MEPACRINE PSYCHOSIS.

By DAVID PERK, M.D., D.P.M.,
Late Lt.-Col. R.A.M.C.

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FROM time to time in the Middle East, cases were admitted into hospital bearing the diagnosis of Mepacrine Psychosis. This was a label which one hesitated to accept because, for one thing, the cases presented no single clinical type, and for another, they showed, with few exceptions, little or no evidence of symptoms of an organic reaction type such as might be expected in a toxic psychosis. It was, moreover, important, in view of the widespread use of mepacrine both as prophylactic against malaria and in the treatment of it, that the occurrence of a psychosis during the exhibition of mepacrine should not be ascribed to it, except on the irrefutable evidence of a causal connection between the two. Though I have no figures to indicate the incidence of mepacrine psychosis relative to the number of cases of malaria treated with the drug in the M.E.F., I believe the ratio to be very small indeed. Kingsbury mentions 12 cases among several thousand cases of malaria treated with mepacrine ; Allen *et al.* quote Greene as having encountered 2 cases in a series of 750 so treated, in Malay. Hoops had 1 case of mental excitement among 1,207 cases ; Briercliffe 15 cases of delirium among some hundred persons taking mepacrine. Field estimated the incidence of mepacrine psychosis to be less than 0·1 per cent. of cases treated. Gaskill and Fitz-Hugh noted 35 cases of toxic psychosis in 7,064 cases of malaria treated with mepacrine in an army hospital during the recent war ; Mergener reports 1 case in 1,000, and quotes Udalagama, who recorded 7 such cases in a series of 644, and Bispham, who noted only 1 case in 7,915 cases that came under his personal supervision, and who up to 1941 found only 35 instances in the literature. Burnham quotes Dove as having noted no case of alarming reactions (presumably including psychotic reaction) in a series of 30,000 cases treated with mepacrine.

The present review is based on 33 cases, 25 of which I had myself had the opportunity of seeing during their stay in hospital. It was possible to determine in 10 of the cases that the psychotic symptoms had commenced prior to the exhibition of mepacrine, and had been precipitated either by the malaria or by circumstances antecedent to it. In 7 of these cases the symptoms were aggravated by the mepacrine, and in 3 it had no influence. It is possible, therefore, to divide the cases into 3 groups : those in which psychotic symptoms followed the exhibition of mepacrine and which can, therefore, be legitimately

regarded as having been precipitated by it, designated group A; those aggravated by mepacrine, designated group B; and those that appear to have been precipitated by the malaria, designated group C. Groups B and C have cases in common, which fall to be included in each of the groups. The number of cases in each of these groups is, 23 in group A, 7 in group B, and 8 in group C. This division permits of the rejection in the study of mepacrine psychosis of groups B and C, and of their utilization for the purpose of making comparisons between the groups in several particulars. All the observations that follow relate to group A, therefore, unless otherwise specified.

Cases Precipitated by Mepacrine: Aetiology.

All 23 cases are of the male sex, and all British except for 2 Palestine Jews. The average age is 28; the extremes of age are 20 and 44; and 87 per cent. of the cases fall into the 20 to 35 age-group. The proportion of officers and N.C.O.s to privates and equivalents (11 to 12) is high compared to their ratio in the services. The intelligence levels of the cases, though the records are incomplete in this respect, point, as far as they go, to a scatter not differing from that found in the Services generally. The types of psychological make-up found in the series show perhaps an unduly high proportion of the schizoid type, and evoke the suggestion that the schizoid personality may possibly be more susceptible to mepacrine than the other types. But the immunity shown by the many schizoid individuals who have taken mepacrine without ill-effect and the occurrence of mepacrine psychosis in other than the schizoid types indicate that susceptibility to mepacrine does not reside exclusively in the mental and emotional constitutions of the individuals affected. The distribution of the various types was as follows: Schizoid type 27 per cent.; obsessive, anxious and immature types, each 13 per cent.; an assortment of cyclothymic, psychopathic and hysteroid types 21 per cent., and unclassified 13 per cent.

As with most psychiatric breakdowns, the aetiology of the mepacrine-precipitated cases reveals a multi-factorial origin. In addition to the toxic effect of the malaria, which can be presumed to have been an active contributory factor in all the cases, the following other factors are recorded in more than half the cases (13):

Emotional stress (other than that of battle)	7 cases.
Recent battle stress	3 ,,
Alcoholism	2 ,,
Infective hepatitis	1 case.
Sundry factors (P.U.O., septic process, ? cholecystitis)	3 cases.

A noteworthy feature of the cases in the series is that 11 of them (47·8 per cent.) give a history of one or more attacks of malaria in the 18 months prior to the psychiatric episode, and 2, malarial attacks prior to that. Gaskill and Fitz-Hugh have recorded that most of the 35 cases reviewed by them had had one or more attacks of malaria in the past. A constitutional pre-disposition to psychotic breakdown is evident in only 3 of the present series, these having

had previous psychotic breakdowns, whilst the third had a further attack of mania 14 months after the mepacrine-precipitated attack. Three cases give a family history of psychopathy or insanity. Kingsbury noted that one mild and one severe case, in his series of 17, gave histories of previous mental breakdowns. Four of the 9 cases reviewed by Allen *et al.* had had previous " nervous or mental symptoms," and 6 had associated physical conditions which could have been predisposing factors.

