The effects of mepacrine on the gastrointestinal tract of man / by the Army Malaria Research Unit and the Nuffield Institute for Medical Research, Oxford.

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Dr. E. M. LOURIE

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BY

THE ARMY MALARIA RESEARCH UNIT

AND

THE NUFFIELD INSTITUTE FOR MEDICAL RESEARCH, OXFORD

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THE EFFECTS OF MEPACRINE ON THE GASTRO-INTESTINAL TRACT OF MAN

BY

THE ARMY MALARIA RESEARCH UNIT*

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THE NUFFIELD INSTITUTE FOR MEDICAL RESEARCH,† OXFORD

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The most frequent toxic effect of mepacrine administration is a disturbance of the gastro-intestinal tract, which varies in severity from a slight diarrhoea to intense nausea, vomiting and severe diarrhoea accompanied by fever and prostration. Fortunately these unpleasant side-effects are seldom seen when mepacrine is given in doses of 0·1 gm. a day. Shortly before the Army Malaria Research Unit began its work, however, diarrhoea and vomiting suddenly occurred on a large scale in North Africa among troops who had recently begun to take suppressive doses of mepacrine, and it was decided to make a study of the effects of the drug on the gastro-intestinal tract. Preliminary experiments were done in animals to determine the relative toxicities of different salts of mepacrine, to estimate the effects of different modes of administration, and to work out the mechanism of the disturbance. These experiments have in part been reported (Army Malaria Research Unit, 1945). Human experiments were then undertaken. Observations were made on a large number of volunteers taking various amounts of mepacrine, and a limited number of cases were submitted to intensive investigation by means of fractional test meals, barium meals, cholecystography, gastroscopy and bacterial examination of the stools. The results of the human experiments are presented in this paper. They show that when mepacrine is given in what is now the common suppressive dose, 0·1 gm. a day, gastro-intestinal disturbances are slight and infrequent, and they suggest an explanation of the serious effects seen after the intermittent dosage used in North Africa in 1943.

TECHNIQUES

Barium Meals. All the women volunteers had two control barium meals before the exhibition of mepacrine. The soldier volunteers had one control meal. There was no preliminary preparation, and the volunteers were on their normal diet the day before the experiment. On the morning of the barium meal they had a cup of tea on awakening. After the three-hour film they were given two cups of tea and some sandwiches, and they resumed their normal diet after the six-hour films. The opaque meal consisted of 1/8 pint of Horlick's Shadow Food mixed with an equal amount of water. All the films were taken with a Lysholm Grid but without the use of a Potter-Bucky diaphragm. Films were taken, after preliminary screening, immediately after the barium meal was given,

* Lt.-Col. B. G. Maegraith, R.A.M.C., Major Malcolm Brown, R.C.A.M.C., Major R. J. Rossiter, R.A.M.C., Major K. N. Irvine, R.A.M.C., Capt. J. C. Lees, R.A.M.C., Capt. D. S. Parsons, R.A.M.C., Capt. C. N. Partington, R.A.M.C., Capt. J. L. Rennie, R.A.M.C., and Surgeon Lt. R. E. Havard, R.N.V.R.

Major H. W. Davies, R.A.M.C., Capt. E. H. Hanson, R.A.M.C., and Miss I. M. Pearson, with † Dr. K. J. Franklin, Dr. A. E. Barclay and Miss M. M. L. Prichard.

and at 20 minutes, 40 minutes, and 1, 2, 3, 4, 5, 6 and 24 hours. Reductions of the 15" by 12" films were made to facilitate the examination of comparable series.

Gastroscopy. All gastroscopic examinations were made with a Hermon Taylor gastroscope, and there was one control examination before the exhibition of mepacrine. Premedication consisted of hyoscine hydrobromide gr. 1/100 one hour before gastroscopy.

Plasma Mepacrine Estimation. Plasma mepacrine concentration was estimated by a modification of the method of Masen (1943).

Bacteriological Examination of the Faeces. The relative numbers of Gram positive cocci and bacilli and Gram negative bacilli were estimated from stained films. The proportions of coliform bacilli and faecal streptococci were estimated in inoculating McConkey agar plates with tenfold dilutions of a suspension of faeces.*

THE EFFECTS OF LARGE DOSES OF MEPACRINE

Mepacrine in doses from 0·6 to 1·4 gm. was given to 16 women volunteers so that the gastro-intestinal effects of the drug could be studied in a severe form and their characteristics easily identified. Twelve women received a single dose of mepacrine 0·6 to 1·0 gm. one and a half hours before the barium meal. The other four were given 0·6 gm. on the preceding day and 0·2 to 0·8 gm. one and a half hours before the barium meal. Eleven of the subjects had never received mepacrine before; the remaining five had been on a suppressive dosage for several months, but two barium meals which preceded this experiment were normal in each case and were regarded as controls.

