is diagnostic, but often is complete only in the terminal stages of the illness, and any component may be absent. The disease should be considered in the diagnosis of all cases which present the association of haemolytic anaemia and thrombocytopenic purpura; biopsy may be of value.

Examination of the tissues shows a unique histological picture of widely disseminated thrombosis of the smallest-calibre blood vessels, with endothelial hyperplasia, conspicuous dilatation of many of the affected vessels, and no inflammatory reaction.

The disease has been fatal in every case which has been reported. Treatment with A.C.T.H. or cortisone deserves trial, and splenectomy should be considered.

Two new cases are reported.

I wish to thank the many colleagues who have been patient with my interest in this disease, particularly Dr. D. F. Barrowcliff for his help in reviewing the literature, and Dr. D. R. Humphreys for allowing me to report the case of his patient (Case 2).

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NEWER SYNTHETIC ANALGESIC DRUGS

BY

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During the last ten years a group of new synthetic analgesic drugs has become available to the medical profession. The purpose of this paper is to present the results of a comparison made between the individual members of this group of new drugs, and between them and morphine. The drugs of the new series are:

Pethidine ("dolantin," "dolantal," "demerol," "meperidine") 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride.

Amidone ("physeptone," "miadone," "dolphine," "methadon") DL-6-dimethylamino-4:4-diphenylheptan-3-one hydrochloride.

Phenadoxone ("heptalgin," "heptazone") DL-6-morpholino-4:4-diphenylheptan-3-one hydrochloride.

Höchst 10581 (for purposes of convenience it will be referred to here as "hexanone") DL-6-morpholino-4:4-diphenylhexan-3-one hydrochloride.

Patients suffering from the following painful conditions were used: post-herpetic neuralgia, tuberculous cystitis, pubic osteitis, sciatic pain due to prolapsed intervertebral disk, rheumatoid arthritis, ankylosing spondylitis, lymphosarcoma with abdominal pain, and carcinoma of the cervix, vagina, colon, stomach, glosso-tonillar sulcus, larynx, breast, and bronchus, with metastases in the spine. The effect of these analgesics was not investigated on the following pains for the reasons given: the pains associated with coronary thrombosis, trigeminal neuralgia, burns, or childbirth, as the pain is insufficiently chronic; the pains associated with colic or peptic ulcer, as they are best treated with spasmolytic drugs; the pain of headache, as many different types of pain might be included under this heading, including psychogenic pain. The conclusions drawn in this work, then, do not refer to these pains. In most patients tested the pains were severe; only in those with rheumatoid arthritis and ankylosing spondylitis was this not so. In all patients the pain was chronic, and never disappeared spontaneously. Unless some analgesic drugs were given, sleep or occupations such as reading were impossible in all patients, except those with rheumatoid arthritis or spondylitis.

Morphine, being a well-known and effective analgesic, was compared with the newer group of drugs. It was given by injection intramuscularly, in the form of the sulphate or as papaveretum ("omnupon"), or by mouth as the hydrochloride, as "nepenthe," or as papaveretum. The new drugs were given orally in tablet form or intramuscularly.

The method of clinical assessment was that reported by Keele (1948), by Hewer, Keele, Keele, and Nathan (1949), and by Robson and Keele (1950). Trials were carried out on a few patients whose pains were constant over periods of weeks and who were able to keep pain charts. These patients were given various drugs and inert substances, and recorded hourly the state of their pain, using the categories severe, moderate, slight, or nil. The method is entirely subjective. The results obtained on

each patient with certain doses and drugs were compared with those obtained by using other doses and drugs. A minimum of 10 administrations of each dosage of a drug given to one patient had to be attained before the results were incorporated in the series; in many patients 40 to 50 administrations were made. It is believed that valuable information on the effectiveness, speed of onset, and duration of effect of analgesics is obtainable from many administrations of various substances to such reliable witnesses. As the patients did not know what drug or what dosage they were receiving on any occasion, each administration of an analgesic drug formed a valid experiment comparable with every other administration to the same patient. As many as four experiments could be carried out on one patient in a day; and so, although the number of patients used was only 75, the number of results on each satisfactory witness was large enough for statistical analysis. A possible source of error in the method is due to spontaneous variations in the intensity of pain during the course of a series of administrations. With every patient pain charts have been kept occasionally while no drugs were given, so that such spontaneous fluctuations in the categories of pain might be observed. As mentioned, all patients were given inert substances in order to exclude a possible psychological factor responsible for the relief of pain.