Gaskill and Fitz-Hugh found infection with *P. falciparum* to be twice as frequent as infection with *P. vivax*, but this applied equally to the 7,064 cases of malaria as to the 35 cases that developed toxic psychosis. They found no evidence of mental instability in their cases, and suggested vitamin deficiency as a possible contributory cause.

Idiosyncrasy.

No evidence of idiosyncrasy to mepacrine is forthcoming in the author's series. It is inconstant in its toxic effect. Fourteen cases had had mepacrine with impunity in the 18 months prior to their breakdown, and 3 subsequent to it. In only one case did psychotic symptoms reappear with the treatment of malaria, and in that case mepacrine was not exhibited: quinine and plasmoquine were employed. Gaskill and Fitz-Hugh noted that 16 of their recovered cases were at a later date retreated with mepacrine, 15 without any manifestation of untoward symptoms. Shiers reports a case which does, however, suggest that idiosyncrasy for mepacrine may exist. During a period of 10 months his patient had taken mepacrine on 3 occasions in different daily and total dosages, and developed mental symptoms on each occasion.

Dosage and Toxicity.

The dosage of mepacrine used undoubtedly has some influence. In only one instance in the present series did the prophylactic dose (1–2 tablets daily, equal to 0·1–0·2 g.) produce psychotic reaction. The patient was employed in a highly malarious area and had been taking 2 tablets daily for 9 months when symptoms appeared. The breaking-off of the engagement by his fiancée probably played a contributory part. He recovered following convulsive treatment (6 convulsions), but no sooner had that happened than he had a malarial relapse, was given mepacrine and promptly reacted with psychotic symptoms again. With cessation of the mepacrine and two convulsions he was once more restored to normality. Kingsbury records the occurrence of mepacrine psychosis after a dosage as low as 0·6 g. The medical consultants of the United States Army, without adducing supporting figures, give their opinion that psychological disturbances in association with mepacrine are mostly due to " unduly large doses," and note that they have also occurred in connection with suppressive medication. Burnham, on the other hand, records a case of attempted suicide with mepacrine, in which 90 gr. were probably ingested, though an undetermined amount was rejected in the vomit, and though the patient became unconscious and stuporose within 6–7 hours, he regained full consciousness within 48 hours with no development of psychotic

symptoms. Greene's 2 cases developed psychotic symptoms at the end of 6 and 7 days respectively after taking 3 daily tablets (0·3 g.). The case described by Shiers first developed mental symptoms following suppressive mepacrine, 0·1 g. daily, and subsequently during the treatment of malaria, with a daily dose of 0·6 g.

The relation of mepacrine dosage to body weight has been offered as explanation for its toxic effect. In the present series 4 cases are recorded as underweight and of poor physique.

Kingsbury ascribes the toxic effect of mepacrine to two factors, one, to the liberation of toxins by the action of the drug on the malarial parasite, and the other, to the toxic effect of mepacrine on the C.N.S. Turner considered the effect to be due to drug idiosyncrasy, pointing out that the amount of mepacrine taken was not sufficient to produce the symptoms usually associated with the toxic effects of the drug. The study made by two interns, quoted by Allen *et al.*, who gave 1½ gr. mepacrine 3 times daily for 5 days to 2 normal male subjects, who showed no signs of malaria, suggests, however, that mepacrine is toxic in therapeutic doses. Both cases felt exhilaration on the fifth day, one also noted insomnia, and one, at the end of the course, showed flight of ideas, distractibility and a constant stream of irrelevant talk. The factor of suggestibility could not be ruled out in either case. They incline to think that the delayed excretion of mepacrine, for one reason or another, may account for its toxic effect.

The factors that probably act adjuvantly to mepacrine and render it toxic in medicinal doses are: the total amount taken relative to body weight; bodily conditions delaying its excretion, such as constipation, hepatic and renal diseases, disturbed water balance; idiosyncrasy to the drug in rare instances; predisposition to mental breakdown, inherited and acquired; intercurrent stress, physical (infection, especially), emotional and mental. It is necessary in addition to postulate the existence of an individual factor of transient nature to explain the inconstant effect of mepacrine where such factors as have been mentioned above have remained constant, as far as can be judged, but where the mepacrine has induced a psychotic reaction on one occasion and not the next. Investigation of the mepacrine blood level in relation to the onset of mental symptoms may yield useful information, but so far none is available in the literature.

Time of Onset of Symptoms.

About the middle of 1944 the dosage of mepacrine used in the treatment of malaria in the Middle East for cases arriving from Italy and Sicily was standardized at 3·4 g., given over 6 days, followed by maintenance doses of 0·1 g. daily for at least a month. This became the standard treatment for British and other European troops in 1945. Prior to 1944 the standard Q.A.P. treatment of malaria was used, entailing a dosage of mepacrine of 1·5 g. given over 5 days. Where psychotic symptoms developed they occurred during the course of the intensive mepacrine treatment, usually on the third or fourth day (33 per cent.), or at various times following it, mostly within a