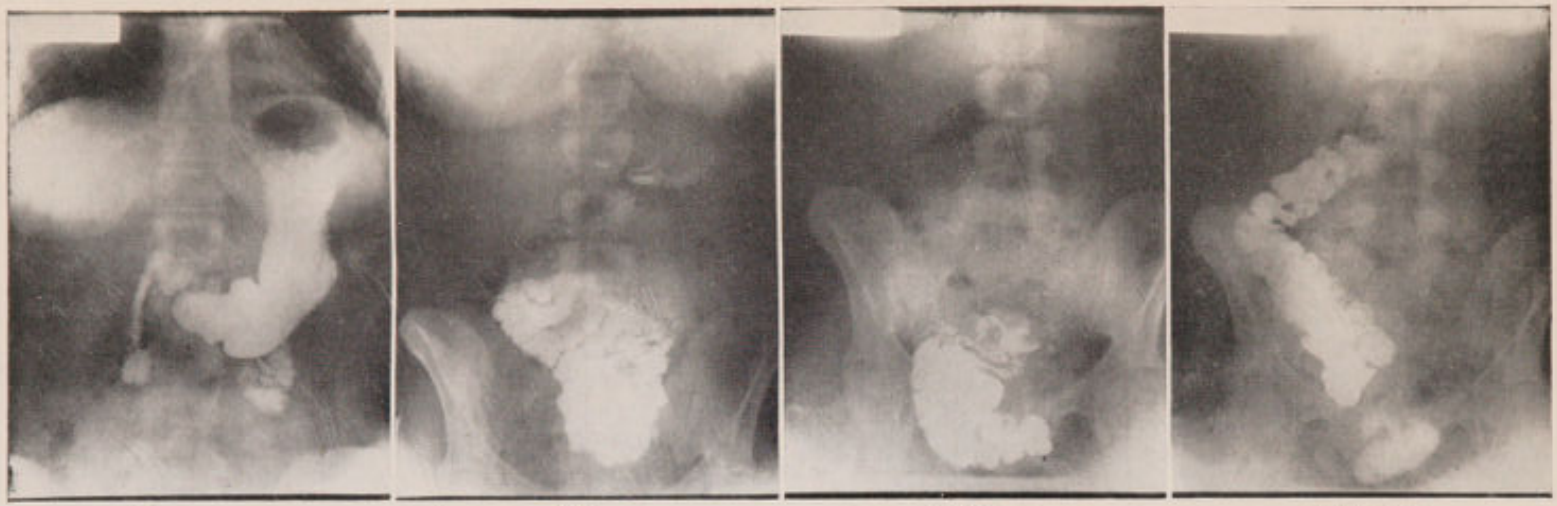
Clinical Observations. A regular sequence of symptoms was seen in all but three of the volunteers. During the first two hours after taking the drug there was headache, nausea, and sometimes a single emesis or a loose bowel motion. For the next two to four hours the subjects usually felt well except for a slight headache. After this period of relative well-being, the headache usually became more severe, nausea returned, sometimes accompanied by sudden and repeated vomiting, and colicy abdominal pain and diarrhoea were frequent. In the more severe cases there was fever and prostration. Pallor and coldness of the extremities were the only abnormal physical signs. Eight to nine hours after the administration of the drug, improvement set in and recovery was usually completed in a few hours.

Barium Meals. Radiographically there were abnormalities in the appearance of the stomach or intestines in all but two of the cases. One exception was a woman who received a single dose of 1·0 gm. and felt well until the end of the fourth hour, when she developed a headache. After seven hours she became nauseated and vomited twice. In her case the disturbance occurred after the barium had left the part of the gastro-intestinal tract which was involved, and no radiographic record was obtained. The second exception was one of those who had no symptoms. The other two volunteers who had no symptoms had abnormal radiographic findings of moderate severity.

