Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Therapeutic Malaria

Volume XV | Friday, February 18, 1944 | Number 16

STAFF MEETING BULLETIN
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Volume XV | Friday, February 18, 1944 | Number 16

INDEX

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
February 21 - 26, 1944

Visitors Welcome

Monday, February 21

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff, Todd Amphitheater, U.H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U.H.

12:30 - 1:30 Pediatrics Seminar; Immunological Studies in Pollinosis; A. V. Stoesser, W-205 U.H.

12:30 - 1:30 Pathology Seminar; The Alloxan Diabetes; Paul Heise, 104 I.A.

4:00 - Preventive Medicine and Public Health Seminar; Influenza Studies; E. R. Rickard, 116 M.H.

Wednesday, February 23

10:30 - 12:00 Otolaryngology Case Studies; Out Patient Ear, Nose and Throat Department; L. R. Boies and Staff.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Hodgkin's Disease with Purpura; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff, Todd Amphitheater, U.H.

12:30 - 1:30 Pharmacology Seminar; Bactericidal Activity of Serum; P. Stansly, 105 M.H.

4:30 - 5:30 Neurophysiology Seminar; The Liberation of Acetylcholine in Sympathetic Ganglia; Dr. Wang, 129 M. H.

Thursday, February 24

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater, U.H.

10:00 - 12:00 Medicine Rounds; C. J. Watson and Staff, East 214 U.H.

12:30 - 1:30 Physiological Chemistry Seminar; Oral and Dental Biochemistry; W. D. Armstrong, 116 M.H.

5:00 - 6:00 Roentgenology Seminar; Pleural Pericardial Cyst; Captain K. K. Fellows, M-515 U.H.

Friday, February 25

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

8:30 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U.H.

11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Bone Repair in Skull Defects; J. Levin and W. T. Peyton, Powell Hall Recreation Room

1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff; Eustis Amphitheater.

1:00 - 2:30 Dermatology and Syphilology; Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U.H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff, Todd Amphitheater, U.H.

Saturday, February 26

9:00 - 10:00 Medicine Case Presentation, C. J. Watson and Staff, Main 515 U.H.

9:15 - 11:30 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler and Staff, Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff, E-214 U.H.

11:30 - 12:30 Anatomy Seminar; Studies on Intravenously Administered Fat; Nylene Eckles, 226 I.A.

II. THERAPEUTIC MALARIA

M. G. Fredricks

Historical Development

Although the beneficial action of malaria in epilepsy was recognized by Hippocrates, to Wagner Jauregg of Vienna goes the credit for the addition of therapeutic (or induced) malaria to present day therapeusis. In 1887 Wagner Jauregg observed the influence of intercurrent febrile diseases upon the course of psychoses. To produce comparable fevers he tried Koch's Old Tuberculin in the treatment of general paresis, and reported favorably on the method in 1909. He next tried typhoid vaccine, but concluded that the presence of an infectious disease was needed for best results, and in 1917 began systematically to innoculate paretics with malaria. The favorable results achieved by Wagner Jauregg and later others lead to extensive use of induced malaria. Many other methods of producing fevers have since been tried. Innoculation with relapsing fever and rat bite fever were tried. These methods were not as effective as induced malaria and never became popular. O'Leary treated neurosyphilis with injections of typhoid fever. This method has not been widely used although it has value in the treatment of some patients. Physical means were then used to induce fever. Here the term artificial fever therapy came into use. Hot baths and wrapping in blankets proved too cumbersome. Diathermy, the radiotherm, and the Kettering hypertherm were introduced in 1929, 1930, and 1931 and now have enthusiastic adherents. Therapeutic malaria, however, still remains an indispensable and valuable tool in the treatment of syphilis.

Medical requisites

Therapeutic malaria is not without hazard. The prime requisite in its use is therefore a physician experienced with its contraindications and complications as well as its indications and usual action. A successful malaria service cannot be supervised by interns. The physician himself should make daily rounds and personally see each of his fever patients. Responsible and trained nursing personnel and a charge nurse familiar with induced malaria are further requisites. An observing nurse at the bedside will recognize signs of impending danger and by instituting simple measures will often safeguard the patients welfare. Adequate hospital facilities constitute the final medical requisite. The laboratory services must be reliable and emergency medications readily available. It is essential that a close economic relationship be maintained between hospital, doctor, laboratory, and patient. Otherwise too heavy a financial burden will be imposed, and the business side of therapeutic malaria may become more critical than its pure medical phase.

The effect of fever

The beneficial effect of fever in the treatment of syphilis has been explained in various ways. Bruetsch suggested that it stimulates the reticulo-endothelial system to resist disease processes more successfully. That therapeutic malaria has not been successfully used in early syphilis (less than a year from the onset of the infection) is probably evidence that the induced fever plays a supportive and secondary role to the body's own immune mechanisms. Paulian and Tanasescu felt that fever altered the hemato-encephalic barrier and permitted greater penetration of the antisyphilitic drugs into the cerebrospinal fluid. Freeman theorized that fever forced the drainage of treponemes from nerve parenchyma along perivascular channels into the subarachnoid space. The proponents of artificial fever therapy believe that, whatever the underlying mechanism may be, the hyperpyrexia per se is responsible for the benefits. On the other hand the proponents of therapeutic malaria firmly believe that the actual presence of an infectious disease is superior in the production of induced fever. Final judgment on the best method must await the solution of the basic mechanism or combination of mechanisms involved.

