Stumbling blocks in the study of diamorphine

R. G. TWYCROSS
M.A., B.M., M.R.C.P.

St Christopher’s Hospice, Lawrie Park Road, London SE26 6DZ

Summary
Although the centenary of the discovery of diamorphine is soon to be celebrated, much work remains to be done before its mode of action is thoroughly understood. The main stumbling blocks facing the would-be investigator can be summarized as follows:
(1) Diamorphine in solution has a limited shelf-life.
(2) The potency ratio of diamorphine to morphine is still a matter of dispute.
(3) No basic studies appear to have been carried out on the fate of orally administered diamorphine.
(4) Current methods of assay are not sensitive enough to detect diamorphine or its metabolites in serum after the administration of the drug when given in therapeutic amounts.
(5) The undesirable side-effects of diamorphine may vary according to posture and mobility.
(6) As the metabolic handling of the drug may be different in the two sexes, provision for a between-sex comparison should be included in the design of a clinical trial of diamorphine.

Introduction
Diacetylmorphine was first prepared in 1874 by C. R. A. Wright at St Mary’s Hospital, London (Wright, 1874). Initially it was largely ignored by the medical profession but some 20 years later interest rapidly developed as a result of animal experiments conducted in Germany (Dreser, 1898). Commercial production was started in 1898 by the Bayer Company who marketed the alkaloid under the trade name of 'Heroin'. The name was probably derived from 'heroisch', which in German medical terminology means large, powerful, extreme, something with pronounced effect even in small doses. Later this name became a synonym for the drug.

The new drug received a spontaneous and widespread acceptance comparable with that of drugs like penicillin and cortisone in more recent years. It was used initially in a variety of respiratory conditions, such as 'dyspnœa', pharyngitis, laryngitis, bronchitis, asthma and pulmonary tuberculosis. Later, hay fever, colds, coughs, pertussis and pneumonia were added to the advertisers' list of indications for its use. It was also recommended, in the United States of America, as a remedy for morphine dependence. Unfortunately this only served to introduce diamorphine to the addict population of that country and resulted in increasing abuse.

Its reputation as a potent analgesic developed later but, by then, its use in so wide a variety of respiratory conditions was falling into disfavour. Eventually, because of the growing addiction problem the United States banned its medical use in 1924. Since then all but a few countries have fallen into line with what subsequently became the policy of the League of Nations and, later, the World Health Organization.

The most recent attempt to bring the United Kingdom into line with World Health Organization policy was made in Parliament in 1955. The attempt failed, but many doctors, especially general practitioners, have felt less able than formerly to use diamorphine. Since then a number of studies have been completed which suggest that in both coronary and surgical patients no real difference between diamorphine and morphine exists (e.g. Scott & Orr, 1969; Morrison et al., 1971). Even so, many still believe there are real differences in the effects of the two drugs. For example, physicians working with terminal cancer patients claim on behalf of diamorphine that:
(1) Diamorphine causes less nausea and vomiting than morphine.
(2) The administration of diamorphine to patients with anorexia often results in a return of appetite. This is not the case with morphine.
(3) Diamorphine is less constipating.
(4) Diamorphine enhances the mood of a patient, whereas morphine not infrequently causes dysphoria. This does not mean the patient becomes frankly euphoric; the improvement of mood can be seen as a return towards normal.
(5) Patients receiving diamorphine tend to be more alert, active and co-operative compared with patients receiving morphine.
(6) Diamorphine is a more reliable antitussive agent.
(7) Diamorphine is more effective at relieving the anxiety of patients suffering from 'malignant dyspnœa'.

It is important to realise that this is a list of supposed benefits. None has definitely been shown by controlled clinical trial. Nevertheless, it would be
unwise to disregard without question the considerable weight of clinical impression that has accumulated over a period of many years through its use in this sphere. On the other hand, those antagonistic to the continuing British use of diamorphine have not been silent:

'There is a widespread misconception that heroin has effects significantly different from those of morphine. It does not, and this misconception should be dispelled permanently' (Report, 1962).

'Heroin is a drug with no legitimate use. No drug is more habit-forming; none has more deleterious effects' (Washington Post, 1953).

'Heroin should never be used for premedication since even a single dose can lead to addiction' (Today's Drugs, 1964).

In summary

'It is clear that almost all comparisons between morphine and heroin rest upon clinical impressions rather than experimental evidence. This situation is unsatisfactory and needs to be put right' (Consumers' Association, 1967).