In the period immediately following the taking of the barium meal, there was gastric hypersecretion, hyperperistalsis, an increase in tone which was most marked in the pyloric antrum, and pylorospasm. These changes often resulted in a reversed L-shaped stomach, the hypertonic pyloric antrum being at right angles to the body of the stomach. In one case the disturbed tone and motility gave rise to a ' cup and spill ' deformity. Pylorospasm

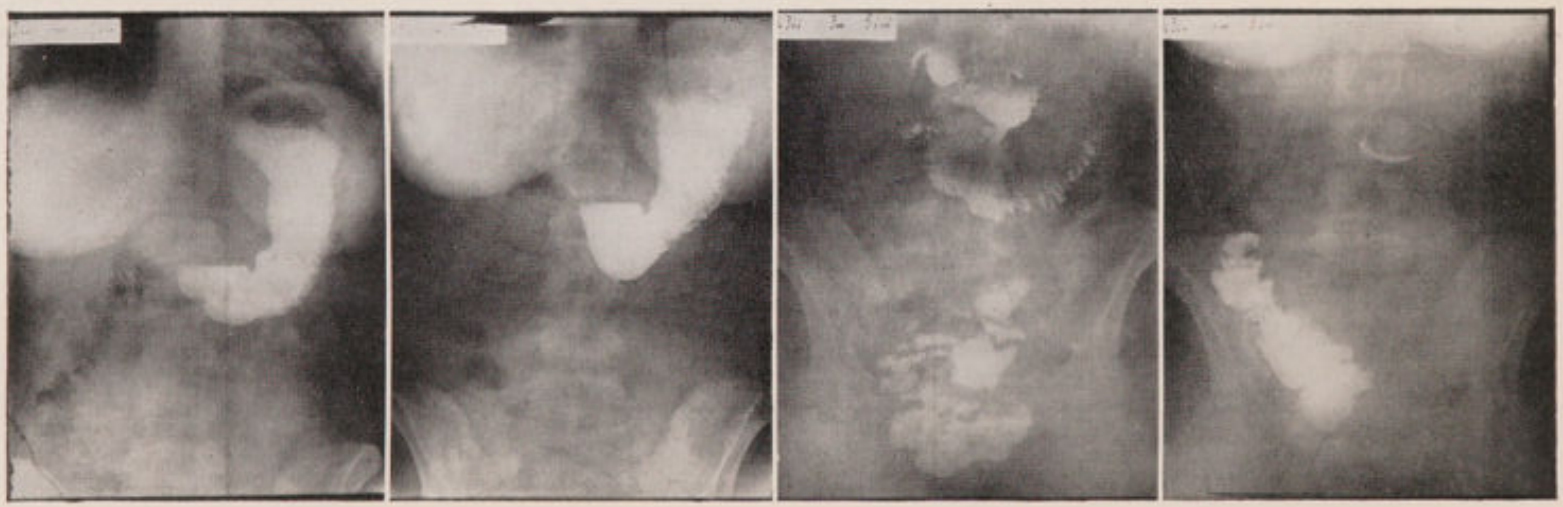
* The bacterial examination were made by Dr. W. D. Fleming.

EFFECT OF LARGE DOSES OF MEPACRINE HYDROCHLORIDE ON THE GASTRO-INTESTINAL TRACT



IMMEDIATE 1 HOUR 3 HOURS 6 HOURS

FIG. 1. Control barium meal series on volunteer no. 364.



IMMEDIATE 1 HOUR 3 HOURS 6 HOURS

FIG. 2. Barium meal series on volunteer no. 364 after 0·6 gm. mepacrine hydrochloride on previous day and 0·6 gm. mepacrine hydrochloride half an hour before the meal, showing marked delay in start of gastric emptying, increase in gastric secretion, marked irritability of small intestine, and delay in passage into colon.

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EFFECT OF LARGE DOSES OF MEPACRINE HYDROCHLORIDE ON THE GASTRO-INTESTINAL TRACT

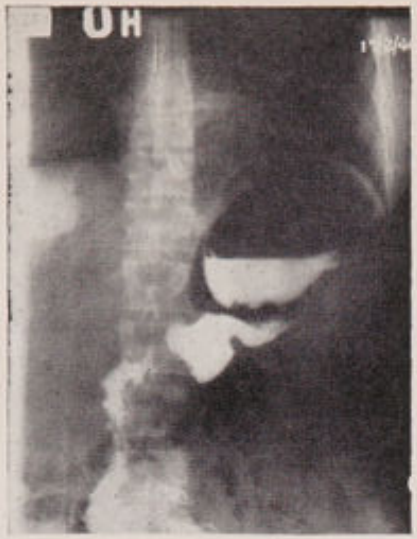

FIG. 3. No. 206. Immediately after barium meal. 1½ hours after 1·0 gm. mepacrine hydrochloride taken orally. Marked irritability of stomach producing 'cup and spill' deformity.