week of termination of intensive treatment (67 per cent.). In only one case did symptoms appear before the third day. Twenty-one days following intensive mepacrine dosage was the latest at which it seemed reasonable to connect the symptoms with the mepacrine. One case was, however, admitted to hospital considerably later (3 months), the symptoms having developed relatively slowly to the point where behaviour was affected;* Kingsbury noted the minimum interval between the commencement of treatment and the onset of symptoms to be 1½ days, and the maximum 12 days (5 days after the completion of the course), with an average of 5½ days; the 9 cases reviewed by Allen *et al.* averaged 6·5 days, the dosage used was 1·5 g. given over 5 days. The dosage given in the series of 35 cases reviewed by Gaskill and Fitz-Hugh was 2·1 g., and the onset of psychotic symptoms ranged from the third day of treatment after 0·9 g. of mepacrine had been taken, to 12 days after the completion of treatment. The most frequent was 6 days after completion of treatment. They note in addition, that the onset was often insidious. Field observes that mental symptoms commence just before or just after the end of treatment. Mergener's case developed mental symptoms on the fifth day, after having taken 2·8 g. mepacrine.

It would appear that the later symptoms become manifest the less favourable is the early progress of the case. As Table I indicates, the cases in which symptoms commenced during the period of intensive mepacrine intake (group A) give a ratio of 1 to 1·5 between those recovering within 2 months and those not recovering within this period, whilst in group B, in which symptoms appeared after the completion of the intensive mepacrine course, the ratio is 1 to 3. The difference, however, is not significant, χ^2 being 1·8 and p 0·15 approximately.

TABLE I.

	Recovered within 2 months.	Not recovered within 2 months.
(*a*) Symptoms commencing during period of intensive mepacrine dosage	4	6
(*b*) Symptoms commencing after completion of intensive mepacrine dosage	5	15

SYMPTOMS.

The types of reactive condition induced by mepacrine may be gathered from Table II.

The two most frequent are the schizophrenic and manic reactive ones. In several cases it was impracticable to designate the reaction as either simply manic or schizophrenic, for they showed features of both types of reaction, an exaltation of psychomotor activity and mood coupled with schizophrenic type of ideation; and the reactions were accordingly designated as manic-schizophrenic in type. One observation stands out clearly, namely, that mepacrine tends to produce a manic rather than a depressive setting. Thus in Table II, though the figures are too small for valid statistical deductions,

* and is included among the mepacrine-precipitated cases.

TABLE II.—*To Show Reaction Types and Main Features of Cases.*

	Group A. (Precipitated by mepacrine.)		Group C. (Precipitated by malaria.)		Group B. (Aggravated by mepacrine.)	
	No.	%.	No.	%.	No.	%.
Schizophrenic reaction	8	34·8	3	37·5	4	57·1
Manic reection	4	17·4	1	12·5	..	
Manic-schizophrenic reaction	4	17·4	..		..	
Depressive reaction	3	13	2	25·0	2	28·6
Confusional reaction	1	4·35	..		..	
Alternating manic and depressive phases	1	4·35	1	12·5	..	
Personality change, ? schizophrenic	1	4·35	..		..	
Behaviour disturbance	1	4·35	..		..	
Paranoid reaction	..		1	12·5	1	14·3
Totals	23	100·00	8	100·0	7	100·0
		% of 23.		% of 8.		% of 7.
Showing schizophrenic features	12	52·2	3	37·5	4	57·1
,, manic ,,	9	39·1	2	25·0	..	
,, depressive ,,	4	17·4	3	37·5	2	28·6
,, confusion ,,	3	13	..		..	
,, personality change	1	4·35	..		..	
,, behaviour disturbance	1	4·35	..		..	
,, paranoid reaction	..		1	12·5	1	14·3

it is seen that mepacrine produces manic and depressive features in the ratio 9 to 4, whilst malaria yields a ratio of 2 to 3. Carrol C. Turner refers to Forrester's experience with the British Salonica Force, 1918–19, that, after mental confusion, depression was the earliest and most prominent symptom found in association with malaria. With mepacrine, as the present series indicates, and as is confirmed by the literature on the subject, the mood change produced is one of elation and euphoria frequently leading to acute mania. A simple confusional picture was present in only one case, though transient and mild confusional symptoms were noted in 2 cases of mania. If there is any one type of reaction that is characteristic of mepacrine psychosis it is the manic-schizophrenic syndrome mentioned above. Though it occurs in distinctive degree in comparatively few of the cases (4 or 17·4 per cent.), it does not appear in group C (precipitated by malaria). Some of the cases diagnosed as schizophrenic exhibited manic features in the early phases, but because they were neither prominent nor persistent they were not labelled manic-schizophrenic. Similarly, several of the cases diagnosed as manic, when fully developed, showed schizophrenic features. These cases reinforce the impression of the peculiar effect of mepacrine in inducing an exaltation of mood coupled with a schizophrenic type of thought disturbance. If the 3

types of reaction manifesting manic and schizophrenic features at one or other time in their course, namely, the manic, schizophrenic and manic-schizophrenic reactions, are grouped together, the incidence of the syndrome comprising the features mentioned is about 70 per cent. It is higher still, 78 per cent., if the 2 cases noted further, which commenced as a manic reaction and personality change respectively and developed later into schizophrenic states, are added.

