

CHAPTER SEVEN

Drugs

- 7.1 At his trial, Shipman was convicted of the murder of 15 of his patients; toxicological tests on the bodies of nine of those patients had revealed evidence of morphine toxicity. The prosecution case was that Shipman had killed each of his victims by administering a lethal injection of morphine or diamorphine.
- 7.2 Evidence about the properties and effects of morphine and diamorphine was given to the Inquiry by Professor Henry McQuay. Professor McQuay is a doctor of medicine and a Fellow of the Royal College of Anaesthetists. He is the Professor of Pain Relief at the University of Oxford and an Honorary Consultant at the Oxford Pain Relief Unit. He has considerable experience in the use of morphine and diamorphine and has published basic scientific and other works on the topic. He gave evidence for the prosecution at Shipman's trial.
- 7.3 Professor McQuay provided for the Inquiry a report dealing with the properties, use, effects and therapeutic and toxic dosages of morphine and diamorphine. He also gave written answers to supplementary questions put by the Inquiry legal team and provided an additional report, dealing with the effects of morphine and diamorphine administered by different routes and the timing of the effects of the drugs when delivered by those routes. He gave oral evidence to the Inquiry on 21st June 2001.
- 7.4 Professor Kevin Park is Professor of Pharmacology at the University of Liverpool. He has more than 20 years' experience in research in drug metabolism and in the mechanisms of adverse drug reactions. He and Professor McQuay provided a joint report with Dr Grenville focusing particularly on chlorpromazine (Largactil), but also dealing with other drugs which might have a depressant effect on the respiration or central nervous system.
- 7.5 As a general practitioner, Dr Grenville has experience of prescribing and administering opiates and of the issues relating to their use, and he also gave evidence to the Inquiry on that topic.

Morphine and Diamorphine

- 7.6 Diamorphine is twice as potent as morphine, when given by intravenous injection; however, once introduced into the body, diamorphine is very rapidly changed into morphine. It is not, therefore, possible to say, as a result of toxicological tests alone, whether any morphine found on testing was originally administered as morphine or diamorphine. In Shipman's case, the overwhelming likelihood is that, during his years in Hyde, diamorphine was his drug of choice. This is apparent from the available evidence about Shipman's acquisition of controlled drugs during the 1990s, which will be discussed in Chapter Eight.
- 7.7 Professor McQuay explained that morphine works by binding to the receptors which carry messages of pain to the brain. Although it has the same chemical constituents as

morphine, diamorphine's different structure means that it cannot bind to the receptors and has to break down into morphine in order to be able to do so. The process of change from diamorphine to morphine takes only about 30 seconds. Dr Grenville pointed out that morphine also has euphoriant and vasodilatory effects, which can be helpful in treating certain conditions.

- 7.8 Whether administered as morphine or diamorphine, the morphine has to be transported in the bloodstream to the brain and the spinal cord, where the receptors are situated. The quickest way to achieve this is by intravenous injection, i.e. administration straight into the bloodstream. Alternatively, the drug can be administered by intramuscular injection, which is much slower because the morphine has to pass from the muscle to the bloodstream before being carried to the receptors. If the drug is taken orally, then it is absorbed from the intestines into the bloodstream, before passing round to the brain and the spinal cord, and this takes longer than either the intravenous or the intramuscular route. The timing of the effects produced by the administration of morphine and diamorphine by different routes is compared at paragraphs 7.29 to 7.36.