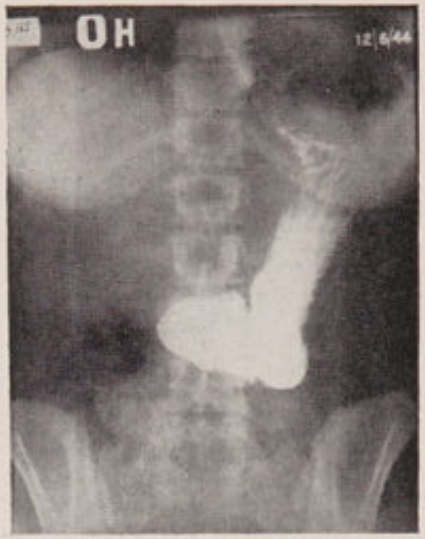

FIG. 4. No. 165. Immediately after barium meal. 1½ hours after 1·0 gm. mepacrine hydrochloride taken orally. Increased resting juice, pylorus not open, over-vigorous contraction of stomach indicative of pylorospasm.

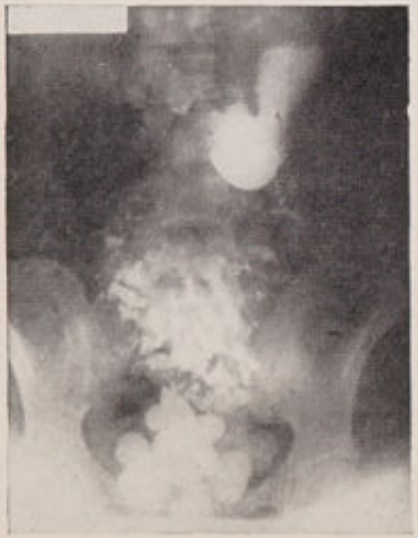

FIG. 5. No. 356. 40 minutes after barium meal. 2 hours after 0·6 gm. mepacrine hydrochloride taken orally. Small intestine shows irregular clumping indicative of irritability.

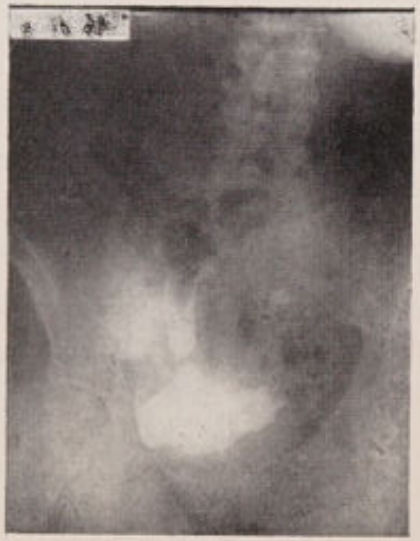

FIG. 6. No. 358. 3 hours after barium meal. 4½ hours after 0·6 gm. mepacrine hydrochloride taken orally. Barium held up in loop of small intestine, possibly owing to ileal spasm.

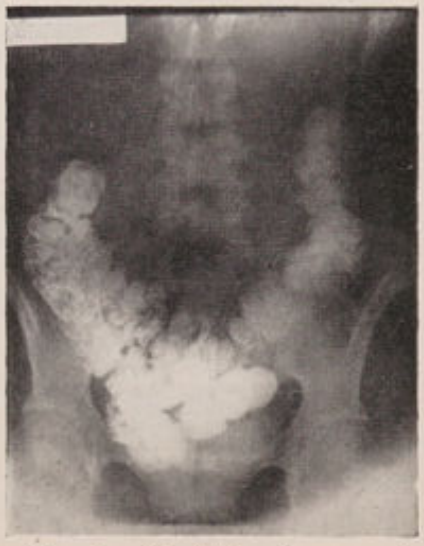

FIG. 7. No. 356. Same meal as fig. 4, but 6 hours after barium meal. 7½ hours after 0·6 gm. mepacrine hydrochloride taken orally. Shows extremely rapid advance of meal.