The onset of psychotic symptoms is signalized by insomnia almost invariably, and in the non-depressive cases by a sudden change of behaviour, with usually an outburst of noisy talkative excitement. The psychotic picture develops rapidly thereafter. There is a brief phase lasting a day or two, characterized by features such as puzzlement, fleeting ideas of influence, a loss of personality and reality sense, a degree of emotionality and, in some cases, transient confusion and disorientation. The mood then changes to the more characteristic and enduring one of elation and euphoria. With this the thought content becomes delusional and the behaviour disordered, sometimes grossly. The delusions are of an exalted character relating mostly to the patient's social position and work. The patient soon begins to interpret his experiences—the loss of inhibition and the elation—in a spiritual, religious light, and this is followed by failure of co-ordination of thought and the expression of bizarre ideas such as are commonly present in typical cases of schizophrenia. The delusional trend of thought is not maintained long enough for the delusions to acquire any degree of systematization. Insight is totally lost only for the brief period of the climax which the development of symptoms quickly reaches; it is present both before and afterwards, if often only fleetingly. When within a few weeks or months improvement commences, it proceeds rapidly to full recovery. In the cases that do not progress to recovery, evidence of dementia quickly supervenes on the acute stage of florid symptoms; there is deterioration of the personality, the manner becomes facile, and affect and interest are dulled.

Turner remarks on the maniacal nature of the reaction to mepacrine; he observes that the condition merges into a "somnolent delirium" or even "deep coma", but this was noted in only 2 cases in the present series, and in both there was a complicating factor that may have accounted for the unusual type of reaction. One case had had infective hepatitis coincidentally with the malaria. Fourteen days after discharge to convalescence the patient became sleepless, restless, noisy, loquacious and aggressive, and was admitted to the psychiatric hospital (78th) in this condition. E.C.T. (twice) and sedation had little effect, and 10 days after admission the patient lapsed into a comatose state, with acetone in the breath and urine and raised temperature (up to 101°). The other case had been treated with mepacrine, though malarial parasites had not been found in the blood. It had, in fact, been labelled as P.U.O., and whatever the nature of the infective agent may have been it appears to have invaded the central nervous system, for the C.S.F. was found to be slightly turbid and the cells increased to 12 per c.mm. No organisms were found. Urine culture was negative, and blood agglutination for typhus, typhoid and *Brucella* not abnormal. The blood showed a leucocytosis with

a count of 12,300 (P. 51%, L. 47%, M. 2%). On the third day of mepacrine treatment the patient developed maniacal symptoms, his physical condition deteriorated with the excitement, and he slipped into a muttering delirium 6 days later.

The two cases seen by Greene, as quoted by Allen *et al.*, are described as cases of "cerebral excitation"—they were hilarious and excited, danced and sang. The 9 cases they review give the following distribution of reactions: excitement, closely resembling mania, 5; mild excitement with confusion, 2; almost no excitement but severe confusion, 2. Gaskill and Fitz-Hugh also note the two types of condition; the one showing increased motor and psychomotor activity, euphoria and expansiveness, auditory and visual hallucinations and delusions, and occasionally disorientation; the other, with insidious onset, showing gradual clouding of the sensorium, disorientation and loss of recent memory and diminished motor and intellectual activity. "The latter patients were withdrawn and seclusive, the affect being one of bewilderment and fearfulness." Udalagma, quoted by Mergener, notes that amnesia follows the acute symptoms of excitement, confusion and disorientation. Mergener's case manifested an initial manic phase followed by a depressive one on the third day in a confusional setting. With improvement, an extensive amnesia was noted. The patient described by Shiers developed exaltation of faculties on each of the three occasions that he took mepacrine.

When psychotic symptoms have preceded the exhibition of mepacrine, their aggravation by it is less dramatic in onset, but is none the less clearly recognizable. The change produced is one of degree and not of kind.

Clinical Pictures.

The clinical pictures presented by the various types of reaction may be better appreciated from the description of a few representative cases:

F. H. B—; aged 36; Flying Officer; bank clerk in civil life; maternal uncle insane, aunt alcoholic; schizophrenic reaction type.

Admitted to hospital for B.T. malaria and placed on mepacrine. Following day suddenly began declaiming to the ward: "The world does not exist, never has and never will. Ladies and Gentlemen, this is the end of the world. I am going to die. For Jesus Christ's sake, kill me," etc. Next day, in more tranquil and clearer state of mind, clearly recalled what he had been saying, explaining that he felt as if the words were being put into his mouth, thought he was going to be killed and felt muzzy. After a fortnight, presumably having shown no further outward symptoms of mental disturbance, he was discharged, but his behaviour became rapidly abnormal again, so that he presented himself at a R.A.F. station completely naked, having walked there in this state some 500 yards from his hotel, and was readmitted to hospital. He reported that he was under the compulsion to find out what was wrong with the world, so as to put it right, that he did not know how he was going to do this, but that as a preliminary he thought he should have his head and legs cut off. His talk was rambling and showed flight of ideas. A week later there was less psychomotor excitement: his manner was, however, facile, and he frequently affected an inane smile. He displayed neither insight nor concern about his circumstances or his future. Occasional thought-blocking was observed. Still referred, but without any display of emotion, to being responsible for the evil in the world. Two months later he was recorded as recovered.