Equiactive Doses

Once a substance has been shown to have analgesic properties it is necessary to determine the dose which gives an effect similar to the usual dosage of well-established analgesics. In assessing the value of analgesics such factors as toxicity, absorption, and effects on certain kinds of pain and not on others have been taken into consideration. The actual equiactive doses found by trial and error of the various drugs are presented first; then possible and useful doses, taking into account toxicity and side-effects; and, finally, maximum tolerated doses and minimal effective doses.

Equiactive doses were calculated for each patient from the various doses given. To most patients the drugs being tested were given in some such scheme as the following: drug A was given for two days, drug B for three days, drug A again for two days, and then drug B for one day. In some instances drug A would be given for a certain time and be followed by drug B; but in other instances drug B would be the first and be followed by drug A. If a given dose of a drug failed to bring any relief it was not included for comparison with other drugs, for comparisons could be made only with doses that were effective.

Figures for statistical analysis were obtained by using the following criteria of failure and success. For each dosage of each drug the number of times the pain was reduced from severe to nil, and/or the number of hours the pain remained at or returned to severe within six hours of administration, and/or the number of hours the pain remained slight or nil, within six hours of administration, were extracted from the charts. Such figures were compared with those obtained when giving another drug to the same patient. By the use of these criteria, from each dose of each drug a certain number of successes and of failures were obtained; and from these a 2 by 2 contingency table was made for each dosage. The tests of significance used were that described by Pearson (1947) and Yates's modification of the χ^2 test ($P > 0.05$). For example, in one patient 100 mg. of pethidine reduced the pain from severe to nil 8 times out of 10, and 60 mg. of phenadoxone reduced it from severe to nil in 8 out of 14 times; these doses were taken to be equiactive. In this same patient 10 mg. of amidone reduced the pain in 34 out of 34 trials; this difference in the number of times the pain was reduced from severe to nil by 10 mg. of amidone and 60 mg. of

phenadoxone was greater than might be expected were these doses equiactive; and so 10 mg. of amidone was taken to be more effective than 60 mg. of phenadoxone.

All the drugs tested, if given by injection, caused a definite analgesic effect within half an hour; when given orally the results were less consistent. These differences were indicative not of the efficacy of the drug but rather of the variability of the patient. In only a few patients did any drug fail to have some analgesic effect within the half-hour; the rapidity with which analgesia is achieved is related more nearly to the degree and type of pain and to the personality of the patient than to the drug or its dosage.

For the sake of brevity, the charts, the figures culled from the charts, and most of the tables of equiactive doses are not shown. Three of the tables are given as examples. Table I shows the equiactive doses of amidone and morphine, as judged by the reduction of pain from severe to nil. Table II shows the equiactive doses of amidone and pethidine, as judged by the number of hours the pain remained severe within six hours of administration. Table III shows

TABLE I.—*Equiactive Doses of Amidone and Morphine, as Judged by Reduction of Pain from Severe to Nil*

Patient	Dosages having Equal Analgesic Effect Amidone : Morphine or derivative
Col	20 mg. (parenteral) = $\frac{1}{4}$ gr. (32 mg.) (parenteral)
Pa	20 mg. (parenteral) = $\frac{1}{4}$ gr. (32 mg.) (parenteral)
Ha	20 mg. (parenteral) = $\frac{1}{4}$ gr. (32 mg.) (parenteral)
Ma	20 mg. (parenteral) = 30 min. (1.8 ml.) nepenthe (oral)
MI	20 mg. (parenteral) = 30 min. (1.8 ml.) nepenthe (oral)
Be	20 mg. (parenteral) = 30 min. (1.8 ml.) nepenthe (oral)
Ph	10 mg. (oral) = 15 min. (0.9 ml.) nepenthe (oral)
Hu	10 mg. (oral) = 25 min. (1.5 ml.) nepenthe (oral)
Mu	10 mg. (oral) = $\frac{1}{4}$ gr. (16 mg.) (parenteral)
Ca	10 mg. (parenteral) = $\frac{2}{3}$ gr. (45 mg.) papaveretum (parenteral)
W	20 mg. (oral) = $\frac{2}{3}$ gr. (45 mg.) papaveretum (oral)
Ba	15 mg. (oral) = $\frac{1}{4}$ gr. (16 mg.) (parenteral)
L	15 mg. (parenteral) = $\frac{1}{4}$ gr. (16 mg.) (parenteral)
Pe	30 mg. (parenteral) = $\frac{1}{4}$ gr. (48 mg.) (parenteral)
R	30 mg. (parenteral) = 1 gr. (65 mg.) (parenteral)

TABLE II.—*Equiactive Doses of Amidone and Pethidine, as Judged by Number of Hours Pain was Severe within Six Hours of Administration*