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was sometimes so severe that no emptying occurred for more than an hour. These changes were followed by a decrease in gastric tone and peristalsis, and this with continued pylorospasm caused delay in final emptying of the stomach.

A disturbance of the pattern of the small intestine was the most frequent abnormal finding in the series. The normal pattern of the valvulae conniventes was replaced in most cases by a fragmentation of the barium into small ragged clumps of irregular size and shape. Sometimes exaggerated segmentation resulted in columns of barium a few inches in length, and the edges of these columns showed irregular smooth indentations. Numerous small flecks of barium were often left in the jejunum and upper ileum after the main mass of the meal had passed on. In the lower ileum there was a combination of rings of contraction and decreased tone in the intestinal wall, which led to the accumulation of barium in round masses a few centimetres in diameter. In one case there were multiple fluid-levels in the small intestine. The rate of passage of the meal through the jejunum and upper ileum was usually much increased, but there was often delay at the ileo-caecal valve before the meal entered the colon. More often there was an ileal residue at six hours which was much greater than that seen in the control meals.

Once the meal entered the colon it usually advanced very rapidly, and in some cases it reached the pelvic colon in six hours. The only other change noted in the colon was an outpouring of secretion. (Scudi, Jelinek and Kuna (1944) observed that in rats dying after the administration of large doses of mepacrine the gastro-intestinal tract was distended with fluid. The Army Malaria Research Unit (1944) with Mr. E. H. Leach showed that in the rat mepacrine stimulates the discharge of the neck mucous glands, the cardiac glands of the stomach and the cells of Brunner's glands in the duodenum.)

Cholecystography. Mepacrine 1·0 gm. caused no radiographically demonstrable disturbance in the function of the gall-bladder in two women volunteers.

Bacterial Flora of the Faeces. There was no significant change in the flora of the faeces of eight volunteers after the exhibition of large doses of mepacrine.

THE EFFECTS OF A SUPRESSIVE DOSAGE OF MEPACRINE

When the abnormalities which may be caused by mepacrine were thus identified, observations were made on a large number of volunteers who took a suppressive dosage of mepacrine for periods of from a few days to several months. Symptoms were recorded in all volunteers and special investigations were undertaken in a selected number. The results showed that gastro-intestinal disturbances which can be attributed to the administration of a suppressive dosage of mepacrine are infrequent and slight.

Clinical Observations. Out of a group of 85 healthy Oxford women undergraduates, who were on various suppressive régimes and who were closely observed and asked to report all symptoms, no matter how trivial, 12 complained of gastro-intestinal disturbances during periods of mepacrine-administration which covered three to eleven months. The symptoms reported were nausea, vomiting, flatulence, colicy abdominal pain and mild diarrhoea. These occurred in most cases during the first week on the drug and disappeared in a short time despite continued drug-administration. In six cases the organic origin of the symptoms was demonstrated when symptoms immediately disappeared after the substitution of a placebo without the subject's knowledge. Vomiting was seen in only

three cases—cases who had been on a régime of 0·2 gm. twice a week. In other cases the symptoms were mild and never incapacitating.

In a group of 35 healthy male undergraduates, who received mepacrine 0·1 gm. daily for five months and who were given the opportunity each week to report symptoms on their own initiative, no gastro-intestinal symptoms were brought to the notice of the medical officers-in-charge. This was not surprising, in view of the facts that the symptoms reported by the women were mild and that none of the men was on a régime of 0·2 gm. twice weekly.

Fifteen soldier volunteers under daily supervision reported no symptoms.

Fractional Gastric Analysis. Fractional gastric analyses were performed in 12 soldier volunteers the second day after beginning a course of mepacrine 0·1 gm. a day. The test meal was given one half-hour after the tablet. Except for a diminution in the volume of the resting juice, the results of the analyses were not significantly different from the results obtained after previous control meals.

Gastroscopy. The gastric mucosa was examined in 12 soldier volunteers the fourth day after beginning a course of mepacrine 0·1 gm. a day. The mepacrine tablet was swallowed five minutes before the introduction of the gastroscope, and in some cases it was possible to observe the tablet lying on the mucosa for as long as half an hour. In no volunteer was the appearance of the mucosa as a whole different from that seen at the control examination, but a zone of hyperaemia developed around the tablet in five to ten minutes, a small amount of thick ropy mucus accumulated, and the rugae were increased in size. This is evidence of a direct local action, but the effect was slight and not sufficient in itself to explain the symptoms which are sometimes seen.