However, there are hidden dangers in the clinical investigation of diamorphine and as these have not always been appreciated, it is possible that some, if not most, of the clinical trials completed in recent years may be of little or no value.

Stability

In any clinical trial, information about the stability of the preparation being studied is of fundamental importance. Morphine appears to be stable whether stored in crystalline form or in solution. Unfortunately, such is not the case with diamorphine. Although crystalline preparations may be stable (Table 1), in solution diamorphine hydrolyses first to O*-monacetylmorphine and then to morphine itself (Table 2). The rate of hydrolysis depends on a number of factors such as the initial acidity of the solution, the presence or absence of a suitable buffering agent and the storage temperature (Davey & Murray, 1969). It is possible, therefore, that clinical trials comparing diamorphine and morphine have, in fact, compared an O*-monacetylmorphine-morphine mixture with morphine. It should, however, be recalled that until less than 20 years ago much of the diamorphine administered in British hospitals was prepared immediately before injection by dissolving a tablet of diamorphine hydrochloride in water on a teaspoon. It was prior to this date that the claims for diamorphine's superiority were originally made and it is since this date that many of the 'no difference' studies have been completed (Scott & Orr, 1969; Dundee et al., 1966; Morrison et al., 1971; Muir et al., unpublished observations). Of these only Muir and his associates appear to have been aware of the need to take precautions to preserve the purity of diamorphine used (Muir, 1972). This they achieved by deep freezing the solution for injection until just before use.

Potency ratio

A true comparison of the side-effects of any two therapeutic agents can only be made when equally effective doses are compared. In most trials in which the two have been compared it has been assumed that diamorphine is twice as potent an analgesic as morphine. Therefore, the drugs have been used in a 1:2 ratio. That this is an over-simplification can be seen from work of Beecher and his associates (Reichle et al., 1962). They specifically set out to assess the comparative analgesic potency of the two drugs in post-operative patients. They concluded that there is no single dose of diamorphine which is equianalgesic to 10 mg of morphine. The ratio they obtained varied between 1:4 and 1:2. If a comparative study were conducted using a 1:4 ratio diamorphine would almost certainly be shown to have significantly less unwanted side-effects (Seevers & Pfeiffer, 1936).

In terminal cancer, a between-patient comparison measuring the side-effects at the effective analgesic dose would, in theory, be the simplest way to test the claims of the 'diamorphine is best' school. It would by-pass the difficult problem of determining the equianalgesic dose for each patient. However, in practice, this approach has several major limitations and it seems likely that a within-patient cross-over comparison will be the only way to settle the present controversy.

The fate of orally administered diamorphine

As many of the terminal cancer patients prescribed diamorphine receive it as an oral mixture the effect

<table>
<thead>
<tr>
<th>Time of storage (months)</th>
<th>Diamorphine %</th>
<th>O*-MAM %</th>
<th>Morphine %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>12</td>
<td>0.05</td>
<td>0.9</td>
<td>Trace</td>
</tr>
<tr>
<td>16</td>
<td>--</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>19</td>
<td>--</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>22</td>
<td>--</td>
<td>0.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 2. Serial analysis of a 1% solution of diamorphine hydrochloride (after Rizzotti, 1935)
on it of gastric and upper intestinal juices needs to be considered. Several papers refer to the alimentary absorption of morphine but little appears to be known about the fate of orally administered diamorphine. It is known that diamorphine is absorbed fairly well sublingually whereas morphine is not (Walton, 1935) and that in the normal stomach virtually no absorption of either drug occurs (Travell, 1940). Necropsy studies have suggested that diamorphine is stable in the acid medium of the stomach (McNally, 1916). However, nothing is known about the effect of the alkaline upper intestinal juices on diamorphine. Do they, by facilitating the rapid absorption of diamorphine, allow it to reach the circulation intact? Or do they, in view of the known hydrolysis-accelerating effect of alkalinity, bring about the rapid degradation of diamorphine to O*-monacetylmorphine and morphine? These and other questions remain unanswered.

Furthermore, even if diamorphine can survive the double hazard of gastric acidity and upper intestinal alkalinity, can it survive the degrading action of liver enzymes? Evidence from animal experiments suggests not (Wright, 1942). In vivo human studies have yet to be attempted.