Therapeutic Malaria versus Artificial Fever Therapy

Apart from debate of fever produced by an infectious agent versus artificial hyperpyrexia, there are practical considerations for the predominant use of theropeutic malaria here and in many other treatment centers. It is conceded that both methods are effective. The lessened mortality attributed to physically induced fever by some observers must be seriously considered by advocates of malarial therapy. Induced malaria, however, is more adaptable to our facilities. The few cubic centimeters required for innoculation are readily available and their cost is negligible. Our physicians and nurses are well trained and experienced in the care of malaria patients. Several patients may undergo treatment at the same time. On the other hand fever cabinets are costly, both in the initial expense of the apparatus and in maintenance. A skilled mechanic must be available for their readjustment. One skilled technician per cabinet must be always present to watch the patient during the induced fever. One patient usually, and at the most two, can be treated in one cabinet per day. Limited to one Kettering cabinet here, we do not have adequate facilities to treat adequately the patients who come to us.

A Classification of Syphilis

A workable classification of syphilis is needed to better appreciate the use of therapeutic malaria. (Tables I and II) In the main, the one submitted is that used by Moore. Acquired or congenital syphilis are obvious separations. The subdivisions of early syphilis suggest development of immunity in the patient. The success of the immune mechanisms is indicated by the subdivisions under late syphilis. A more detailed classification of acquired neurosyphilis is added to clarify the indications for therapeutic malaria.

Table I
CLASSIFICATION OF SYPHILIS

- Acquired
  - Early
    - Primary
      - Seronegative
      - Seropositive
    - Secondary
      - Early
      - Delayed
    - Latent (and potentially relapsing)
  - Late (2 to 4 years after onset of infection)
    - Latent
    - Benign late
    - Serious
      - Hepatic (very rare)
      - Cardiovascular
      - Neurosyphilis
- Congenital
  - Early
    - Active
    - Latent
  - Late
    - Latent
    - Benign late
    - Serious
      - Interstitial keratitis
      - Nerve deafness
      - Neurosyphilis

Table II
CLASSIFICATION OF ACQUIRED NEUROSYPHILIS

Asymptomatic neurosyphilis
- Minimal and moderate spinal fluid abnormalities
- Spinal fluid with paretic formula

Meningovascular neurosyphilis
- Early meningeal (including neurorecurrences)
- Vascular
- Late diffuse meningovascular

Tabes dorsalis
- Arrested
- Active

Primary optic atrophy

Taboparesis

General paresis (dementia paralytica)

Table III
INDICATIONS FOR THERAPEUTIC MALARIA IN ACQUIRED SYPHILIS

Early
- Never before one year (natural immunity should have a start)
- Delayed and chemo-refractive secondary syphilis (artificial fever and concomitant chemotherapy better)

Late
- Neurosyphilis
  - Asymptomatic
    - Chemo-refractive cases with minimal or moderate spinal fluid abnormalities
      - Immediately in cases with paretic formula spinal fluid
  - Meningovascular
    - Chemo-refractive early meningeal and late diffuse meningovascular
  - Tabes dorsalis
    - Arrested cases never
    - Immediately or later after chemotherapy depending on particular case
  - Primary optic atrophy
  - Taboparesis
  - General paresis
    - Immediately

Table IV
INDICATIONS FOR THERAPEUTIC MALARIA IN CONGENITAL SYPHILIS

Early
- Never

Late
- Latent
- Benign late
  - Never
- Serious
  - Interstitial keratitis
    - Immediately
  - Nerve deafness
    - All therapy ineffectual
  - Neurosyphilis
    - Asymptomatic (except with paretic formula spinal fluid)
    - Meningovascular
      - Chemo-refractive cases
  - Juvenile paresis
    - Immediately
  - Juvenile tabes
    - ? value

Indications

The established field for malarial therapy is that of general paresis. (Table III) Asymptomatic neurosyphilis in which the spinal fluid has a paretic formula foretells probable severe neurosyphilis and therefore indicates immediate fever therapy. Asymptomatic neurosyphilis with minimal or moderate spinal fluid abnormalities indicates fever therapy if refractive to an adequate trial of antisyphilitic chemotherapy. Malarial therapy is not indicated in early meningeal neurosyphilis, (including neuro recurrences), except in patients refractive to chemotherapy. Recurrent bone and skin lesions in untreated patients with early meningeal neurosyphilis have been noted to appear during the course of malarial fevers. Therapeutic malaria is indicated in vascular neurosyphilis only if there is an associated paresis. In these patients the risk of fever is much greater.

Late diffuse menigo vascular neurosyphilis indicates malarial therapy if refractive to an adequate trial of antisyphilitic chemotherapy. Arrested tabes

dorsalis may be made much worse by malarial therapy and is not an indication for fever therapy. In active cases of tabes dorsalis there is variance of opinion among the observers as to the indications for fever therapy. Some favor immediate innoculation with malaria. There is, however, a grave risk in fever therapy given to patients with cord bladders. Acute retention during the fever often occurs and death from ascending urinary infections following malarial therapy have been reported. Other observers feel that therapeutic malaria may be used in active tabes dorsalis after and in conjunction with chemotherapy; that the incidence in the improvement in certain tabetic symptoms, notably gastric crises and lightning pains, is higher in patients so treated than with chemotherapy alone. Optic atrophy, usually associated with tabes dorsalis, indicates the immediate use of fever therapy. The delay brought about by a preliminary trial of chemotherapy may lead to blindness. Taborparetics should be treated the same as paretics and therefore the prompt instution of malarial therapy is indicated.

Interstitial kerstitis is the most common lesion of late congenital syphilis (Table IV) About half of all patients with late congenital syphilis seek medical aid because of it. Although some advocate intensified chemotherapy first, we believe that fever therapy is immediately indicated. Congenital neurosyphilis often indicates malarial therapy, particularly the patients with spinal fluid abnormalities resistant to an adequate trial of chemotherapy. Juvenile paresis indicates the immediate use of therapeutic malaria.

