rare.

He made similar investigations of all cases of general paralysis who had been treated by malaria in the same period. The number of cases so treated was 438. Of these he found that there were living, in 1927, 247 of whom 108 had been discharged from hospital; 191 patients had died in the interval.

It will be seen from these figures that 56 per cent. of the treated cases were alive, whereas only 14 per cent. of untreated cases were alive in 1927. Conclusive evidence is thus furnished that treatment by malaria does extend life.

It is interesting to note the results reported in the first cases of general paralysis treated by malaria. Of the nine cases treated in 1917 by Wagner von Jauregg, three patients have maintained a state of good remission for over a period of ten years. Of twenty-five cases treated between September, 1919, and March, 1920, eighteen were originally discharged enjoying a remission of varying degree, seven of whom had a full remission. In 1928 only one of these seven had relapsed and died. The remaining six were still enjoying a full remission. Thus of the first thirty-four cases treated between 1917 and March, 1920, nine, or 26 per cent., were enjoying a full remission in 1928 after periods varying from eight to eleven years.

Altogether several thousand cases have been submitted to this treatment in all the stages of the disease. A rough analysis of the results shows that one-third of the patients improve sufficiently to leave hospital, one-third show improvement but require to
remain in hospital, and the remaining third die.

The question that now arises is, are there any factors which help to determine the effect of treatment? There are. What appears to be the most important factor is the duration of the illness before treatment. Von Jauregg has stated that improvement may be obtained in 100 per cent. of patients if only early cases are treated. I should like, therefore, at this point to stress the value of a diagnosis while the disease is in its early stages. The type of illness in which the greatest number of remissions occurs is the exalted manic variety. It is quite likely that the fact that such patients come under observation at a much earlier period than those presenting depressive or neurasthenic symptoms partly accounts for this. A similar reason might partly explain the relative greater frequency of remissions among men than women. The age factor has been advanced by some investigators, who state that increase of age is a deterrent factor. This, however, does not appear to be greater than what would be expected at an age when the recuperative powers are not so active as formerly, and I have obtained a full remission in a man over 60 years of age treated within the first month of presenting symptoms.

It is therefore of extreme importance that such cases should come under treatment at the earliest possible moment. Only too frequently, when taking the anamnesis of such patients, one hears from the relatives that they have been complaining for a period of years. The symptoms frequently are very vague. The most frequent early mental phenomena involves changes in character and mood. Irritability, restlessness, memory changes and defective judgment are the earliest features in some; others again become indifferent, apathetic, and desire to be left alone. That such symptoms are not pathognomonic of general paralysis is granted, but their incidence in this condition should always be remembered in the investigation of any indefinite nervous complaint in a patient after 30 years of age. If accompanied by any neurological signs such as inequality, or irregularity in outline of the pupils, fine tremors around the angle of the mouth, or of the fingers or tongue, or any speech defects, a blood Wassermann ought to be done. If this gives a positive result, then examination of the cerebrospinal fluid is essential in the best interests of the patients.

Another point of value is the frequency of the incidence of congestive and convulsive attacks of general paralysis. The onset of such attacks in persons in the forties and fifties is to be remembered and investigations made as to their real nature.

In this connection greater use might be made by general practitioners of the psychiatric out-patient departments now attached to nearly all general hospitals, or the out-patients departments of neurological and psychiatric hospitals. It is recognized that there has been difficulty in obtaining adequate treatment for patients who were not certifiable. It was impossible for such to enter, even as voluntary boarders, any of the rate-aided mental hospitals, had they been willing to do so. This state of affairs may be remedied under the new Mental Treatment Bill now before Parliament. As it is easy for patients who are certifiable to receive proper treatment, we have at the Maudsley Hospital restricted our admission to those cases in the early stages who would not be admitted to a mental hospital. If, however, careful observation is made patients may be treated at home, in nursing homes, or in general hospitals. If treated at home, a day and a night nurse would require to be provided. It is, of course, advisable, and during the summer months essential, to prevent mosquitoes getting in contact with the patients during the fever. This may be done by fixing suitable netting over the windows and door. It may be accomplished more simply by erecting a wooden frame around the bed, which may then be enclosed with suitable gauze netting.