Barium Meals. Six of the women undergraduates who had gastro-intestinal symptoms while on mepacrine submitted to examination by barium meal and radiography, and each of them presented slight abnormalities. These were hypertonicity of the stomach, pylorospasm, irritability of the small intestine, and delay at the ileo-caecal valve.

No abnormalities were found in 12 soldier volunteers who were given barium meals one hour after their third daily dose of mepacrine 0·1 gm.—the time at which symptoms were most frequently seen in the women volunteers. Six women volunteers who had been taking a suppressive dosage of mepacrine without symptoms for three to five months were also normal on examination after a barium meal.

Bacterial Flora of the Faeces. All volunteers who complained of diarrhoea submitted specimens of stool for examination. A non-lactose fermenting organism was discovered in one case; otherwise no abnormality was encountered. Duplicate quantitative examinations of the faecal flora of six women volunteers who had been receiving a suppressive dosage of mepacrine showed the relative numbers of different organisms present to be the same as in a group of eight women who were controls.

Effect of a Suppressive Dosage of Mepacrine on the Inflamed Colon. Mepacrine 0·1 gm. daily was given to two patients with chronic ulcerative colitis, who were under the care of Professor L. J. Witts, to determine whether the drug had an adverse effect on the inflamed colon. One patient was in an active phase of the disease and was having five or six loose motions daily. The other patient had been in a quiescent stage for two or three months before the experiment and was having one or two formed motions daily. Suppressive mepacrine for a fortnight did not cause any change in the symptoms or general condition, and there was no change in the bacterial flora of the stools.

THE EFFECTS OF MEPACRINE 0·2 GM. TWICE DAILY

Finally, work was undertaken on the problem presented by the large-scale vomiting and diarrhoea which occurred in North Africa in 1943 following the administration of two tablets of mepacrine on Tuesdays and Thursdays. The Consulting Physician, A.F.H.Q., Brigadier E. R. Boland, gave the following description of the clinical picture seen at that time.

'The attack generally began with nausea and vomiting accompanied by headache, chilliness, pains in the epigastrium or muscles. In milder cases there was nausea without vomiting and with abdominal discomfort, followed after an interval by a loose stool or two. When it occurred, vomiting was repeated and generally succeeded by diarrhoea, the motions being soft or loose and often frankly fluid. In a few cases diarrhoea preceded the vomiting and sometimes vomiting or abdominal pain or discomfort was a single feature. Headache and depression were very common. Initial or repeated shivering and pains in the back or legs or joints were general. The temperature was raised to 99°, 100° to 103° F., in many, especially the more seriously ill.'

Symptoms occurred most frequently after the third dose, and they developed in from three to ten hours after the dose had been given.

It seemed strange that a dose of two tablets should have caused more severe disturbances than those which occurred after a single dose of 10 tablets. Of the many explanations offered none survived examination. The suggestion that the entire episode was psychogenic in origin was rejected by clinicians on the spot. That the batches of mepacrine involved were not especially toxic was proved by examination of samples which were returned to England. No bacteriological cause was found by the pathologists of the area, and the short interval between the ingestion of the tablets and the onset of symptoms made it impossible that the cause had been some action of mepacrine on the bacterial flora of the intestine. The suggestion that mepacrine has more than the usual irritative effect on the inflamed colon was negated by our own experiments with cases of ulcerative colitis. It was decided, therefore, to put a group of volunteers on the twice-weekly régime and to study them by means of radiography and by frequent estimations of the plasma mepacrine.

Eight officers from a British General Hospital were given mepacrine 0·2 gm. at 9.00 a.m. on the 1st, 6th, 8th, 13th and 15th days, which was precisely the régime used in North Africa. On the 1st, 6th, 8th and 15th days blood was taken for plasma mepacrine estimation at 1-, 2-, 4-, 8- and 12-hour intervals after ingestion of the tablets. The officers lived on the ordinary Army diet and remained on duty except when prevented by symptoms.

Six of the volunteer-officers showed no untoward effects. The other two were severely affected on the 8th day, less affected on the 13th day and only slightly on the 15th day.