J. J. G—; aged 30; Sergeant, Regular; married; manic reaction type.

Had two attacks of malaria and two complete courses of mepacrine therapy, over a period of 3 months. At the end of the last course became sleepless and restless and his manner changed: was argumentative and paranoidal in outlook. On admission he was talkative, overactive, euphoric and exalted; declared there was nothing wrong with him, and smiled inanely and was generally facile; claimed to have a scheme for repaying the National Debt and asked to see the O.C. hospital regarding it. He recovered rapidly within 3 weeks of admission.

W. H—; aged 31; Regular Officer; manic-schizophrenic reaction type.

Seen when he had more or less recovered from the acute symptoms a fortnight after their commencement, he gave the following account of their development. On completion of mepacrine course and on the eve of his discharge from hospital, he began to experience acceleration and press of thought and a feeling of excitement. Next morning, returning to unit, felt he was talking brilliantly and more than was his wont. Then quickly followed a feeling of light-headedness and puzzlement and disordered thought and behaviour. His talk became rambling and disjointed. Had idea that he was being watched and that he was being influenced in his actions, and resisted this. In recall, says of this period, he felt as if in a trance, only hazily appreciating his surroundings and his actions, and that on admission to hospital he felt worried by changes he noted since he was previously there (2 days ago). Thought he had been dead for a year, and that he had resuscitated himself through will-power. "If I wished I could be God, but preferred to remain on earth. I could live for ever. I felt I was a saint and dead, turned to dust, a speck on top of the pyramid. I could get right within myself outside space. My body was indestructible. I had split the atom and feared I might blow up the whole earth. Black and white had met, I had won a colossal sweepstake and was the Supreme Being. I thought I was the genius who was running the war, and that Churchill, Roosevelt and Stalin had met to consult me." Conceived the idea that he was Prince John (who was born same year as himself), and that he was being used as a "whispering gallery for deception." "I have had ups and downs whilst here. In my ups I think I am God, marvellous at everything; in my downs worry whether I am a degenerate, whether I have infantile palsy and worry about my recent experiences." On admission to hospital, he looked vacant and bewildered, addressed the M.O. casually, asking, "Who am I, what am I?" He was not, however, disorientated, and his memory was unimpaired. His manner was grandiose: mood, one of elation. He was talkative, wrote many disjointed letters, and drew up scribbled plans for finishing the war, for demobilization, etc. Expressed numerous delusions of exaltation—that he belonged to Royalty, was to receive the V.C., get high promotion, etc., and showed such poor sense of reality that he was frequently bidding the staff farewell as he was about to set off in execution of his ideas. At one time or another he mistook identities and manifested depersonalization and feelings of passivity. He frequently passed irrelevant remarks, was hallucinated, especially at nights. At times noisy and overactive. He was, however, possessed of a degree of insight, and was not altogether detached from reality; though he behaved at times as if he were unable to distinguish between fantasy and reality.

He had only one testicle; the other had atrophied he said, following a kick at 17. He was unmarried and was a latent homosexual with strong though repressed homosexual urges. Had guilt feelings regarding masturbation. Had never had intercourse. Was a hard-working and very conscientious officer, and had gained the M.C. at Dunkirk.

R. C. E—; aged 31; Private; manic-schizophrenic reaction type.

In the night following completion of course of mepacrine for M.T. malaria became restless and rowdy, talked irrationally. On admission to hospital was disorientated as to place and person, showed psychomotor over-activity and mild flight of ideas. Slightly elated, and later euphoric, expressed a number of bizarre delusions—his thoughts were being read, he was a Brigadier, had put an end to the war—but he had fleeting insight. The psychiatrist in charge expressed the view that the case had never appeared as a true toxic confusional picture, and considered it a schizophrenic episode. Five months later he was declared recovered.

B. N—; aged 24; Private; single; manic-schizophrenic reaction type.

Whilst having mepacrine treatment for malaria became elated and excited; declared he had received the gift of the Holy Spirit, felt raised above worldly things and believed he would never be able to procreate. He wrote to the Under Secretary of State for War outlining a scheme for establishing a training college for social and religious workers. "I have the greatest message for the world in 2,000 years," he wrote, "I shall never sleep again in this life for the simple reason that it would be totally unnecessary. I am Christ reborn." At times grinning and mumbling to himself. Despite his delusions, his behaviour was correct. Recovered within fortnight of onset of symptoms. Though S.G. 1, had failed twice in his matriculation examination prior to the war; had fallen in love with his crammer's wife. Had recently started studying for it again in off-duty hours.

G. B—; aged 37; Lieutenant; married; depressive reaction type.

Father committed suicide at 44; mother had mental illness prior to death at 55. Trained as solicitor, but not feeling fit to practice took up teaching. History of mood swings. Whilst undergoing mepacrine treatment for M.T. malaria developed mental symptoms, depression without retardation, marked ideas of unworthiness, ideas of reference. Demanded to be sent back to unit to stand trial for desertion, believing his army career to have been a succession of failures. "My name must be mud all over the Arakan. They are talking of throwing me into the water as a fifth columnist." His *rapport* was good and there was no disharmony of mood and thought. Had a slight stammer, tachycardia, exaggerated reflexes.