Is it then desirable or expedient to treat
all cases of general paralysis by malaria, whatever the stage of the illness? Most observers are agreed that it is, provided there are no signs of disease which contra-indicate its use, such as renal or cardio-vascular disease. Surprising results are sometimes obtained in those who appear to be advanced cases, and consequently the ultimate outcome is a matter of doubt. It is also important to remember that the rate of improvement following treatment may be very slow, and is only manifested in its full degree many months after the treatment is concluded. As a rule, in advanced cases one can only hope to arrest the disease, and it is a matter of opinion whether the gain to such patients who are transferred to what are regarded in mental hospitals as “good-working dments” is a material one.

**Mechanism of Malarial Therapy.**

The mechanism of malarial therapy remains a matter of conjecture. Various theories have been elaborated but none are satisfactory. It has been suggested that the effect may be a direct result of the high temperature obtained during the fever, which thereby directly destroys the parasites. The degree of fever attained during the course of the illness is very rarely that required experimentally to prevent development of the spirochæte.

That the improvement may be due to metabolic changes with a quickening of metabolism and removal of waste products has been suggested. If this were the real explanation, one might reasonably expect a re-accumulation within the period during which many of the remissions have lasted, and their relapse ere this.

A further theory suggested is that the improvement results from a mobilization of the defensive powers of the body resulting from a vital reaction of the total organism to the infectious disease.

One of the bodily reactions to syphilitic infection is an increase in the mononuclear cell-content of the blood. It is known that in both malaria and relapsing fever, which has also been employed in the treatment of general paralysis, the mononuclears are increased. It has therefore been suggested that this increase may partly account for the benefit which results.

Another theory is that the malarial parasites may act as antigens and give rise to the production of antibodies which may act on the spirochæte. Plaut suggests, on account of this possible biological reaction, that an infecting organism should be employed more closely related to the spirochæte, and consequently he has advocated the use of relapsing fever.

Various other suggestions have been made, but as yet we are ignorant of the true mechanism. One has to assume that there is a destructive or at least a deleterious effect on the spirochætes as a result of malarial therapy, since they are practically never obtained in the brain of those who have improved after this treatment and have later died of an intercurrent disease.

**Other Forms of Pyrexial Treatment Employed.**

The advantages pertaining to treatment by malaria may be summarized as follows:—

(1) Frequent high temperatures are produced; (2) a great majority of people are susceptible to the disease; (3) the rises of temperature recur at short intervals; (4) the disease is readily controlled by quinine.

Unfortunately there are several disadvantages to this form of treatment.

(1) The most important is that the reaction produced in some patients is sometimes very severe and produces a certain mortality. This necessitates a careful examination and selection of cases to be submitted to this form of treatment. In all patients treated there is a severe degree of anæmia due to the destruction of the red cells, and jaundice may develop. (2) The infecting organism cannot be kept alive in culture or in labora-
tory animals, and it must be transmitted by the mosquito or directly from patient to patient. (3) Objection has also been raised to the carrying over from one patient to another of syphilitic blood with the infecting organism. (4) There is also the practical difficulty arising through the fact that some are not susceptible to malaria, and some have only a limited number of paroxysms which then spontaneously cease.

To overcome these difficulties two other methods have been advocated and are worthy of mention. In 1919, Plaut and Steiner introduced the treatment by relapsing fever. They thought that the therapeutic action might be intensified if a micro-organism were employed that was closely allied to the Spirocheta pallida.

This they claimed for the infecting organism of relapsing fever, namely, S. duttoni. In addition, this organism could be kept alive in laboratory animals and the fever was alleged to be less severe than malaria. Moreover, the fever was said to be readily controlled by the administration of arsenic.

This form of treatment was tried at the Maudsley Hospital in 1926. The infecting organism was obtained by Dr. Golla, Director of the Pathological Laboratory, direct from Professor Plaut. The strain could be kept alive in mice, but it required to be carried over from one mouse to another every fourth day. In the inoculation of patients the mouse was killed and a small quantity of blood, 1 to 2 c.c., was removed aseptically from the heart. This was diluted with saline and injected into the patient. As with malaria, inoculations could be performed by either the subcutaneous, intramuscular or intravenous methods. After the fever had developed further inoculations could be made by direct blood inoculation from one patient to another. The incubation period varied from five to seven days. At the onset of the fever the patient complained of headache and general malaise. Thereafter the temperature rapidly rose to 103° F. and 105° F. and was associated with generalized pain throughout the body. The fever lasted about four days, during which time the spirochaetes of relapsing fever were easily found in the blood. At the end of this period the temperature fell by crisis with marked sweating. Thereafter the patient felt more comfortable, his pains subsided, and he began to take nourishment freely again. He improved somewhat until about the sixteenth day, when he had his first relapse with the original symptoms. This was expected to last about three or four days again and subside as before. Such intermissions and relapses should follow one another regularly, and in the ordinary infection as many as from five to eleven are said to occur. Instead of this, however, an irregular temperature developed, which persisted after four days and showed no sign of abating. The patient complained of severe pain throughout the body and the spleen became enlarged. Arsenical compounds were administered, but they did not affect the fever. This inability to control the pyrexia was obviously a great difficulty and consequently this form of treatment was discontinued.