The Side Effects of Morphine and Diamorphine

- 7.9 One of the two most important unwanted side effects of morphine and diamorphine is respiratory depression; the other is addiction. Morphine, when administered, has the potential to slow the rate of breathing and, ultimately, to stop breathing altogether. This must be taken into consideration when deciding whether to prescribe morphine or diamorphine and, if so, how much to prescribe. If a patient is in acute pain, respiratory depression is less likely to occur, since the potential of morphine to stop breathing is combated by the pain itself. If a person has no pain or distress when the drug is administered (for example, if he or she is taking the drug for 'recreational' purposes), there is no opposition to the potential to depress respiration and breathing is liable to become slower. Euphoria will also occur very rapidly. If a patient already has a condition causing respiratory depression, such as chest disease, the further depressant effect of the drug on the patient's breathing may easily give rise to danger. Other side effects of morphine, usually evident when a patient is first started on the drug, are dizziness, constipation and nausea.
- 7.10 Morphine injections are delivered ready-mixed as a transparent liquid in little glass pots called ampoules; they are available in a variety of strengths. They are administered by drawing up the contents of the ampoule into a syringe by means of a needle. Diamorphine comes in powder form, also in an ampoule, and has to be mixed with sterile water for administration as an injection. The water is drawn up from an ampoule into a syringe and then squirted into the powder ampoule. The diamorphine solution is then drawn back into the syringe ready for injection. Diamorphine is easy to dissolve, so only a little liquid (about 1 to 2ml for a 10mg ampoule of diamorphine) is required. With an intramuscular injection, the smaller the volume used, the less uncomfortable the injection. Diamorphine is supplied in 5mg, 10mg, 30mg, 100mg and 500mg ampoules.
- 7.11 An intravenous injection is most commonly administered into the large vein in the crook of the elbow, the next most favoured site being a vein on the back of the hand. The most

usual sites for an intramuscular injection are the buttock, the big muscle on the outside of the thigh or the deltoid muscle in the upper arm.

The Use of Morphine and Diamorphine in the Treatment of Severe Acute Pain or Distress

7.12 Dr Grenville described the circumstances in which he would use morphine and diamorphine for the treatment of severe acute pain, for example, after severe trauma, or for the pain of a heart attack. He would also use the drug to alleviate distress caused by left ventricular failure, a condition not characterised by pain. He told the Inquiry that he usually uses morphine in the form of Cyclimorph, which also contains cyclizine (a drug which prevents sickness). He carries for this purpose two ampoules of Cyclimorph 15, each of which contains 15mg morphine. Dr Grenville has had to administer Cyclimorph on only four occasions in his career, two of which were emergencies which occurred when he was off duty. In recent years, the use of morphine and diamorphine by doctors in acute circumstances arising in the community (as opposed to hospitals) has reduced, due to the greater role played by trained paramedics in the treatment of heart attacks and other acute conditions.

7.13 Dr Grenville emphasised that it is important to use the drug in the minimum quantities required to give pain relief; in other words, the drug is titrated against the patient's problem, be that pain or distress. This is best done by injecting the drug intravenously, so that it passes straight into the bloodstream and rapidly moves to the brain and spinal cord, where it exerts its effects; those effects can be observed as the drug is administered. Dr Grenville described this process:

' So you inject the drug into the vein very, very slowly and you observe the patient as to what effect it is having upon them. By observing a patient, you can tell how much pain they are in; whether their pain is being relieved; whether life is becoming easier for them.

You are also observing the patient to watch for the onset of unwanted effects, such as sedation or respiratory depression. It is always a question of titrating the dose against the problem for which you are using it'.

7.14 Dr Grenville uses a long, narrow, low volume insulin syringe so as to achieve greater control over the dose and aims to inject about 1mg morphine a minute.

7.15 Dr Grenville went on to make the point that the intravenous route is to be preferred, because titration is possible. With the intramuscular route, there is no possibility of titrating and it is necessary for the doctor to decide beforehand how much of the drug he or she is going to give. The only circumstance in which Dr Grenville would inject morphine intramuscularly would be, he said, if he had to give an opiate to a patient in severe pain and he could not get venous access because the veins were collapsed or for some other reason.

7.16 As to the effects of the drug, Dr Grenville said that the first effect was likely to be the euphoriant effect but, in a patient with severe pain, an intravenous injection will very quickly start acting to help the pain and it is necessary to ask the patient to report any

differences which he or she may notice as the drug is delivered. In the case of acute left ventricular failure, the patient will be distressed with rapid, laboured breathing and, probably, secretions. The aim of the injection is to try to ease the patient's distress and panic and thus reduce the production of adrenaline and other hormones. Opiates also have a vasodilatory effect which might reduce the pooling of blood in the lungs. In this case, morphine would be used in conjunction with a large intravenous dose of a diuretic.

- 7.17 An injection could also be given subcutaneously; if this is done as a 'one-off', which would not be usual, it could be given anywhere on the body under the skin, most likely on the thigh, the stomach or the chest wall.