Patient	Dosages Having Equal Analgesic Effect Amidone : Pethidine
T	10 mg. (oral) = 100 mg. (oral)
K	10 mg. (oral) = 150 mg. (oral)
Coo	10 mg. (parenteral) = 200 mg. (oral)
Ca	10 mg. (oral) = 150 mg. (oral)
Hu	20 mg. (parenteral) = 100 mg. (oral)

TABLE III.—*Equiactive Doses of Phenadoxone and Pethidine, as Judged by Number of Hours Pain was Slight or Nil within Six Hours of Administration*

Patient	Dosages Having Equal Analgesic Effect Phenadoxone : Pethidine (all oral)
L	30 mg. = 100 mg.
Ch	40 mg. = 50 mg.
Cu	40 mg. = 50 mg.
E	45 mg. = 100 mg.
H	50 mg. = 100 mg.
Co	55 mg. = 100 mg.
P	60 mg. = 100 mg.

the equiactive doses of phenadoxone and pethidine, as judged by the number of hours the pain was slight or nil within six hours of administration. Only the actual equiactive dosages are shown; the many figures scattered on each side of the equiactive amounts are not given, and they have not been used in the calculations. From these tables the following equiactive dosages were found.

Comparing amidone and morphine, the mean of the dosages employed was 18 mg. of amidone equiactive with 23 mg. of morphine. The limits of scatter were 15 mg. of amidone equiactive with 16 mg. of morphine, and 30 mg. of amidone equiactive with 64 mg. of morphine. Thus for

practical purposes 18 mg. of amidone may be taken as analgesically equivalent to $\frac{1}{3}$ gr. (24 mg.) of morphine; 12 mg. of amidone is roughly equivalent to $\frac{1}{4}$ gr. (16 mg.) of morphine, and 25 mg. of amidone to $\frac{1}{2}$ gr. (32 mg.) of morphine.

Comparing pethidine and morphine, the mean of the dosages employed was 125 mg. of pethidine equiactive with 16 mg. of morphine. The limits of scatter were 100 mg. of pethidine equiactive with 32 mg. of morphine, and 200 mg. of pethidine equiactive with 16 mg. of morphine. Thus for practical purposes 125 mg. of pethidine can be regarded as equivalent to 16 mg. of morphine.

Comparing phenadoxone and morphine, the mean of the dosages employed was, when the drugs were given by injection, 10 mg. of phenadoxone equiactive with 16 mg. of morphine, and when the drugs were given by mouth, 55.5 mg. of phenadoxone equiactive with 16.6 mg. of morphine. The limits of scatter for the oral dosages were 60 mg. of phenadoxone equiactive with 22 mg. of morphine, and 50 mg. equiactive with 10 mg. of morphine. Thus when the drugs are given by injection 10 mg. of phenadoxone is equivalent analgesically to 16 mg. of morphine; but when they are given orally, roughly 50 mg. of phenadoxone is equivalent to 16 mg. of morphine.

Comparing amidone and pethidine, the mean of the dosages employed was 12 mg. of amidone equiactive with 130 mg. of pethidine. The limits of scatter were 10 mg. of amidone equiactive with 200 mg. of pethidine and 5 mg. of amidone with 100 mg. of pethidine, and at the other extreme 20 mg. of amidone equiactive with 100 mg. of pethidine and 15 mg. of amidone with 75 mg. of pethidine. Thus for practical purposes 10 mg. of amidone may be regarded as equivalent to 100 mg. of pethidine.

Comparing phenadoxone and amidone, the mean of the dosages employed was, when the drugs were given by injection, 10 mg. of phenadoxone equiactive with 10 mg. of amidone, and, when the drugs were given by mouth, 50 mg. of phenadoxone equiactive with 7.8 mg. of amidone. The limits of scatter for the oral dosages were 50 mg. of phenadoxone equiactive with 5 mg. of amidone and 50 mg. equiactive with 10 mg. of amidone. Thus for practical purposes 50 mg. of phenadoxone may be taken as equivalent to 7.5 mg. of amidone.

Comparing phenadoxone and pethidine, the mean of the dosages employed was 47 mg. of phenadoxone equiactive with 84 mg. of pethidine. The limits of scatter were 40 mg. of phenadoxone equiactive with 50 mg. of pethidine and 30 mg. of phenadoxone with 100 mg. of pethidine. Thus for practical purposes about 25 mg. of phenadoxone may be regarded as equivalent to 50 mg. of pethidine.