Mucotaneous lesions of secondary syphilis which progress in spite of chemotherapy indicate fever therapy and here induced malaria may be used. However, in such cases artificial fever therapy has the advantage of concomittant use of antisyphilitic drugs which would interfere with malarial fevers.

There is some economic justification for the earlier use of therapeutic malaria in those conditions in which chemotherapy would usually be advised first. The greater chance of prolonged clinical improvement and the shortened total course of treatment with the ultimate lessened expense in both time and money made possible by the employment of induced malaria first may in some cases justify its use. Moore, for example, feels that as much may be accomplished with fever therapy plus 12 to 18 months of chemotherapy as with 3 years of chemotherapy alone.

There has been another group of patients with neurosyphilis in our experience in which the immediate use of therapeutic malaria is justified. The inability of these patients to receive chemotherapy is felt certain. They will not co-operate in taking a prolonged course of treatment or adequate medical care is not available in their particular community. The treatment given to them here will probably be the only antisyphilitic treatment they will receive. We feel that the immediate use of therapeutic malaria is indicated for the treatment of neurosyphilis in such patients. Finally it should be stressed that patients with latent syphilis who have received adequate chemotherapy but remain sero fast should not be given fever therapy.

Table V
CONTRAINDICATIONS TO THERAPEUTIC MALARIA

Lack of medical requisites
- Inexperienced physicians and nursing personnel
- Inadequate hospital facilities

Advanced age
- Patients over 60 years
- Good general physical condition required in patients 50 to 60 years

Cardiovascular disease
- Decompensation in spite of cardiac treatment
- Aortic aneurysm
- Other conditions in which strenuous exercise is dangerous

Table V cont.

Severe generalized arteriosclerosis

Diabetes not easily controlled

Pulmonary tuberculosis
Active
Lighting up of latent foci ?

Inadequate renal function

Marked hepatic disease

Severe anemias refractive to therapy

Severe debilitating disease in general

Contraindications

The contraindications to the use of therapeutic malaria in most instances are more relative than absolute. (Table V) The greater the need for the fever therapy, the more the risk may be taken. One must think of the induced malaria as only a part of the treatment scheme and balance in each particular case the advantages gained with the risk involved. The lack of the medical requisites mentioned earlier contraindicates the use of therapeutic malaria. A mortality of 10 per cent in unselected patients and of 1 to 2 percent in carefully selected patients in the hands of experts and in hospitals specially equipped for treatment should make the inexperienced physician hesitate before he employs induced malaria in the treatment of syphilis. Advanced age is a contraindication. The general physical status of the patient is more important, however, than the age in years alone. It is obvious that the physical resources and resistance of two patients the same age may differ greatly. As a rule, patients over 60 years of age are not considered candidates for fever therapy. Patients between 50 and 60 years of age should be in good physical condition apart from their syphilis if they are to be given malaria. Again the need for fever therapy will often determine its use. Patients as old as 70 years have undergone malarial therapy without apparent ill effects.

Severe cardiovascular disease is the most important single contraindication to malarial therapy. The cardiovascular disease need not be syphilitic, and on the other hand cardiovascular syphilis does not always contraindicate the use of malaria. Decompensation, whatever the cause, not controlled by general cardiac treatment contra-indicates induced malaria. Aortic aneurysm and any other cardiac condition in which strenuous exercise would be dangerous contraindicates malarial therapy. The competent cardiologist should always decide for or against fever therapy in the borderline individual case. Severe generalized arteriosclerosis contraindicates malarial therapy. In this regard diabetics in younger age groups must be carefully evaluated. Diabetes not easily controlled contraindicates malarial therapy. Active pulmonary tuberculosis is a generally accepted contraindication to fever therapy. Stokes believes that there is a definite tendency to light up even latent tuberculous foci by malarial therapy. Arrested pulmonary tuberculosis is not a contraindication to fever therapy in our experience.

Inadequate renal function, marked hepatic disease, severe anemias refractive to therapy, and any severe debilitating disease contraindicate fever therapy.

Again it must be stressed that all contraindications to therapeutic malaria are more relative than absolute. If the hazard to like from syphilis is greater than the risk of the contraindication whatever it may be the use of induced malaria may be justified.

Medical Workup

The indications and contraindications mentioned clearly indicate that the physician must carefully select and evaluate all candidates for therapeutic malaria. It has been the policy of the dermatosyphilologists here -- and the policy of the neuropsychiatrists is much the same -- to examine these patients in the following manner. A general

history and physical examination paying particular attention to the personal, marital, and family history as related to syphilis is first done. An exact record of previous treatment is sought. A routine urinalysis including a qualitative urobilinogen test is performed. A blood count including hemoglobin and leukocyte count with differential is obtained. A blood urea nitrogen determination and special liver function studies are performed. Fluoroscopic examination of the chest is made and in many cases roentgen film of the chest is added. Electrocardiographic studies are performed. Consultation with a neuropsychiatrist, internist and an ophthalmalogist then follow. Urologic consultation is requested if the presence of a cord bladder is suspected in tabetic patients. Spinal fluid examination, if not recently or previously performed, is done, and this examination should include a cell count, protein determination, complement fixation test and a colloidal gold test. Quantitatively titered complement fixation tests, although not used here, are preferred since they better measure the immunologic response of the patient. The patient is weighed. The temperature, pulse, and respirations are taken every 4 hours during waking hours. The blood pressure is taken daily. The patient is given a general diet and encouraged to drink water freely. A test dose of quinine is given to anticipate possible drug sensitivity. With the medical evaluation then completed and the indication verified, the patient is given therapeutic malaria.