Solomon, on the other hand, could not obtain a sufficiently virulent strain of relapsing fever, and so he commenced the use of rat-bite fever or soduk. This fever has been met with in Japan and has been mentioned in their medical books for many years. It has been recorded occasionally in England, France and the United States. Infection results from the bite of a rat infected with a spirochaete, morsus-muris. The incubation period varies considerably, the average duration being about ten to twelve days. Thereafter at the site of infection a sore develops. This area becomes red and swollen and an ulcer forms which is said to be not unlike a chancre. A lymphangitis occurs from the infected area to the proximal lymph glands, which in turn become enlarged and tender. The temperature now rises and may reach 105° F. or over. It is of the intermittent type and may drop within a few
hours to normal again. An eruption of purplish coloured spots spreads over the body, particularly the trunk, quite similar to those found in the secondary stage of syphilis. The patient feels ill with pains in the muscles and joints. The illness may continue with febrile exacerbations for a period of several months. It is said to respond very quickly to arsphenamine, and the dangers attached to its use are few in number. It has been found that if the intravenous method of inoculation is employed, the occurrence of a primary lesion with lymphangitis is apparently avoided. The advantages claimed are that the organism can be maintained in laboratory animals and consequently they are always available for use. The disease is less exhausting to the patient than malaria. It may be given to patients who are immune to malaria, and it is apparently possible to give it either before or after malaria without modifying the clinical course of either condition. No results are as yet available as to the efficacy of this treatment, and at present malaria remains the safest and most effective form of fever therapy.

The present consensus of opinion, however, is in favour of a combination of non-specific therapy. Von Jauregg begins the specific treatment as soon as the fever is stopped. With the first dose of quinine he gives 0.3 grm. of neosalvarsan, five days later 0.45 grm. is given, and thereafter eight injections of 0.6 grm. are given at intervals of eight days. Varying doses of neosalvarsan, with or without bismuth, are generally recommended to complete the treatment. Personally, I have employed treatment by malaria in combination with tryparsamide, which is an arsenical preparation with an unusually high degree of penetrability. Intravenous injections of 3 grm. are given as soon as a diagnosis is made. The malarial treatment is carried out as already described, and the injections are administered throughout the fever and at weekly intervals thereafter, so long as the serological findings remain positive. By this method a relatively higher proportion of negative serological findings has been obtained, associated with clinical improvement.

In conclusion, I would reiterate that there is no doubt as to the beneficial effects of malarial therapy, and also that such are increased if combined with specific treatment.

A careful physical examination should be carried out prior to submitting patients to this treatment, to exclude the possibility of renal, cardio-vascular or other disease. If there is no evidence of such, then with proper skill and nursing the treatment is not such a serious matter as has sometimes been maintained. The factor of great value is the early diagnosis of such cases, and for this we must look for the greater co-operation of the general practitioner.

THE RÔLE OF HYDROLOGY IN MEDICAL PRACTICE.

POST-GRADUATE LECTURE DELIVERED FEBRUARY 11, 1930.

By MATTHEW B. RAY,

D.S.O., M.D.EDIN.

Senior Physician, The British Red Cross Clinic for Rheumatism; Physician, The St. Marylebone General Dispensary.

(Continued from p. 126.)

VAPOUR BATHS.

The air is charged with water vapour, which has a distinct "thermal" effect on the skin according to the temperature. The vapour bath has been in use from time immemorial, and the ancient method of preparing it was by placing a tub of hot water in a building and throwing hot glowing stones into it. The vapour bath checks evaporation from the surface of the body, in consequence of which heat is retained and the bodily temperature raised.

After a varying period in the "vapour"
The Treatment of General Paralysis by Malaria

Thomas Tennent

Postgrad Med J 1930 5: 129-137
doi: 10.1136/pgmj.5.56.129

Updated information and services can be found at:
http://pmj.bmj.com/content/5/56/129.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article.
Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/