Comparing phenadoxone and hexanone, the mean of the dosages employed was 42 mg. of phenadoxone equiactive with 40 mg. of hexanone; and the scatter was only 45 mg. of phenadoxone equiactive with 30 mg. of hexanone. For practical purposes these two drugs may be regarded as analgesically equal.

The results obtained when using phenadoxone and hexanone by mouth have been less consistent than those obtained with the other drugs. The probable effect of these drugs given orally could never be foretold: a dose of 60 mg. of either of them could be adequate in one patient and almost useless in the next one. This kind of inconsistency has not been found with any of the other drugs; though they might be found useless on account of unpleasant side-effects, the analgesic effect could be foretold. This discrepancy is not shown in the tables. For often a dose such as 40 mg. would be found no better than an inert substance; when this occurred the number of experiments would necessarily be so few that no useful conclusions could be drawn. The great variability in the effectiveness and toxicity of these two drugs is probably due to variability in absorption. Such inconsistencies, however, do not mean that these two drugs are always useless. In some patients, when the dose has been adequate, they have been found to be useful and satisfactory analgesics.

Duration of Analgesic Effect

In order to examine the duration of the analgesic effect of the various dosages of the different drugs more closely, 15 of the most satisfactory witnesses were used. For each patient the drugs were placed in the order of efficiency. The criterion employed was the total number of hours the pain remained in a lower category than that at which it was when the drug was given, six hours being regarded as the maximum possible time. At least six trials were made for each dosage used; usually at least 12 trials were made.

From these results the following facts were obtained: hexanone has a longer-lasting analgesic effect than phenadoxone in the same dosage, and phenadoxone is a poor analgesic from this point of view. Amidone always has a longer-lasting effective action when given parenterally than when given orally.

Toxicity and Side-effects

As only a few patients have been used in this investigation, information about toxicity and side-effects needs to be seen as only suggestive.

The toxic effects of the four new drugs investigated were largely confined to symptoms. Repeated blood counts were carried out on patients who had these drugs for periods of up to a year; no toxic effects were found on the red or white cells or the platelets. In the doses used no form of skin eruption, no allergic manifestations, and no depression of respiration were encountered.

Symptoms severe enough to cause the administration of the drugs to be stopped were sleepiness, lassitude, a dull mental state that the patients usually described as "the pills make me feel dopy," nausea and vomiting, severe anorexia, dizziness, a sensation of "swimminess in the head," vertigo, tinnitus, headache, sweating, dryness of the mouth. All these symptoms were obtained in a marked degree when the drugs were given intravenously, showing that the prominent side-effects of nausea, vomiting, and anorexia were not due to an irritant effect on the alimentary canal. Objectively, the only sign that occurred more than once consisted in myoclonic jerks.

Three patients had transient disturbances of cerebration. One of them had been on amidone four-hourly for a fortnight without any toxic effects; one evening she got a temperature of 103.5° F. (39.7° C.), due to an infection, and had two attacks of vertigo, associated with a feeling of psychological remoteness and some confusion; at the same time the usual noises of the ward appeared to her to be insupportably loud. However, amidone was given regularly after this episode, the temperature never again reaching this height, and she never again had a similar attack. It cannot be known whether this episode was due to the fever alone or to the combined effects of fever and amidone. Another patient after receiving 20 mg. of phenadoxone by injection became confused; with 10 mg. by injection she said that all her thoughts became jumbled up and she felt dazed; it was noted that no similar effect was obtained when she took 70 mg. by mouth. Another patient after having more than one dose of 20 mg. of amidone by injection in 24 hours always had slight confusion, hallucinations, and delusions: she imagined that she was holding a cup of tea, when nothing was in her hand, and believed that she was about to be discharged from hospital, whereas in fact she had not yet had the operation for which she had been admitted.

The side-effects due to the new analgesic drugs are largely the same as those due to morphine and its derivatives. The exception is myoclonic jerks, which have not been seen to follow the administration of morphine. In large doses morphine may cause difficulty in starting micturition; this has not been seen after the administration of the newer drugs. Euphoria has only very rarely been seen in these patients having chronic pain; but it has occurred with

morphine, amidone, and phenadoxone. Although, in general, the presence of toxic symptoms is related to dosage, 10 out of 33 patients who received pethidine, amidone, and phenadoxone had the toxic symptoms mentioned above with all these drugs, and at dosages inadequate to give analgesia.

Approximately one-third of all patients having morphine or its derivatives had the same symptoms. Some were unable to take any of the synthetic drugs tested or morphine and its derivatives owing to the side-effects. With all the drugs investigated light-headedness, nausea, and vomiting were found to be more likely to occur if the patient was up than if he was in bed, and if he sat up and moved about than if he lay still.