H. C—; aged 31; Sergeant, Regular; single; confusional reaction.

Had 5 attacks of malaria in the past 2 years. A month ago broke off his engagement. With present malarial relapse was placed on mepacrine and on third day his speech became slow and incoherent, his mood oscillated between elation and depression, vomited after food and was incontinent. Twelve days later his answers were monosyllabic and absurd; he was slow in carrying out physical movements to order and was still incontinent. Physical examination and investigation of blood and C.S.F. were negative. By the time of his admission to hospital, 3 weeks after commencement of symptoms, the mental state had cleared and he rapidly regained normality.

J. W. W—; aged 31; C.S.M., Regular; single; instance of aggravation of pre-existing symptoms by mepacrine.

Returned home after 8 years' service abroad. Had difficulty in accommodating himself to the changed circumstances of life. In his absence overseas, mother and brother had died, and on returning felt alone in the world. Also felt he could not measure up to the job of instructor which he was given. Developed a mild reactive depression, and was recommended for admission to a neurosis centre. Whilst waiting to enter the centre he had a malarial relapse, was admitted to hospital and placed on mepacrine. Insomnia and depression increased, feared he was going insane, and in a state of utter misery, 3 days after commencing mepacrine treatment, made suicidal attempt by cutting wrist. The acute depressive symptoms cleared quickly, but anxiety symptoms persisted for more than 6 months.

Prognosis.

Fourteen of the 23 cases (68 per cent.) recovered within 6 months of onset of symptoms; 1 in 14 days, 4 in 22 to 25 days, 4 in 2 months, 2 in 3 months, 2 in 7 months, 1 in 5 months. The average was 62 days. In Table III the development reached at the end of 2 months is shown. The cases are divided between the manic and schizophrenic sub-group and the remainder. The figures point to an earlier recovery for the manic and schizophrenic sub-group than for the other cases in the group: the ratio of recovered to non-recovered is 7 : 9 for the former and 2 : 5 for the latter. The difference, though suggestive,

is not significant. What the recovery rate would be had it been possible to follow up all the cases to, say, 6 months, it is difficult to say, but of the 15 cases followed up for that period, 14 recovered.

TABLE III.

	Manic and schizophrenic sub-group.		Remaining cases.		Total.	
	No.	%.	No.	%.	No.	%.
Recovered* within 2 months	7	43·8	2	28·6	9	39·1
Not recovered† at end of 2 months	9	56·2	5	71·4	14	60·9
Totals	16	100·0	7	100·0	23	100·0

* Included improved.
† Including improved followed by relapse.

No appreciable difference in the tendency to early recovery between the various clinical types included in the manic and schizophrenic sub-group is detectable (see Table IV).

TABLE IV.

	Schizophrenic type. No.	Manic type. No.	Manic-schizophrenic type. No.
Recovered within 2 months	3	2	2
Not recovered at end of 2 months	3	1	..
Total	6	3	2

Greene's cases, quoted by Allen *et al.*, recovered within 24 to 48 hours. The 9 cases reviewed by them give an average duration of symptoms of 15·1 days. The symptoms in Field's case lasted approximately 1 week. Thirty-three of the 35 in the Gaskill and Fitz-Hugh series recovered within a range of 8 to 85 days, with an average of 23 days. In the 2 patients who failed to recover, they considered a schizophrenic reaction had been precipitated. Five of Udalagama's 7 cases recovered in from 17 hours to 41 days, one died of exhaustion and other complications, and one developed chronic mental symptoms. Bispham's case recovered in 22 days, Mergener's in 14 days.

The stages reached at the end of 2 months by the non-recovered cases in the author's series were as follows:

(*a*) Schizophrenic reaction type:
  (i) Showing further deterioration 1
  (ii) Showing relief of acute symptoms but with residual dilapidation 2
(*b*) Manic reaction type:
  Showing schizophrenic development . . . 1
(*c*) Manic-schizophrenic reaction type:
  Showing dilapidation and instability . . . 1

(*d*) Depressive reaction type :
(i) Showing schizophrenic development . . 1
(ii) Unchanged 2
(*e*) Personality change—? schizophrenic development . 1

It will be observed that in addition to the immediate manic and schizophrenic reactions to mepacrine, 2 cases, commencing in other guises, developed schizophrenic symptoms.

Age-Incidence.

A comparison between cases precipitated by mepacrine and those precipitated by malaria suggests that mepacrine psychosis is more likely to occur in the older than the younger soldier. This may be connected with the observation previously made, that there is a relative preponderance of officers and N.C.O.s amongst the cases of mepacrine psychosis reviewed. In the 20–25 age-group the ratio of officers and N.C.O.s to private and equivalent ranks is 2 : 7, whilst above 25 the ratio is 4 : 3. Table V indicates a ratio of approximately 2 : 3 for the incidence of mepacrine psychosis in the age-groups below and above 25, whilst with psychosis precipitated by malaria it is the reverse—5 : 3. The difference is not, however, statistically significant.

Table V.

Age-period.	Group A. (Pptd. by mepacrine.)				Group C. (Pptd. by malaria.)			
	No.	%.	No.	%.	No.	%.	No.	%.
20–25	9	39·1			5	62·5		
26–35	11	47·8	14	60·9	1	12·5	3	37·5
36–44	3	13·1			2	25·0		

The reaction is more likely to be schizophrenic in type in the younger age-group, 20–25 ; the other reactions mostly occurring in the older age-groups, 26 and above. This may be gathered from Table VI.

Table VI.