Volunteer 402. *8th Day.*—9·00 a.m.: mepacrine 0·2 gm. 2·00 p.m.: nausea, epigastric discomfort and frontal headache. Pale, sweating, and thirsty. Tenderness in epigastrium and right hypochondrium. Temperature 101·6° F. 7.30 p.m.: began to vomit, and vomited frequently during the next five hours. At 7.00 p.m. a barium meal was given and examination of the gastro-intestinal tract begun. There was delay in opening of the pyloric sphincter and an excess of gastric secretion. For two hours no barium left the stomach. The normal pattern of the valvulae conniventes in the small intestine was replaced by ragged clumps of barium. The stomach remained full of secretion at four hours. The colonic outline was normal.

9th Day.—Marked general malaise; vomited once early in the morning. No abdominal tenderness. Temperature 101·4° F.

10th Day.—No complaints. Temperature 98·8° F.

13th Day.—9.00 a.m.: mepacrine 0·2 gm. 12.30 p.m.: nausea, followed by retching and vomiting which lasted for two hours; one loose motion. Detectable enlargement of the spleen. Examination by barium meal showed changes similar to those seen on the 8th day, but this time they were less marked.

15*th Day*.—9.00 a.m.: mepacrine 0·2 gm. 2.00 p.m.: slight nausea for one hour. Spleen no longer palpable.

Volunteer 404. 8*th Day*.—9.00 a.m.: mepacrine 0·2 gm. 2.30 p.m.: headache, dizziness, severe abdominal pain, onset of profuse and finally watery diarrhoea. No abnormal physical signs on examination. Temperature 101° F. 7.00 p.m.: barium meal given. There was marked hypersecretion and some spasm of the stomach. The pylorus was open and emptying occurred at a fairly normal rate. The duodenal cap was grossly enlarged—probably a congenital abnormality. The small intestine pattern was abnormal and showed irregular fragmentation of the barium column and an increase in segmentation. The colon was spastic and there was an excess of secretion.

9*th Day*.—Marked general malaise and slight abdominal discomfort. Two loose bowel motions. Spleen one inch below costal margin and slightly tender. Temperature 101° F.

10*th Day*.—No complaints. Spleen remained enlarged. Temperature 99·6° F.

11*th Day*.—Spleen just palpable. Temperature 98·6° F.

13*th Day*.—9·00 a.m.: mepacrine 0·2 gm. 1.45 p.m.: nausea, vomiting and watery diarrhoea. Spleen one-half inch below costal margin. Temperature 98·6° F. Barium meal showed changes similar to those seen on the 8th day, but they were less marked.

15*th Day*.—9.00 a.m.: mepacrine 0·2 gm. 2.00 p.m.: headache, which lessened towards the evening.

17*th Day*.—Spleen no longer palpable.

There was no significant difference between the plasma mepacrine concentrations in the affected and in the unaffected volunteers. The peak plasma concentrations during the post-absorption period were approximately the same as on the 1st, 6th, 8th and 15th days, and varied between 35 and 45 micrograms per 1,000 ml. After a single dose of mepacrine 1·0 gm. the peak concentration is of the order of 100 micrograms per 1,000 ml. Bacteriological examination of the stools revealed no pathogenic organisms.

DISCUSSION

It is necessary before attributing symptoms to the administration of a drug to get a clear picture both of the symptoms themselves and of the findings on investigation under circumstances in which it is improbable that there are other causal factors. This is difficult to obtain in the field, where gastro-intestinal disturbances are frequent and their causes varied. Our early experiments with volunteers who took large doses of mepacrine in controlled conditions and after previous examination provided a picture with considerable definition. The syndrome which appeared in these experiments had certain precise characteristics. The vomiting was characterized by forcefulness of the first emesis, and the diarrhoea by the extreme urgency of the first bowel motion. When pain occurred it was always colicy in nature. Recovery was rapid, and in moderately affected cases considerable nausea, with vomiting or diarrhoea, was followed in a few hours by a feeling of complete well-being. There was a strict time-relation between the onset of symptoms and the ingestion of the drug, and a regular march of symptoms which towards the end of the experiment made possible a precise prognosis. The radiographic signs were equally definite. The difficulty in interpretation which arises from the variability of normal subjects was met by the results of the control examinations. The duplicate examinations of 16 subjects provided data on the day-to-day variation which occurs in the motility of the gastro-intestinal tract of healthy persons, and the large number of persons given at least one barium meal provided evidence of the variation to be expected from person to person. Each set of films taken after the administration of mepacrine was considered in relation to the control films of the same subject, and also in the light of our findings in other normal persons. In this way it was possible to form a reliable opinion concerning

the changes which could be considered due to mepacrine. These changes were gastric hypersecretion, hyperperistalsis, hypertony followed by atony, and pylorospasm; a disturbance of the motility and secretion of the small intestine, which caused irregular fragmentation of the barium stream and increased segmentation; delay at the ileo-caecal valve, and an increased rate of passage of the meal through the colon.