The Source of Therapeutic Malaria

Benign tertian, or malaria induced by the innoculation of the Plasmodium vivax is the infective organism of choice in therapeutic malaria. Kopeloff, Blackman, and Mc Ginn demonstrated that the sexual forms of benign tertian malaria disappeared after 2½ years of patient to patient transfer. The screening and isolation of these patients therefore becomes a superfluous procedure if the benign tertian strain is definitely known and has been previously used over a long period of time. It is important, however, that donors who have been in the tropics be rejected since even the demonstrated absence of tropical (aestivo-autumnal) organisms in blood smear does not rule out the possibility of their presence. Deaths have been reported where the tropical organisms have been innoculated either purposely or accidentally.

Quartan malaria induced by the innoculation of Plasmodium malariae, although not used here, has a special field of value in patients previously treated with benign tertian malaria and thereby immune to reinnoculation of its organisms.

Debilitated patients are better able to tolerate the milder course of quartan malaria. Negroes refractive to the tertian strain are usually susceptible to innoculation with the quartan strain. Kroli reported satisfactory results in 43 patients treated with quartan malaria and followed for at least 6 months. Mays, Oden, and Cox think quartan malaria is superior to tertian malaria in the treatment of general paresis.

The Inoculation of Malarial Blood

Direct transfer of malarial blood from one patient to another is generally used in this country. Mosquito transmission is usually employed in Great Britain but is undesirable since such infections are sometimes less susceptible to quinine and more prone to subsequent relapse. In the innoculation of patients by infected mosquitoes there is the possibility that malaria may be disseminated to the surrounding population.

Malarial blood may be inoculated by intravenous, intramuscular or subcutaneous routes. The intravenous route is used by the dermatosyphilogists here since it is time saving. The incubation period of malarial fever following intravenous innoculation averages 4 to 7 days with occasional fevers appearing in 24 hours and at times requiring 10 days. Intramuscular inoculations are employed by the neuropsychiatrists here who feel

that the onset of the fevers is milder, the proportion of tertian fevers as compared to the quotidian higher, and the course in general is therefore less strenuous to the patient. The incubation period following intramuscular innoculation averages 10 to 14 days with occasional fevers appearing in 7 days. Subcutaneous inoculations preferred by others respond much as do intramuscular inoculations. Intraspinal inoculation is dangerous.

The route by which malarial blood is given has economic considerations as well as medical. Expense may be saved by inoculation of the patient outside the hospital and awaiting the fevers before admission. Malaria induced by intravenous inoculation requires on the average 1 month to complete an adequate course whereas malaria induced by intramuscular inoculation requires 6 weeks on the average.

If no more than one minute is required for the bleeding of the donor and the inoculation of the recipient, whole blood may be used. Usually more time is required and the blood must be kept from clotting by citration. Moore recommends that 1 cubic centimeter be drawn into an empty sterile syringe and that 10 cubic centimeters of blood be withdrawn from the donor patient. Blood so prepared will then remain infectious from 12 to 48 hours at icebox, room, or body temperature. Stokes suggests defibrination of the malaria blood by five minutes' stirring with a glass rod as an alternative to citration.

Matching of the donor's and recipient's blood is not necessary if no more than 10 cubic centimeters of blood is given intravenously. The recommended intravenous dosage of malaria blood here is 5 to 7 cubic centimeters.

The incubation period may be shortened and certain patients refractory to the usual amount of unmatched blood given may be successfully infected if 50 to 200 cubic centimeters of matched blood is inoculated intravenously. 1-5 cubic centimeters of malarial blood is recommended for intramuscular or subcutaneous injection.

If no sign of a take from the malarial blood is noted within the expected time limits, reinoculation with fresh infectious blood may be tried. At times the take of malarial fevers may be provoked by adrenalin given intramuscularly or with a small dose (5 to 50 million organisms) of typhoid vaccine. The latter procedure, however, is not without danger, and the patient must be watched very carefully.

The Course of Benign Tertian Fevers

Before the onset of the chill or actual fever which at times is not preceded by a chill, the patient feels out of sorts with a headache and generalized aches and pains. During the chill the patient usually looks profoundly ill. The temperature as a rule does not reach its maximum with the first febrile attack, and at times there is prodromal and sustained fever of 101 to 103 degrees Fahrenheit (oral temperature) for a day or two, or two to three days of irregular fever. A high fever of 104 to 106 degrees Fahrenheit is then reached. The early fever paroxysms are more often quotidian than purely tertian. During the fever the headache and generalized aches and pains continue, profuse sweating is the rule, and anorexia, nausea and vomiting are frequent. The typical fevers remain at 104 to 106 degrees Fahrenheit for 1 to 3 hours, then gradually fall to normal during the ensuing 12 hours. Typical tertian fevers are usually noted after the first 4 or 5 paroxysms. Not infrequently after 6 to 8 paroxysms, the fevers subside spontaneously.

The Medical Care During Fevers

The most successful management of therapeutic malaria requires teamwork by physician, nurse and patient. Each must co-operate in his or her part. A definite routine should be carried out. Written and detailed orders should be available to the nursing personnel at all times (Table VI) These orders should include the general routine to be followed and emergency supportive measures. Strict bed rest should be enforced from the start to the termination of the

fever paroxysms. Fluids should be forced. The fluid intake and output must be recorded. Adults should drink at least 3000 cubic centimeters of fluids daily, children at least 2000 centimeters. Sodium chloride 1 gram 3 times daily after meals should be given. In addition to the regular diet, supplementary nourishments should be given at least 3 times daily. The patient should be constantly encouraged to eat and drink as much as he can since during the fever paroxysms inadequate food and drink are taken. The temperature taken orally (rectally only if necessary), pulse, and respirations should be recorded every 30 minutes from the start of the fever paroxysms until the temperature is within ½ degree of normal. During this time the blood pressure should be taken hourly. During the end of a course of malarial fevers a short paroxysm may be missed if the temperature is taken at 4 hour intervals in the absence of subjective manifestations. The temperature, pulse and respirations should be recorded every 2 hours if the temperature is more than ½ degree of normal although the patient is symptom free. The blood pressure should be taken twice daily on afebrile days since an increasing hypotension is often noted later in the course of the malarial fevers.