It was found that no single one of the new drugs investigated was constantly more toxic than any other. Each of the four drugs caused toxic symptoms in some patients, although the other three could be taken.

The question of toxicity is obviously intimately bound up with dosage. On the whole, a patient who can take one member of the new synthetic group of drugs is likely to be able to take small doses of any other member of the group. Nevertheless, one patient was seen who could take 50 mg. of pethidine yet could not take 40 mg. of phenadoxone; she could not keep awake and suffered from nausea with as small a dose as 2.5 mg. of amidone. Many patients could take 50 mg. of pethidine orally but could not take 50 mg. by injection. All those patients who could take amidone were able to take 10 mg., whereas higher doses might not be tolerated. With regard to phenadoxone, all those who could not tolerate 10 mg. by injection could take 70 mg. by mouth; in fact, in this investigation the maximal oral dose of phenadoxone or hexanone has not been discovered, for 70 mg. of either drug taken orally was tolerated by some subjects. The maximal doses used are given in Table IV.

TABLE IV

Name of Drug	Maximal Tolerated Dosages	
	Maximal Single Doses	Maximal Dosage in 24 hours
Hexanone	{ 70 mg. oral 20 mg. parenteral	360 mg. oral
Phenadoxone	{ 70 mg. oral 20 mg. parenteral	420 mg. oral
Amidone	{ 30 mg. oral 30 mg. parenteral	180 mg. oral 180 mg. parenteral
Pethidine	{ 250 mg. oral 200 mg. parenteral	1,250 mg. oral 1,000 mg. parenteral
Morphine	192 mg. (3 gr.) parenteral	384 mg. (6 gr.) parenteral
Nepenthe	30 min. (1.8 ml.) oral	150 min. (9 ml.) oral
Heroin	8 mg. ($\frac{1}{8}$ gr.) parenteral	40 mg. ($\frac{1}{2}$ gr.) parenteral
Papaveretum	43 mg. ($\frac{2}{3}$ gr.) oral and parenteral	215 ($3\frac{1}{2}$ gr.) oral and parenteral

As toxic effects are symptoms rather than signs, attention was paid to the comments of patients having the various drugs. Sometimes no difference was noted between two drugs, particularly within the group of synthetic drugs. As patients were not told when another drug was being given, such comments were not sought, but they were noted when they were made spontaneously. Certain preferences were shown: 12 patients preferred amidone to morphine and 2 preferred morphine to amidone; 6 preferred amidone to pethidine and 3 preferred pethidine; 5 preferred pethidine to phenadoxone and 2 preferred phenadoxone.

It is useful to have analgesics that dull mental activity and tend to bring on sleep, and others that do not do so. All the new drugs investigated and the morphine group of drugs, when given in doses adequate to cause analgesia, have some tendency to cause drowsiness. If drowsiness is taken to be different from a tendency to sleep and to be a state of some clouding of general perception and alertness—a state that some patients liked and others disliked—it is found that of the 32 patients who had all the new drugs and morphine and nepenthe, 10 became drowsy; 2 were drowsy on all the drugs, 5 were drowsy on morphine but

not on the new drugs, and 3 were drowsy on the new drugs but not on morphine or nepenthe. No evidence was found to support the common belief that amidone interferes less with a patient's alertness than morphine. One cannot foretell how a given patient will react to these drugs: one patient will fall asleep on one group of drugs, whereas another will be awake and free from pain on the same drugs but will fall asleep on the other group. Further, some will tend to fall asleep on 2.5 mg. of amidone, while others will not sleep on 30 mg.; some will be drowsy on 100 mg. of pethidine, others will be vigilant on 250 mg. four-hourly. Neither drowsiness nor falling asleep in the daytime has been caused by the oral doses employed of phenadoxone or hexanone. It is likely that insufficient dosage of these drugs was used, the reason being that the dosage was based on the results of injecting them into rats. As these drugs are so much less reliable when given orally to humans, the results of rat experiments were not transferable to man.

It will be seen that the problem of providing analgesic drugs that will always cause dulling of alertness and sleepiness, and drugs that will never do so, has not been solved.

There is a tendency for all the new drugs and morphine and related drugs to cause constipation, but this has rarely been a complaint of consequence. The spasmolytic action of these new synthetic drugs has not been investigated.

It will be understood from this section on side-effects that the search for the perfect analgesic drug has certainly not reached its end. All of the drugs investigated have been found to be useful in some patients. And also, if it is found that a certain patient cannot take any one drug he may be able to take all, none, or any one of the others tested here.