**Diamorphine assay**

The official pharmacopoeial assay for diamorphine is colorimetric and requires the preliminary hydrolysis of the sample to morphine (British Pharmacopoeia, 1968). The morphine is then estimated as the yellow compound nitroso-morphine, formed by adding sodium nitrite in ammonia buffer. By estimating the morphine content before and after hydrolysis, the degree of degradation of a solution of diamorphine can be assessed. However, the method has two major limitations. Although it can be used to measure the degree of degradation of diamorphine solutions it is far too insensitive to assess the presence of either diamorphine or morphine in urine or serum after medicinal administration. Secondly, as the nitrosoamine reaction is characteristic of all phenolic compounds, the method cannot differentiate between the individual phenolic alkaloids, morphine and O*-monacetylmorphine.

In recent years other techniques have been investigated in an attempt to overcome these two problems (Gold, 1971). Currently chromatographic methods are the most widely used (Nakamura & Ukita, 1967; Davey et al., 1968; Curry & Patterson, 1969), though a quicker and cheaper method for routine use based on electronic spin resonance is being used in some centres (Robinson, 1972).

As a result of these advances solutions of diamorphine can now be analysed quantitatively with a high degree of accuracy. However, to measure diamorphine and its degradation products, O*-monacetylmorphine and morphine, in simple solution is comparatively easy compared with measuring the same substances in serum. Quantities of morphine as small as 25 ng have been identified (Wilkinson & Way, 1969) but in serum and urine the presence of considerable 'background noise' means that 200 ng/ml is about the lowest concentration one can reasonably hope to detect in practice (Blackmore et al., 1972). This is not nearly sensitive enough to detect a drug which is active at concentrations far lower than this.

With the development of a more sensitive technique the answers to several questions concerning the fate of orally administered diamorphine could be obtained with relative ease.

**Mobility**

Studies assessing the incidence of vomiting following the administration of morphine demonstrate a clear relationship to mobility. For example, vomiting occurred in only 2-3% of 776 patients given morphine at the Massachusetts General Hospital (Lee, 1942). These were post-operative patients confined to bed. On the other hand various physiological studies of morphine reveal a very high incidence of vomiting: 57% (Ivy et al., 1945) and 93% following 16 mg (Chapman et al., 1943) and 100% after the injection of 30 mg morphine (Wolff et al., 1940).

Since it was unlikely that groups of individuals vary so widely in their response to a drug, a possible explanation for the widely divergent figures was felt to lie in the different experimental conditions. It seemed probable that the divergence could be accounted for in terms of recumbency and mobility. This hypothesis was thoroughly tested by Comroe & Dripps (1948). In one test the incidence of nausea in a group of postoperative patients up to 2 hr after a subcutaneous injection of 15 mg of morphine was 12%. The corresponding figure in normal ambulatory subjects was 90%. As many of the cancer patients receiving opiate-containing mixtures orally are not bedfast, it is not unreasonable to suggest that a real difference between diamorphine and morphine might exist when used regularly in such patients whereas none might be noted in bedfast patients receiving an opiate on no more than one or two occasions post-operatively.

**Sex difference**

It has been suggested that the female rat is able to deacetylate diamorphine more quickly than the male rat (Wright, 1942) but whether or not a similar difference exists between the sexes in man is not known. However, in the British National Formulary (1968) it is said that morphine commonly causes nausea and vomiting, especially in women. It is a matter of regret, therefore, that either those clinical
trials known to the author have been limited to one sex (Smith et al., 1962; Dundee et al., 1966) or the results have not included a between-sex comparison (Scott & Orr, 1969; Morrison et al., 1971; Muir et al., unpublished observations).

Conclusion

Diamorphine, in some ways, appears to be a phenomenon rather than just another drug. It is felt by some to be one of the biggest unnatural disasters ever to afflict mankind but others continue to regard it as the unrivalled analgesic for all forms of severe pain especially that of terminal cancer.

In the interest of science and for the possible benefit of future patients the need for a scientifically conducted trial comparing diamorphine and morphine in patients with advanced malignant disease is apparent. If diamorphine is the better drug for patients of this kind then the reluctance of doctors to use it will have to be overcome. If diamorphine is shown to be no better or, indeed, worse than morphine there would remain little justification for the Government of the United Kingdom continuing to sanction its medical use in view of the policy of the World Health Organization. It should, however, be stated that the contribution to the total problem of heroin addiction by diamorphine prescribed on medical grounds is negligible. Banning the licit manufacture of diamorphine will do nothing to stem the flow of illicitly produced material reaching this or other countries.

References


Stumbling blocks in the study of diamorphine

WASHINGTON POST, 4 November 1953.