Table VI

ROUTINE ORDERS TO NURSING PERSONNEL AFTER START OF MALARIAL FEVERS

Strict bed rest.
Force fluids (at least 3000 c.c. daily to adults, 2000 c.c. to children).
Record fluid intake and output.
Give supplementary nourishments tid. plus general diet.
Give sodium chloride 1 gram tid. pc.
Take T P R (oral temperature with pulse and respirations) every 30 minutes from start of fever paroxysms until T within ½ degree of normal; take blood pressure hourly during this time.
Take T P R every 2 hours otherwise (not during fever paroxysm) if T more than ½ degree above normal.
Take T P R every 4 hours and blood pressure bid. on afebrile days.

Table VI cont.

Elevate foot of bed for impending shock (drop of more than 20 millimeters mercury below usual systolic level or below systolic level of 90)
If shock still threatens, call intern or staff physician.
Give adrenalin 1:1000 minims 3 to adults (minims 2 to children) by hypostat and repeat every 15 minutes until blood pressure has returned to normal (usually only a few such injections are needed and seldom more than a total of 1 c.c.).
Tepid sponges to patients unduely prostrated from fever or to patients with temperature of 106 degrees Fahrenheit or higher.
Report the following as indications of impending trouble:
- Significant blood pressure drop,
- Sudden and subnormal temperature after fever paroxysm,
- High pulse rate persisting after temperature returns to normal,
- Inability to eat, drink, and retain foods and fluids,
- Inability to void.

The minor complications of therapeutic malaria are frequently encountered. They represent the border line between normal and abnormal physiologic responses. Temperature 106 degrees Fahrenheit or higher increases the risk beyond the Benefits of the fever and should be lowered with tepid sponges. Likewise a prolonged fever within the high but acceptable limits may unduely prostrate the patient and should be lowered with tepid sponges. Aspirin grains 5 may be given but probably gives the physician more mental relief than the patient physical, since it usually has no effect on malarial fevers. The frequent headaches and generalized aches and pains are not complications in a true sense. However, excessive discomfort experienced by the patient may destroy his willingness to co-operate. ½ to 1 grain of codeine by mouth given not oftener than every 4 hours will alleviate considerably such discomfort. Dehydration will be frequently encountered if an adequate fluid intake is not maintained. The inability

to take fluids adequately by mouth requires the parenteral administration of 10 percent glucose in normal saline solution. The addition of glucose and salt also replaces needed nutritional requirements in these patients.

The most commonly encountered complication of more serious import is that of shock. Rarely does more than impending shock develop in well managed patients. Bedside nurses are instructed to watch for a sudden drop in the systolic blood pressure which not infrequently occurs at the end of a fever paroxysm or just after it. They are told to elevate the foot of the bed if the systolic pressure falls more than 20 millimeters of mercury below its usual level or if it falls below 90. Usually shock position quickly corrects such instability. However, if shock still threatens, the charge nurse is advised to call the intern or staff physician at once, and is authorized to give adrenalin 1:1000 minims 3 by hypo immediately and every 15 minutes thereafter until the blood pressure has returned to normal. As a rule, only a few such injections are needed. Seldom is more than a total of 1 cubic centimeter of adrenalin required. A systolic pressure below 70 indicates immediate interruption of the malarial fevers. The nurse should be further instructed to watch for sudden and marked fall of the temperature to subnormal levels which may be noted after the fever paroxysm. They are instructed to report high pulse rates persisting after the temperature returns to normal. Both reactions indicate vascular instability but in almost all instances respond readily to supportive therapy. It is necessary that the physician himself be on constant guard against the cardiovascular complications of therapeutic malaria. The judicious use of adrenalin and parenteral fluids will do much to control such cardiovascular distress; the timely use of ephredrine grains 3/8 tid. will usually forestall the occurrence of these complications.

Anorexia is a common feature of induced malaria. Weight losses of 10 to 20 pounds are often sustained during the febrile periods. Protective diets are needed and may play an important role in the future by more favorably maintaining the nutritional needs of the body during such febrile states. The severe vomiting which at times accompanies the fevers may be markedly lessened by the parenteral injection of glucose in saline. Protracted vomiting if it cannot be controlled by such treatment indicates interruption of the malarial fevers.

The lightning pains in tabetics are usually increased in severity early in the course of the malarial fevers, often much improved by the end of the course. In dubious early tabetics lightning pains make their first appearance during the malarial fevers and help to confirm the diagnostic impression.

Bedside nurses are instructed to report any difficulty the patient may experience in voiding. In cases of urinary retention encountered during the malarial fevers one must distinguish between retention secondary to prostration and that due to a cord bladder. The danger of an ascending kidney infection in the case of the latter is considerable if the condition is not recognized. Instrumentation should be avoided unless absolutely necessary. If it is at all possible the patient should be trained to empty the bladder frequently and regularly. The management of the cord bladder should be under the supervision of the urologist, and the interruption of the malarial fevers may be required.

Rare instances of rupture of the spleen have been reported. The almost uniform and striking enlargement of the spleen affords a potential danger to all malarial patients, and it is advisable to avoid too active palpation of this organ.