The Use of Morphine and Diamorphine in the Treatment of Chronic Severe Pain

- 7.18 Subcutaneous injections are usually administered over a period of time, using a butterfly needle, which is placed under the skin on the chest wall or on the abdominal wall, and held in place by two 'wings' taped onto the surface of the skin. Such injections are used in the management of persistent, severe pain, usually as a result of cancer.
- 7.19 Both Professor McQuay and Dr Grenville gave evidence about the use of strong opiates in relieving pain caused by terminal conditions. They described how the patient's pain is managed by using progressively stronger pain-relieving drugs, usually in tablet form. When strong opiates are introduced, they are often in the form of slow-release morphine tablets, which are designed so that the morphine within the tablets is absorbed slowly into the bloodstream over 24 hours; thus, if the tablets are taken regularly, a constant level of the drug within the bloodstream is maintained, the aim being to keep the drug at a level whereby the patient is pain-free. Often, a patient can be maintained on an oral opiate, such as morphine, for a long time – for months, even years. If breakthrough pain is experienced, this should be dealt with by giving a single dose (a 'bolus' dose) of the drug by some convenient means, often an oral morphine solution. However, breakthrough pain is an indicator that the current regular dose of oral medication is inadequate and should be increased so that the pain is effectively controlled.
- 7.20 When a patient with a terminal illness becomes unable to swallow, opiates have to be administered by a route which does not involve swallowing, most usually by the subcutaneous route using a syringe driver attached to a butterfly needle. A syringe driver is a pump, into which a standard-sized syringe will fit. It is designed to drive home the plunger of the syringe over the course of a 24 hour period. By making up the solution of the opiate to be put into the syringe in different quantities, the drug can be delivered to the patient at different rates. As the rate is increased, the level of the drug in the patient's bloodstream increases and that level can be titrated against the degree of pain experienced by the patient. If a syringe driver is in use, any breakthrough pain is best dealt with by an intravenous injection although, once again, the occurrence of breakthrough pain may signify the need to reassess and increase the dose of the drug being delivered through the syringe driver. Syringe drivers have been a common method of treating a patient who is unable to swallow for the last 20 to 30 years, according to Professor McQuay, although Dr Grenville said that they have become more widespread in the community (as opposed to hospital) over the last 10 to 15 years. The

first use, known to the Inquiry, of a syringe driver among Shipman's patients was in November 1993; it is, however, possible that one or two had been provided to other patients before that time.

The Appropriate Dose of Morphine or Diamorphine

- 7.21 Both Professor McQuay and Dr Grenville gave evidence about the doses of morphine and diamorphine, which would be appropriate in various different circumstances.
- 7.22 Dealing first with the relief of acute pain, for example after a heart attack or an operation, Professor McQuay stated that the standard adult dose would be 10mg morphine or 5mg diamorphine, repeated four hourly as necessary, administered intramuscularly. If injecting intravenously, he would give about half those quantities and probably, he said, with some caution. That would be the amount of the drug which would be given by way of 'pre-med' to a patient before undergoing an operation.
- 7.23 Dr Grenville observed that the dose of morphine usually required in circumstances of acute pain by a previously healthy, opiate-naïve adult patient is extremely variable, but the commonest range would be 5 to 10mg morphine or 2.5 to 5mg diamorphine by the intravenous route. If constrained to give an intramuscular injection, he said that he would probably give 5mg morphine and observe the effects, hoping that the patient was not a person who was particularly susceptible to morphine and aware that, if the dose given proved inadequate, he could always give a further dose. Dr Grenville said that the maximum amount of morphine he had ever needed to use in circumstances of acute pain was a full ampoule of Cyclimorph 15, i.e. 15mg morphine.
- 7.24 Where a patient has protracted chronic pain, such as that produced by cancer, the average daily dose of oral morphine is, according to Professor McQuay, about 120mg, although the dose can be much larger – in rare situations up to 2 to 3g per day. If a change is then made to subcutaneous delivery (because the patient cannot swallow), but the pain has not increased, then the dose will be reduced to between a third and a half of that being given orally. In other words, morphine delivered by the subcutaneous route is generally considered to be between twice and three times as potent as morphine delivered orally. Professor McQuay explained that, in practice, the change from the oral to the subcutaneous route often occurs towards the very end of life, at a time when the pain is escalating, so that a simple conversion is not appropriate. In that event, it is usual to start with the equivalent of the current oral dose, giving 'extras' as necessary and then calculating, by reference to the number of extras, the appropriate daily dose. Professor McQuay estimated that about 30 per cent of patients requiring subcutaneous morphine need more than 200mg morphine per day.
- 7.25 Professor McQuay told the Inquiry that previous exposure to morphine frequently has the effect of increasing a patient's tolerance to the drug, resulting in more being needed to achieve the same level of pain relief. The effect of the drug is also subject to factors such as age, size and state of health. In general, the older the patient is, the greater the effect of a given dose of morphine. All these factors have to be taken into account when determining the dose of morphine or diamorphine to be used. The effect of the drug is