Are these symptoms and signs seen after the administration of mepacrine 0·1 gm. a day? They were not complained of by any of a group of 50 men receiving this dose of mepacrine over a period of five months, and neither in those men who were examined radiographically on the third day of their course nor in the women who were examined after several months were abnormalities found after barium meals. In a group of 70 women the same dose caused symptoms in seven cases, most frequently after the first few tablets. The symptoms were mild and never incapacitating, and they disappeared when the drug was continued. They were attributed to mepacrine because they disappeared when a placebo was substituted for the mepacrine tablet, and because those cases which were examined presented radiographic abnormalities similar to those found in our early experiments. Only very slight and unimportant gastro-intestinal disturbances can be attributed to mepacrine during a suppressive régime of 0·1 gm. a day, and such disturbances occur most frequently during the first week of administration and disappear when the drug is continued. Bispham (1941) arrived at the same conclusion after a study of 49,681 cases in which mepacrine had been used.

When mepacrine is given twice a week, gastro-intestinal symptoms occur more frequently, and on some régimes may be very severe. This has been noted by other observers. Loughlin *et al.* (1943) found that 0·2 gm. ' twice weekly ' was followed by nausea, vomiting and diarrhoea. Missiroli (1944) found that doses of 0·3 gm. caused similar symptoms in a proportion of a rural population. In our experiments mepacrine 0·2 gm. on 1st, 4th, 8th days, etc., caused symptoms in 20 per cent. of cases. Much the most serious symptoms have followed the use of mepacrine 0·2 gm. on 1st, 6th, 8th days, etc. Any suppressive régime other than the one involving a regular daily dose of mepacrine is strongly contra-indicated.

The explanation of the very severe effects of the dosage used in North Africa in 1943 is not entirely clear, but a hypothesis can be stated. The clinical picture and the radiographic findings were the same as those found in our first experiment with volunteers who had taken very large doses of mepacrine, and it is reasonable to suppose that they were caused by mepacrine. This supposition gains strength from the failure of other suggested explanations to survive experimental testing (cf. above). Why did a small dose of mepacrine (0·2 gm.) cause symptoms very much more severe than were seen after a dose five times as large? It could not have been due to an accumulation of the drug, because a much larger amount can be given in daily doses for the same period without effect, and because symptoms disappeared despite continued administration. It could not have been due to the higher plasma mepacrine concentrations seen after doses of 0·2 gm., because the peak concentrations were practically as high on the 1st and 6th days when there were no symptoms, and because they were very much lower than the levels seen after a dose of 1·0 gm., when symptoms occurred but were less severe. Evidently at the time of the third dose in this régime (8th day) a proportion of subjects have a diminished tolerance of a dose of mepacrine which previously had no effect and later has no effect if the drug is continued. The spacing of the first two doses results in some subjects being less tolerant of

the drug than other subjects, and less tolerant than they themselves were at the beginning. It is probable that the catastrophe in North Africa in 1943 was due to a temporary diminution of tolerance to the drug, the unfortunate result of the particular régime which was used. Any régime with intervals between doses greater than two days will give rise to some trouble, but this particular régime causes the most severe disturbance.

SUMMARY

1. The gastro-intestinal effects of mepacrine have been investigated clinically, and by radiographic examination after a barium meal, cholecystography, gastroscopy, fractional gastric analysis, and bacteriological examination of the faeces.

2. Gastro-intestinal disturbances during a suppressive régime of mepacrine 0·1 gm. a day are unusual and are slight and unimportant.

3. A suppressive régime with intervals between doses greater than two days will cause more trouble, and such a régime should never be used.

ACKNOWLEDGEMENTS.—Great credit should be given to the 135 men and women on whom these observations were made. The co-operation and fortitude of the 25 women undergraduates and the 15 soldiers who submitted to intensive special investigation were particularly commendable.

Our thanks are due to the Director of the Nuffield Institute for Medical Research, Professor J. A. Gunn, F.R.C.P., for permitting this work to be carried out in the Institute. We should like also to acknowledge with thanks the great assistance which we received from Mr. M. S. Tuckey, Sergeant P. B. Wood, R.A.M.C., and Private G. E. C. Ince, R.A.M.C.

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