The neuropsychiatric complications constitute an important group. Delirium, hallucinosis, and excitement precipitated or exaggerated by the fevers may present grave problems in the management of therapeutic malaria. Reassurance and persuasion may be helpful. Restraints may be needed for the patient's own

protection. Suicides in malaria patients have been reported. Paretics in some instances have become much worse during the course of malaria.

The laboratory studies employed here in the management of therapeutic malaria are important indices of blood destruction, kidney and liver function. Routine blood counts and urinalyses are checked at least twice weekly. The blood urea nitrogen is checked at least once a week. A moderate to marked fall in hemoglobin is to be expected. A reduction of the hemoglobin below 50 per cent contraindicates further malarial therapy. Leukopenias are quite commonly seen and if below 2000 necessitate interruption of the fever paroxysms. The differential count must be checked as well since granulocytopenias offer serious hazards. The urine is examined with special reference to the presence of red blood cells. Albuminuria is common during the febrile period. Transient and mild elevations of the blood urea nitrogen are not infrequent, are usually due to dehydration, and disappear with an adequate fluid intake. However, levels above 60 millimeters per 100 cubic centimeters contraindicate further malarial fevers.

The full significance of jaundice and abnormal liver function studies in therapeutic malaria has not been determined. Moore states that jaundice, although as a rule only faintly visible in the sclerae, occurs in about half of the patients treated. He feels that it need not be feared, that it is probably largely hematogenous in origin, from the rapid destruction of red cells by the plasmodia. He does admit, however, that in rare instances toxic hepatitis with deep and progressively increasing jaundice may be the direct result of induced malaria. Bruetsch agrees that in some instances actual damage to the liver may occur, that atrophic cirrhosis is eventually produced. Milbradt found no permanent damage to the liver in 1000 cases of induced malaria. He stated that in the few instances in which slight damage was detectable by liver function tests performed immediately after treatment, later tests were normal. It is our impression here from cases studied during the past 6 months that abnormalities in liver function tests are common in therapeutic malaria, that these abnormalities represent more than blood destruction. Further studies of liver function in therapeutic malaria are now being carried out here.

The Termination of Therapeutic Malaria

About 10 per cent of malarial fevers cease spontaneously before the minimal desired course is given. It is felt here that 8 to 12 fever paroxysms or 40 to 50 hours of 103 degrees Fahrenheit or higher constitute an adequate course of therapeutic malaria. Because of complications arising before such a course is completed, it is necessary to change quotidian fevers to tertian. Thiobismol (sodium bismuth thioglycollate), first used by Cole, Schwartz, et al, is an effective drug for this purpose. Young, McLendon, and Smarr showed that thiobism in dosage of 0.1 to 0.2 gram injured the half grown parasites of Plasmodium vivax but did not affect the younger or older parasites. Therefore, by giving the drug during the 16 to 28 hour period after a paroxysm, that series of paroxysms was eliminated and the fevers were converted from quotidian to tertian. In the event that more serious complications arise and the fevers must be prematurely terminated, it should be remembered that reinoculation with malarial blood may be successful if it is carried out within 3 months. Later than this, the infective tertian organisms fail to take unless mor than 5 years have elapsed. If the fevers stop spontaneously before an adequate course is given, typhoid vacine may be employed in the same manner as in the provocation of fevers previously mentioned. Given in stepped up doses, intravenously, typhoid vacine will usually enable a successful completion of the course of fevers. Quinine in small doses (3 to 5 grains) may also be used to temporarily interrupt a stormy course of fevers in some cases.

On the completion of an adequate course of benign tertian fevers, quinine is the drug of choice to terminate induced malaria. Moore recommends that either quinine sulphate or the dihydro-chloride dosage 5 grains by mouth be given tid. for 10 to 14 days. In our experience quinine grains 5 tid. for 4 days, bid. for 3 days, and daily for 2 weeks thereafter has proved very satisfactory.

During the immediate post-malarial convalescence of the patients treated here, bed rest is continued the first 4 days, graduated exercise is then started, the patient is discharged from the hospital on the sixth to eighth day, and advised to gradually increase his activity at home. It is usually recommended that full time activity be not resumed until a month has elapsed. At that time the patient is re-examined in the out-patient clinic whenever possible, and follow-up chemotherapy (usually courses of tryparsamide and bismuth) is started. Re-examination including lumbar puncture is advised 6 months later, unless special conditions indicate an earlier return, for all patients who do not continue with their medical care here.

The Results of Therapeutic Malaria

Since induced malaria is not recommended as a single form of therapy, except in unusual circumstances, it is not possible to evaluate the ultimate benefits of this therapeutic agent alone. However, once recovered from the immediate post-malarial weakness, the patient usually experiences an early marked tonic effect. Previous symptoms in severe neurosyphilis will often be strikingly relieved. Early interstitial keratitis will frequently show remarkable improvement.

Moore's summary based on 12,000 cases of general paresis reported in the literature is certainly an impressive appraisal of therapeutic malaria. The clinical material was unselected and included all types of paresis. Complete remission was obtained in 25 per cent, incomplete remission in 20 per cent, some improvement but permanent hospitalization still required in 25 per cent, no improvement in 20 per cent. The 1940 report of the Cooperative Clinical Group showed the following results in 1100 patients treated with malaria and pooled for statistical study. Sufficient clinical recovery to permit the patient to return to his former socio-economic status was considered a remission. The remission rate after 1 year was 36.4 per cent in mild paresis, 13.7 per cent in intermediate, and 0.0 in severe paresis. The remission rate after 3 years was 51.7 per cent in mild paresis, 24.2 per cent in intermediate, and 0.9 per cent in severe paresis. Moore's summary based on about 1000 selected patients in his own clinic showed 35 per cent complete remission, 28 per cent incomplete remission in which the patients were able to work, 25 per cent some improvement but permanent hospitalization still required, and no improvement in 10 per cent. Most of these paretics were early cases and in good physical condition.