Useful Effective Doses

In practice equiactive doses, judged by criteria previously described, are not equally efficacious, because of the side-effects that are common to all these analgesic drugs. For example, 200 mg. of pethidine may not in fact give an analgesic effect similar to 20 mg. of amidone, for it may cause such vomiting and dizziness that the patient refuses to take it. One patient in this series, who needed 32 mg. of morphine for the relief of her pain, preferred to stand the pain without any analgesic drug rather than have the unpleasant effects accompanying 20 mg. of amidone or phenadoxone intramuscularly. Thus side-effects fix a ceiling to dosage; the heights of different ceilings permit larger amounts of one drug to be taken than equivalent amounts of another.

Although the analgesic effect of a dose of pethidine is the same whether given orally or intramuscularly, yet the same dose may be tolerated orally but not intramuscularly. Presumably, when the drug is given parenterally it reaches a higher level in the blood stream than when given orally. Although 30 mg. of phenadoxone intramuscularly gives the same analgesic effect as 30 mg. of amidone intramuscularly, this dose of amidone has often been given without undue depression of respiration, but this dose of phenadoxone is lethal. Hewer (personal communication) gave 30 mg. intramuscularly to a man of 70; in three minutes respiration stopped completely, and the pulse became weak in spite of efficient artificial respiration; nikethamide, 10 mg., had a transitory stimulating effect lasting three to four minutes, after which the patient's condition relapsed; in spite of three further injections of 10 mg. of nikethamide, spontaneous respiration did not return for 45 minutes.

The practising doctor is not concerned with the log-dose-response graphs of two or more analgesics; he wants to know equivalent doses of the drugs within the range of the usual practical dosages.

In considering useful effective doses, we may reckon that the traditional $\frac{1}{4}$ gr. (16 mg.) of morphine has the same analgesic effect as 12 mg. of amidone or 125 mg. of pethidine, whether the drugs are given by mouth or by injection; it is equiactive with 10 mg. of phenadoxone or

hexanone when these drugs are given by injection. Of nepenthe, 25 min. (1.5 ml.) may be reckoned to be equivalent to $\frac{1}{4}$ gr. (16 mg.) of morphine. As phenadoxone and hexanone are so unreliable when given orally it is meaningless to give equiactive doses for any route other than parenteral.

The suggested upper and lower limits of useful single doses of these drugs are given below, the upper limit being fixed in nearly all cases by intolerable side-effects and the lower limit by analgesic ineffectiveness.

Morphine	.. $\frac{1}{4}$ to 1 gr. (11 to 65 mg.), oral or parenteral
Nepenthe	.. 10 to 30 min. (0.6 to 1.8 ml.)
Amidone	.. 5 to 30 mg., oral or parenteral (with slight pain, 2.5 mg. is sometimes enough)
Pethidine	.. 50 to 250 mg. oral or parenteral
Phenadoxone	.. 30 to more than 70 mg. oral; no upper limit has yet been found. 10 mg. parenteral. By injection, 20 mg. may be dangerous
Hexanone	.. As for phenadoxone

Addiction

Circumstances were favourable in this investigation for going into the question of addiction to morphine and amidone. All patients receiving large doses of these drugs over a long period had cancer; they were therefore a sample of the population unselected from a psychological standpoint and no more psychopathic than any average sample. Further, these patients were all in hospital for pain-relieving operations. After the operation no more of the drug to which they were accustomed was given. Before one can consider addiction in a patient having pain it is necessary to stop the pain, for any patient will ask for a drug that experience has taught will relieve the pain. Some patients would, under the stress of pain, impotence, and frustration, break down and cry when the drug that they usually had was withheld; it might have been concluded that they were addicted to the drug in question. But the opportunity of seeing these patients after a successful pain-relieving operation has shown that this was not so. These patients have not asked for a single dose of the drug once the pain had gone. They were neither addicted psychologically nor had they acquired physical dependence. (It is possible that the withdrawal syndrome made its appearance during the first 40 hours after the operation, while the patients were miserable and unwell anyway; but certainly no tremor was seen or any psychological distress.) In one patient the operation failed. He had been having amidone orally for months before the operation, and continued to ask for it after the operation.

These facts are not to be taken to indicate that addiction depends on only psychological factors, for it is known that once addiction has become established metabolism is carried on efficiently only in the presence of the drug or some similar drug. Nevertheless, experience with 12 patients in whom pain-relieving operations were successful has shown that none of them asked for or received any more analgesic drug after operation, although they had been receiving large doses before.