Age-period.	Schizophrenic reaction.		Other reactions.	
	No.	%.	No.	%.
20–25	6	75·0	3	20·0
26 and over	2	25·0	12	80·0
Totals	8	100·0	15	100·0

There does not appear to be any notable connection between personality make-up and the type of psychotic symptoms precipitated by mepacrine. Two of the 3 depressed cases gave a positive family history of psychopathy or insanity, whilst in the manic and schizophrenic sub-group a positive history occurred in 2 of the 16 cases. Emotional stress, other than that of battle, figures as a contributory factor in 4 of the 8 cases of schizophrenic reaction type, as against its occurrence in 3 of the 15 other cases. It is, perhaps, noteworthy that the schizophrenic reaction type is not associated with any history

of earlier breakdowns. There are no significant differences in the previous incidence of malaria amongst the different types of reaction.

Mepacrine staining was noted in 7 cases of group A (30·4 per cent.) and in 3 cases in group B (42·9 per cent.). It was more or less proportionally distributed among the various reaction types. Eight of the 9 cases of Allen *et al.* developed pigmentation. Mepacrine pigmentation is said (Manson) not to occur before the third day, and probably it is not without significance that mental symptoms likewise appear from the third day on, as a rule. The intensity and duration of the staining are affected by intercurrent infections and factors interfering with the elimination of mepacrine, as, e.g., constipation. It may persist as long as 3 months (Manson). The elimination of mepacrine from the body is slow, and may not be completed for as long as a month. The rate of elimination probably influences the duration of symptoms resulting from the mepacrine.

Effect of Convulsive Treatment.

Four cases in group A and 2 in group C received electrical convulsive treatment. Cessation of mepacrine will, no doubt, have played a part in determining such favourable results as were obtained, but the symptoms did not promptly disappear with the stoppage of mepacrine, and the beneficial influence of the convulsive treatment cannot be denied. Four (2 cases of schizophrenia and 2 of depression) of the 6 cases showed improvement and remission against 2 unchanged. Two (one case of schizophrenia and one of depression), however, relapsed shortly after treatment. The number of convulsions given ranged from 2 to 6, averaging 4·6.

Combining such figures cited in the literature, as are relevant, with those of the writer's series provides the following data: The incidence of mepacrine psychosis amongst the cases of malaria treated with mepacrine is 0·25 per cent. (47 in 18,580); the minimum dose of mepacrine which has induced psychotic symptoms has been 0·45 g., and the symptoms have appeared as soon as 1½ days after the exhibition of mepacrine and as late as 21 days. The recovery-rate has been 81·4 per cent. (57 cases out of 70). The duration of symptoms has ranged from half-a-day to 5 months; with an average, for the 51 cases having the averages recorded, of 32 days. 10 per cent. approximately of the cases give a history of previous mental breakdown (8 in 81 cases), and 11·6 per cent. a positive family history (5 in 43).

Differential Diagnosis.

The differential diagnosis of mepacrine psychosis presents two problems: one, the differentiation from cerebral malaria and, two, from an endogenous or biogenic psychosis. The mental symptoms of cerebral malaria, as usually manifested, come on more precipitately and are more acute in nature. In association with hyperpyrexia the patient develops delirious mania or muttering delirium, rapidly becomes unconscious and comatose; or without hyperpyrexia, coma or epileptiform convulsions suddenly develop, preceded perhaps in some cases by such premonitory symptoms as severe headache, drowsiness,

irritability, muscular twitchings. Difficulty of differential diagnosis is only likely to arise in those uncommon instances where mepacrine induces delirium or coma. Similarly, difficulty will be experienced in the presence of the less common and less dramatic forms of cerebral malaria, which may simulate almost any type of mental disorder. The course and severity of the malarial attack and the patient's physical condition may point to the presence of cerebral malaria, whilst the time-relationship of onset of symptoms with the exhibition of mepacrine, and possibly also the improvement of symptoms on ceasing mepacrine, will indicate the presence of mepacrine psychosis. In the cerebral forms, malarial parasites are usually scanty in the peripheral blood. The differentiation from a biogenic psychosis is a more difficult problem, because mepacrine does sometimes precipitate a condition indistinguishable from a biogenic psychosis. If recovery within 2 to 6 months may be taken as presumptive evidence in favour of regarding such cases as those of an acute reaction to mepacrine, there remain 9 of the 23 cases precipitated by mepacrine, which not having recovered at the end of 2 months, become suspect cases of biogenic psychosis. It is likely, of course, as has already been pointed out, that some of these cases, had it been possible to follow them up for, say, 6 months, might have shown recovery. However, reckoning with the possibility that these 9 cases may be instances of biogenic psychosis, we find, on analysing the stages of development reached by them at the end of 2 months, that 2 had developed into schizophrenia, 1 looked very much like a schizophrenia, 3 showed mental deterioration and 3 improvement of the florid symptoms, but with residual dilapidation of the personality. It will be seen, therefore, that at least 5 of the cases, namely, those showing either schizophrenic development or mental deterioration, suggest the presence of a biogenic psychosis. The series of 23 cases divides itself, therefore, into 18 of acute reaction (78·3 per cent.) and 5 of possible biogenic psychosis (21·7 per cent.). It may, of course, be that the biogenic psychosis is to be regarded as a sequel of an acute organic reaction. The evidence is, however, lacking, that it is possible to distinguish in those cases that develop as a biogenic psychosis, an initial stage that can be more accurately described as an acute organic reaction than an acute stage such as commonly ushers in a biogenic psychosis. The fact remains that, whether *via* an acute organic reaction or not, mepacrine precipitates a chronic psychosis in about a fifth of the mental breakdowns attributable to it. The problem of differential diagnosis, therefore, comes to this: whether it is possible in the early stages to distinguish between the acute reaction to mepacrine and a chronic psychosis associated with it. The 5 cases suspected of being instances of biogenic psychosis precipitated by mepacrine comprise 3 cases of depressive state and one each of schizophrenia and mania. The former embrace the total number of cases of depressive state found in the series: at the end of 2 months one was showing schizophrenic development and the other 2 showed no improvement. They were older than the average for the series, their ages being 30, 37 and 43. The two going on to chronic depression gave a positive family history of insanity (father in the one case, sister in the other), and a personal history of life-long feeling of anxiety and inadequacy. The case of