The evaluation of therapeutic malaria in tabes dorsalis is difficult because of the multiplicity of the treatment schemes usually employed. It shall suffice to say that induced malaria is effective in producing definite clinical improvement in a significant number of tabetics refractive to routine chemotherapy. It is more successful in controlling optic atrophy than the other therapeutic measures. It is often effective in the treatment of lightning pains refractive to chemotherapy.

In the treatment of asymptomatic neurosyphilis with a paretic spinal fluid formula, the prophylactic value is generally accepted. Moore has treated 200 patients with asymptomatic neurosyphilis by combined chemo and malarial therapy, and in not a single instance has the development of paresis been observed.

Analysis of 37 Patients Treated With Therapeutic Malaria in 1943

There were 32 patients with acquired neurosyphilis of whom 25 were males, 7 females. (Table VII) 15 patients had asymptomatic neurosyphilis, 11 with paretic spinal fluid formulae. 1 patient

had late diffuse meningovascular neurosyphilis. 4 patients had general paresis, 3 were mild cases and 1 moderate. 5 patients had taboparesis with 3 early cases and 2 moderately advanced. 7 patients had active tabes dorsalis. 1 tabetic also had primary optic atrophy.

Table VII
ANALYSIS OF DIAGNOSIS IN 37 CASES OF NEUROSYPHILIS TREATED WITH MALARIA IN 1943

Acquired neurosyphilis	
Asymptomatic	
with minimal or moderate spinal fluid abnormalities	4
with paretic spinal fluid formula	11
Late diffuse meningovascular	1
Tabes dorsalis (active)	7
Primary optic atrophy	1*
Taboparesis	5
General paresis	4
Congenital syphilis	
Interstitial keratitis	3**
Asymptomatic neurosyphilis	
with moderate spinal fluid abnormalities	1
with paretic spinal fluid formula	1
Meningovascular neurosyphilis	2

* Patient also included among cases of tabes dorsalis

** 2 patients also included among cases of asymptomatic neurosyphilis

Total 40 diagnoses
37 patients

There were 2 patients between 20 and 30 years of age, 13 between 30 and 40, 12 between 40 and 50, 5 between 50 and 60. There was 1 death, a 47 year old woman who was a mild paretic. She also had an unrecognized Laennec's cirrhosis, and she died 49 days after her discharge from the hospital following a course of benign tertian malaria. She was given 12 malarial paroxysms for a total of only 22½ hours at 103 degrees Fahrenheit (oral). The last 3 paroxysms were activated with triple typhoid vacine, and following that procedure she was given 2 treatments in the Kettering hypertherm for a total of 6 hours at 105 degrees Fahrenheit (rectal). Although no untoward symptoms were noted during her hospitalization for fever therapy, 49 days after her discharge she died of acute yellow atrophy, confirmed by autopsy.

Premature interruption of the malarial therapy was necessary in 4 patients. A 45 year old woman developed a leukopenia of 1450 and a urinary retention on the basis of an unrecognized cord bladder. The malarial fevers were terminated after her fourth paroxysm. A 36 year old woman developed marked prostration, hepatomegaly, and spider nevi. Her malarial fevers were also stopped after the fourth paroxysm. A man aged 51 developed marked prostration, anginal pain, and tended to go into shock at the end of several paroxysms. His fevers were stopped after the sixth paroxysm. A man, paretic, aged 36 years, developed a spontaneous remission after his second fever paroxysm. 5 days later he developed acute catarrhal jaundice. He had been given therapeutic malaria twice before.

4 patients were given 1 to 3 treatments in the Kettering hypertherm to supplement their malarial fevers. 1 pernicious anemia patient was given a full course of malarial fevers without trouble. 2 men developed urinary retention on the basis of prostration. 4 patients developed spider nevi during their course of malaria. 1 patient developed a marked purpura which regressed quickly after the fevers were stopped.

5 patients with congenital syphilis were treated. 3 patients, ages 6, 9, 14 had interstitial keratitis. The 14 year old boy had asymptomatic neurosyphilis with a paretic spinal fluid formula. The 6 year old boy had asymptomatic neurosyphilis with moderate spinal fluid abnormalities. 2 patients, age 24 and 26, had congenital meningovascular neurosyphilis. Both were refractive to previous chemotherapy.

Conclusions

Therapeutic malaria has great value in the treatment of severe neurosyphilis. It is particularly valuable in general paresis, taboparesis, and in asymptomatic neurosyphilis with a paretic spinal fluid formula. It should be combined with either preliminary or subsequent chemotherapy in all cases. It is not without risk to the patient and therefore must be carefully selected in its use.

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III. GOSSIP

The following article appeared in a recent issue of the Minnesota Farm Bureau News published in St. Paul. Some of you may not recognize Doctors Black, White, Green and Brown, but in ordinary times they head departments in the clinical branch of the medical school.

DOCTORS SERVED PATIENTS AS FLOOR SCRUBBERS

The College of Medicine, University of Minnesota, is world-famed. It has good buildings and good equipment, but Ward & Roebuck have bigger buildings and more equipment. It takes men of unusual qualities to make good doctors, and the best of these to make good teachers of the science and art of healing. These men are the medical college--the plant is incidental.

There are surgeons on the staff who can excise an adenoid before you can say salpingoophorectomy, but they have their limitations. Your editor can scrub floors with the best of them, and may be just a shade better at dumping slush buckets.