The amounts received by these patients are as follows:

Mrs. C	.. Amidone, 5,400 mg. in four to five months; phenadoxone, up to 300 mg. a day—about 9,000 mg. in same five months
Mr. Ph	.. Amidone, 5,000 mg. in 120 days
Mr. Sa	.. Amidone, 4,500 mg. in 100 days
Mrs. Sy	.. Amidone, 4,305 mg. in 82 days
Mrs. R	.. Amidone, 3,600 mg. in 60 days; morphine 30 gr. (2 g.) in 30 days
Mr. J	.. Amidone, 1,200 mg. in 42 days
Mrs. Sm.	.. Over a period of years, but not every day: amidone, 50 mg. a day; phenadoxone, 250 mg. a day; and pethidine, 500 mg. a day
Mr. Pe	.. Amidone, 600 mg. in 90 days
Mrs. Ma	.. Amidone, 430 mg. in 22 days
Mrs. A	.. Amidone, 410 mg. in 30 days
Mrs. F	.. Morphine, 60 gr. (4 g.) in 120 days
Mrs. C	.. Morphine 30 gr. (2 g.) in 60 days.

This section is not meant to imply that these drugs are not drugs causing addiction. It is well known that they

are. But most patients with severe pain can take large amounts of them without becoming addicted, provided their pain is relieved in some other way.

Comparison Between these Results and Reports from Other Investigations: Equiactive Doses

Batterman and Himmelsbach (1943), using the Woolf-Hardy apparatus, found that 75 mg. of pethidine given intramuscularly was as effective analgesically as 10 mg. of morphine; this is the same equivalence as I found. In clinical trials, however, Batterman (1943) found that 100 mg. of pethidine had the same analgesic potency as 10 mg. of morphine. Batterman and Himmelsbach claimed that pethidine is superior to morphine because it is destroyed so rapidly that it is not cumulative, because it is less likely to cause addiction, and because it has a spasmolytic effect, whereas morphine may cause spasm. Van Dyke (1949) reported that 100 mg. of pethidine given parenterally approached the analgesic potency of 10 mg. of morphine. With regard to amidone, he thought that compared with morphine it caused "less sedation, less respiratory depression, and euphoria less frequently. It appears not to cause constipation." He concluded that amidone "is the most desirable analgesic for the treatment of pain in the chronically ill provided that a drug as powerful as morphine is required."

Scott, Kohlstaedt, and Chen (1947) found that in man 5 mg. of amidone had the same analgesic potency as 100 mg. of pethidine and 40 mg. of hexanone; I found that 5 mg. of amidone was equiactive with 50 mg. of pethidine. They also stated that amidone was approximately twice as potent as morphine, whereas I found it to be $1\frac{1}{2}$ times as potent. Bercel (1948) stated that 15 mg. of amidone seemed to have the same analgesic effect as 15 mg. of morphine sulphate or 100 mg. of pethidine. In the present investigation 15 mg. of amidone was found to be equiactive with 20 mg. of morphine or 150 mg. of pethidine. Troxil (1948) discovered that 10 mg. of amidone was more effective than 150 mg. of pethidine and that 10 mg. of amidone was equiactive with 15 mg. of morphine, whereas I found it to be slightly less effective than 15 mg.

Wilson and Hunter (1948) reported that 20 mg. of phenadoxone was a fairly satisfactory analgesic when taken orally. In the present investigation doses of 30 mg. or less were found to be useless.

Summary

In clinical trials on patients with chronic pain, a comparison has been made between the following drugs: morphine and its derivatives, pethidine, amidone, phenadoxone, and Höchst 10581.

The doses of these drugs found in practice to have equivalent analgesic action are given.

Morphine and its derivatives, pethidine, and amidone can be relied on to give effective analgesia; phenadoxone and Höchst 10581 are rarely effective analgesics. All the drugs tested may cause unpleasant side-effects, such as a dulling of intellectual activity, anorexia, dizziness, nausea, vomiting, and sweating. Because of the unpleasantness of these side-effects some patients cannot take morphine or its derivatives or any of the newer synthetic drugs tested. None of the drugs tested can be relied on to give analgesia without depressing the patient's alertness.

Most patients with severe pain can take large amounts of these drugs without becoming addicts; if their pain is relieved surgically they will not ask for these analgesic drugs.