also influenced by the speed at which it is delivered; maximum effect would be achieved by giving the contents of a syringe by the intravenous route very quickly.

Excessive Doses of Morphine and Diamorphine

- 7.26 Both Professor McQuay and Dr Grenville were asked to identify the dose of morphine and diamorphine which they believed was likely to be fatal in a morphine-naïve patient. Professor McQuay pointed out that the task was a difficult one, since the aim of doctors was to avoid giving such a dose if possible; the answer to the question cannot be found in any textbook and, in any event, would vary according to the patient's age, size and state of health, together with other factors. However, his best estimate was that 60mg morphine or 30mg diamorphine, given over one minute to a fit adult who had not previously been exposed to strong opioid drugs, would be fatal. The most he has ever administered himself was 30mg morphine intravenously over ten minutes, titrated to control very severe pain arising from a trauma suffered by a very large (and presumably fit) man in the course of cross-country skiing.
- 7.27 Professor McQuay said that he would expect a dose of 30mg diamorphine, given intravenously over five minutes or less, to put a fit, normal person, not habituated to the drug, to sleep and eventually stop their breathing. Dr Grenville was a little more conservative in his views. He said that he would expect, on the basis of his own experience of giving therapeutic doses, that a dose of 20mg diamorphine or 40mg morphine would prove fatal. He would reduce those amounts by half in an elderly, small, ill or frail patient. He said that a smaller dose could produce long-term coma with brain damage, without necessarily causing death by total cessation of respiration.
- 7.28 The risk of coma and brain damage is illustrated by the circumstances of two of the deaths for which I have concluded that Shipman was responsible. In the case of Mrs Alice Gorton, who died on 10th August 1979, Shipman plainly believed that she was dead when he summoned her daughter to the house. Shortly after the daughter's arrival, however, Mrs Gorton was heard to groan loudly. She survived in an unconscious state for a further 24 hours or so. Whilst Mrs Gorton was elderly, she was also a large woman and I have found that Shipman injected her with a dose of diamorphine which was not sufficient – possibly because of her size – to kill her immediately, but was enough to render her unconscious and to cause her death from brain damage or bronchopneumonia, or as a result of a combination of the two. I have also found that, on 18th February 1994, Shipman injected Mrs Renate Overton with sufficient diamorphine to cause unconsciousness from which she never recovered. It is not clear whether Shipman used less diamorphine on this occasion than was his habit or whether Mrs Overton, being only 47 years old, was a more robust subject than most of his elderly patients. Whatever the cause, she survived in a persistent vegetative state for 14 months.

The Timing of the Effects of Excessive Doses of Morphine and Diamorphine

- 7.29 Professor McQuay produced a report dealing with this topic, with which Dr Grenville has signified his agreement. Dr Grenville has also commented on the timing of the effect of the drugs in the context of the specific deaths about which he has given evidence.