Dr. Black and Dr. White, Dr. Green and Dr. Brown (they might not care for mention) head departments that have ministered well to the ailing bodies of the destitute. They have contributed much to the cause of humanity, but when it comes to putting a high shine on a terrazo base board, your commentator claims precedence.

The test came on a recent Saturday afternoon, while farmers were just fooling away their time splitting wood or feeding cattle, and the pool room boys were doping out the strategy of the coming elections. Within the hospital were some 400 sufferers, many of them destitute, but enjoying the finest care a generous state can provide. Outside the hospital were all but 9 of the 160-odd workers hired by the state to operate the physical plant. They were on strike, not for higher pay or better working conditions, but to test a theory held by labor union operators--that they could dictate to the Board of Regents.

When the workers left, their duties were taken over by doctors and nurses, by girl and men students and by well-wishers from outside, who had heard of the strike and of the possibility that sufferers might have to be sent away. Your editor was one of these helpers.

It seemed, before the day was over, that University hospital has more floor area then Regent A. J. Olson has pasture, and he's a big operator. It all had to be mopped. Your editor was given a warm welcome, a white dress, a Paul Bunyan broom and orders to get busy. A couple of men followed the broom with scrubbing equipment--pails on wheels and patent mop wringers. They worked hard and fast, but had to be spoken to. Just a little bit careless about slopping up the walls. They were top rank doctors.

There were offices and lecture rooms to be cleaned up, and some young women were working there. They were co-eds. A bull-necked young husky was slamming huge trash cans around and burning stuff in the incinerator. He was a medic student. Down in a sub-basement corridor a gray-haired man was dumping soiled linen. He is known wherever men study the science of pediatrics, the treatment of little children. It was an interesting and instructive afternoon. It gave a person stronger and clearer ideas on the high, and the low, of humanity.

Your editor came out of the experience with more self-confidence. Some months ago he was forced to admit, in the Farm Bureau News, that it took him all Saturday afternoon to learn enough about the electrician's trade to save a Saturday call from a union electrician, a call that would have cost twice that of a doctor's. As a hospital floor scrubber and incinerator engineer, he is as good as the best the hospital staff could produce. But maybe the great talents of these scientists and teachers should not be wasted on waste baskets and garbage cans. They didn't spend any time wondering about that. There was work to be done. They did it. ...

Last Friday I spoke to a group of teachers in Galesburg, Illinois on "Recent Advances in Medicine" and "The School Health Program". Galesberg has just finished a new hospital, the United States Army Mayo General Hospital named after the Doctors Mayo who played a prominent role on the Surgeon's General's Staff in the last war. A professor of education from the University of Nebraska gave an interesting talk on teaching methods. He pointed out the desirability of preparing

students for reading assignments. He felt that most youngsters had to have assignments explored for them. He told of a successful teacher who was preparing her students for the next reading assignment in genetics. She asked a blue eyed girl what color eyes her mother and father had. The teacher learned that all three had blue eyes. She drew the conclusion that this must be true of all blue eyed persons. Immediately hands went up to indicate that blue eyed children could be produced by other combinations. The students were next informed that the answers to this and other questions could be found in their next assignment. Directed reading apparently involves preparation by the teacher for the subject material ahead. Most people believe that the reading should be done in advance. This is effective for superior students but not for the average one.....Bus service through Illinois is hampered by drifts. There are no snow fences and snow plows are not employed except when heavy drifts are to be eliminated. The most effective device for soft snow is a rotary broom. Busses are crowded and the last one I took had such a low roof that everyone standing had to hump over. The lines which run from Peoria to the east have instructed their drivers to make a little speech before they start. Our driver told us when the next rest stop would occur. He advised us to hold on to the back of the seats if we stood up. He hoped that he could keep us comfortable as far as the temperature was concerned, and he also suggested that we look down before we stepped because the center of the bus was lower than the platform upon which the seats were placed. We had not gone 20 miles when a quick stop for passengers on and off was made. When a lady in slacks engaged the bus driver in whispered conversation, he would shake his head violently indicating "no". Finally he gave up and wearily waited for her to come back, racing his motor at periodic intervals to give vent to his feelings. His instructions did not help very much. I visited my old home town and as usual was struck by the aged appearance of my schoolmates. One I had not seen since we were in grade school together. He displayed the artificial front tooth which replaced the one I had knocked out when we were boys. I believe he still resents it. I also visited my first grade teacher. She has recently retired and is now employed part time in another position. She was the one teacher I remember best. One of her games is still vivid in my memory. She would draw a picture of a house on the board. In this house the students wrote different words. When everyone had spotted his word she set fire to the house, using red chalk for the purpose. The whole house was in flames. We became firemen, and when she rang her bell, we hurried to the board and rescued our word by writing it on the board some distance from the burning building. Everybody has a favorite teacher and we should tell this person about it, while we still have the chance Teachers are taken for granted, and although impressions are more vivid in the earlier years, they may actually occur in graduate training.....When sociologists and anthropologists predicted that the hill people from Tennessee and Kentucky would overrun the middle west, it seemed rather far away. In central Illinois they apparently constitute the majority of the farm population. Soft talk is heard on every corner. Ownership of farms by persons who do not farm them has grown until most farmers are renters. Many physicians become interested in farms, and before long it begins to tell on their interest in medicine. Agricultural economists tell us that with a moderate investment for supplies and equipment renters can make more than owners of the farm. Renters never achieve the social distinction of owners so that communities largely populated by renters show little progress.....I went to Chicago to attend the mid-winter meetings on Education and Hospitals. Our room was just below the famous spot at the Drake, where the incident occurred.