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THE CONTROL OF FILARIASIS WITH HETRAZAN

A FIELD TRIAL IN A RURAL VILLAGE (KENEBA) IN THE GAMBIA

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During the last three years the interrelationships and relative importance of parasitization and nutritional deficiency as factors in the causation of ill-health and low capacity for performance among Gambian villagers have been investigated by members of the M.R.C. Human Nutrition Research Unit, in collaboration with the Gambia Government Medical Department. This investigation has involved, among other things, the making of detailed surveys in the village of Keneba, in the West Kiang District of the Gambia Protectorate. The general plan of this work, and the results of the base-line survey, have already been reported (McGregor and Smith, 1952). In Keneba, after the initial surveys, measures were instituted to control or eliminate the major parasitic diseases prevalent in the area. As part of this work, an attempt was made to control filariasis on a village scale by the use of hetrazan (diethyl-carbamazine). The present paper is concerned only with the results of the hetrazan trial. The general effect of control measures on health and performance of the population will be reported later. The treatment was directed primarily against microfilariae of *Wuchereria bancrofti*, but, as some of the people with this infection also carried microfilariae of *Acanthocheilonema perstans*, some information was gained concerning the effect of the drug on the latter parasite also.

Methods

Blood for enumeration of microfilariae was taken by finger-prick between the hours of 9 p.m. and midnight. It was spread thickly over a measured area of slide marked by grease pencil. The amount of blood required to cover

the marked area had previously been found by measurement to be approximately 20 c.mm. It is to this volume of approximately 20 c.mm. that all microfilaria counts are referred in this paper. The thick films were dehaemoglobinized, fixed in methyl alcohol, and stained with haemalum.

The dosage of hetrazan chosen was 25 mg. base per kg. of body weight given in five equal daily doses—that is, 5 mg. per kg. daily for five days. This dosage was based on results reported by the East African Filariasis Research Unit (1950), and seemed to be the smallest dosage likely to remove most of the microfilariae permanently. Tablets of hetrazan citrate were used, each tablet containing 250 mg. of the salt, equivalent to 125 mg. of the base. One of us invariably saw that the prescribed dose was actually swallowed. The occurrence of unpleasant effects attributed to the drug was recorded and investigated, but no attempt was made to question individuals who did not themselves complain.

Incidence of Filariasis

The total population of Keneba is 710. In February, 1951, the night blood of the 603 persons present at that time in the village was examined. It was found that 118 were infected with *W. bancrofti* alone, 101 were infected with *A. perstans* alone, and 102 carried microfilariae of both parasites; thus, in all, there were 220 cases of *W. bancrofti* infection and 203 of *A. perstans*. The age and sex distribution of these infections is summarized in Table I, and has

TABLE I.—Age and Sex Incidence of Filariasis in Keneba Villagers Before Treatment (February, 1951)

Age Group (Years)	Male			Female		
	No. Examined	No. having <i>W. bancrofti</i>	No. having <i>A. perstans</i>	No. Examined	No. having <i>W. bancrofti</i>	No. having <i>A. perstans</i>
0-10	93	10 (11%)	7 (8%)	83	13 (16%)	5 (6%)
11-20	83	33 (40%)	39 (47%)	69	23 (33%)	14 (20%)
21-30	35	19 (54%)	19 (54%)	63	28 (44%)	21 (33%)
31-40	35	19 (54%)	25 (71%)	55	33 (60%)	23 (42%)
41-50	18	9 (50%)	10 (56%)	29	12 (41%)	17 (59%)
Over 50	19	9 (47%)	11 (58%)	21	12 (57%)	12 (57%)
Total	283	99 (35%)	111 (39%)	320	121 (38%)	92 (29%)

been discussed in the communication already quoted (McGregor and Smith, 1952). In the course of repeated clinical examinations during the previous year, three individuals were found suffering from elephantiasis and three had hydroceles. This gives a total incidence of such filarial sequelae of less than 1%.

It was our original intention to treat all the 220 persons found to be carrying microfilariae of *W. bancrofti*. In effect, 22 individuals were treated with another drug and 17 were not available in the village at the time the treatment was started; thus 181 persons began the course and 171 completed it. Of these, 164 were present in the village at the time of re-examination in December, 1951, 10 months after treatment, when, in all, 569 people were examined.

Results

(a) *W. bancrofti*.—Of the 154 infected persons who completed the prescribed course of treatment, 99 (64%) had blood free of microfilariae 10 months later (Table II). In the remaining 55 patients infection was still present, but the parasitaemia was substantially reduced; before treatment the sum of the microfilaria counts in the films of these 55 patients was 2,859, whereas 10 months later it was 305, a reduction of 89%. The overall reduction of microfilariae in the 154 infected and treated persons was 94% (5,131 in February; 305 in December). In the group of 10 cases in which treatment was incomplete and in which dosage varied from 5 to 15 mg. per kg., total elimination of microfilariae was achieved in two cases only; the remaining eight subjects showed a considerable reduction (80%)