mania developed into schizophrenia. In neither this case nor the one manifesting frank schizophrenia from the start was it possible to point to any features hinting that their prognosis was less favourable than that of the other cases of mania and schizophrenia in the series. The most that can be said, therefore, on the subject of differential diagnosis between a biogenic psychosis and an acute reaction precipitated by mepacrine, is that where the complex of symptoms is predominantly depressive in character the prognosis is less favourable and the condition is likely to become chronic, and that the condition was possibly a biogenic psychosis from the start.

There is not, when all is said and done, much to commend drawing a distinction between an acute reaction and a biogenic psychosis in the early stages of psychotic reaction to mepacrine. Even more unsatisfactory than regarding a case as one of biogenic psychosis, because the symptoms progress into chronicity, is that of calling it, in the final analysis, an organic reaction, when, in fact, the characteristic features of an organic reaction are absent. It is more rational to drop both terms, acute organic reaction and biogenic psychosis, and to diagnose a psychotic reaction to mepacrine simply as an acute reaction, which, because of its specific character in many instances, can, with truth, be termed a mepacrine psychosis.

Precautions in Use of Mepacrine.

Though there is ample statistical evidence that the risk of mepacrine psychosis is infinitesimal compared to the advantages that mepacrine yields both in the prophylaxis against, and treatment of, malaria, it nevertheless calls for alertness to the danger of mepacrine in the odd case. The circumstances which should put the medical attendant on his guard in exhibiting mepacrine are :

(*a*) Recent attacks of malaria (the more so when there has been more than one).

(*b*) Hepatic derangement.

(*c*) Injudicious over-dosage with prophylactic mepacrine.

(*d*) The presence of any factor that may delay the excretion of mepacrine, such as constipation, renal insufficiency, inadequate liquid intake or excessive fluid loss (Allen *et al.*).

The danger signals calling for the stoppage of mepacrine in the treatment of a malarial attack are :

(*a*) Staining of skin.

(*b*) Appearance of insomnia, alteration of conduct—restlessness, talkativeness—or confusion.

If the occurrence of the comparatively uncommon untoward effects of mepacrine are borne in mind, and the appearance of danger signs heeded, there is little risk in giving the dosage of the standard course. To exceed this dosage is, however, asking for trouble. Kingsbury appears to favour limiting the daily dose to 0·2 g. The U.S. Army medical consultants recommend that 0·7 g. as a suppressive dose, and 2·8 g. in 7 days, as a therapeutic dose, should not be exceeded.

SUMMARY.

Thirty-three cases of psychosis associated with mepacrine have been reviewed. In about 70 per cent. a reaction, characterized by schizophrenic or manic or both manic and schizophrenic features, occurs. Depressive reactions are possibly instances of biogenic psychosis precipitated by it. Aetiological factors contributing to the toxic effect of mepacrine are considered. Figures are given for the time of onset of symptoms, their duration and the rate of recovery. The differential diagnosis is considered.

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REFERENCES.

ALLEN, E. W., *et al.* (1937), *J. Med. Assoc. Georgia*, **26**, 62–66.
BRIERCLIFFE, R., (1937), *Bull. Hlth. Org. L.O.N.*, **6**, 1079.
BURNHAM, R. C. (1946), *U.S. Naval Med. Bull.*, **46**, 434–437.
FIELD, J. W. (1938), *Bull. Inst. Med. Res., Fed. Malay States*, No. 2.
GASKILL, H. S., and FITZ-HUGH, T., jun. (1945), *Bull. U.S. Army Med. Dept.*, No. 86, p. 63.
HOOPS, A. E. (1937), *Bull. Hlth. Org. L.O.N.*, **6**, 1079.
KINGSBURY, A. N. (1934), *Lancet*, **2**, 979–982.
Manson's Tropical Diseases (1945). London: Cassell & Co., p. 101.
MERGENER, J. C. (1945), *War Medicine*, **8**, 250–252.
Report of Medical Consultants Division, Office of the Surgeon-General, United States Army (1945), *J. Amer. Med. Assoc.*, **129**, 1091–1093.
SHIERS, D. (1946), *Brit. Med. J.*, **1**, 762–763.
TURNER, CARROL C. (1936), *Southern Med. J.*, **29**, 578–585.