- 7.30 If a fit adult with no previous experience of opioid drugs were given 30mg diamorphine intravenously over one minute, Professor McQuay said that he would expect breathing to stop within one minute and death to ensue within five minutes, because of lack of oxygen to the brain. The patient would be incapable of moving from the position in which he or she had been injected and would be unlikely to vomit. Larger doses would, Professor McQuay said, have the same effect.
- 7.31 Professor McQuay observed that he was unable to predict with precision the effects of an intravenous dose of less than 30mg diamorphine. He said that, after any dose over 5mg, the patient would be aware that something had happened, would be aware of feeling strange and drowsy and, if he or she tried to move about, would probably be nauseated and vomit. Professor McQuay observed that a dose of 20mg could well prove fatal in an elderly, unfit and opioid-naïve person. Dr Grenville said that a patient to whom a fatal intravenous injection was administered would rapidly become unconscious and would be unaware that he or she was dying; he drew a parallel with the anaesthetic given before an operation, after which the patient usually falls asleep and is aware of nothing else until the effects of the anaesthetic wear off.
- 7.32 An intramuscular injection takes longer to work and the effects are less predictable. The effect of an intramuscular injection of 30mg diamorphine would be maximal between 30 and 60 minutes after its administration. The degree of the effect would also be slightly less than for the same dose delivered intravenously, since absorption of the drug would be less complete. Nevertheless, Professor McQuay would expect a 30mg intramuscular dose of diamorphine to be fatal in an opioid-naïve person. Because of the slower absorption, it is possible that there would be a period of time after administration of the injection when the patient would be able to walk and talk. As the drug began to take effect, the patient would feel nauseated and might vomit, particularly if he or she were trying to move about. Although an onlooker may not notice any immediate effect, by a period of 15 minutes after the injection – and certainly by 30 minutes after – it would be clear that ‘something strange’ was happening. The general proposition, confirmed by Dr Grenville when giving his evidence in the case of Mr Samuel Mills, is that, if a person is going to die as a result of an intramuscular injection of opiates, he or she will do so within about an hour of its administration.
- 7.33 The oral route is the slowest and the onset of the effects of a dose of 60mg tablets of morphine (i.e. the equivalent of 30mg diamorphine) would, according to Professor McQuay, be 30 to 45 minutes after its ingestion; again, there would be a period of normality before the patient began to feel nauseated and act strangely. This would probably be evident by 45 minutes after ingestion, certainly by 60 minutes. The ‘lucid interval’ would be increased further if the oral morphine were given in a slow-release formulation; the onset of the effects would then be delayed to 1½ to 2 hours after administration. Dr Grenville stressed that different people have a different susceptibility and, in the case of frail and elderly patients, the onset of the effects of the drug could be quicker than the estimates set out above.
- 7.34 Professor McQuay has described how, if a needle is placed in a vein in order to deliver an intravenous injection, it can slip out of the vein so that fluid which had been intended

to go into the vein is instead extravasated, i.e. it goes outside the blood vessel and into the tissues around the vein. The injection thus becomes subcutaneous but the timing of the effect will, Professor McQuay said, be similar to that for an intramuscular injection. In order to avoid the risk of giving an extravasated injection, the injector usually checks, by intermittent pulls on the syringe plunger, that there is a back flow of blood which shows the needle is still in the vein. However, a needle can come out of the vein if the recipient or the injector moves position or the needle shifts. There can be problems also with small, very mobile veins which are sometimes present after excessive weight loss; also, many elderly people have veins with calcified walls, which are difficult to penetrate. The veins may also have collapsed or be difficult to find, for example in a person who is obese.

- 7.35 If a needle comes out of the vein and part of the drug is extravasated, Dr Grenville said that the effect produced by the injection is likely to be significantly slower than if it had been delivered intravenously. He said:

‘ If it became extravasated, then you may be looking at the effects within a few minutes up to maybe tens of minutes, depending upon the patient’s condition and the amount of the dose that is being given, how much was given intravenously, how much was extravasated; there would be all sorts of factors. Clearly, I have to say it is something I have no experience of’.

- 7.36 If the dose administered were of such a size as to be fatal, Dr Grenville said that, as with an intramuscular injection, there may be a period during which the patient might be able to move around, albeit feeling unwell, dizzy and perhaps sick, before lapsing into unconsciousness and death.

Double Effect

- 7.37 Professor McQuay and Dr Grenville gave evidence about the phenomenon known as ‘ double effect’, whereby the administration of a dose of opiates sufficient to relieve a patient’s pain might also have the effect of reducing the patient’s respiratory drive to such a degree that the patient’s life is shortened. Dr Grenville pointed out that, as well as considering the effect of the drug on respiratory drive, a doctor must also consider the fact that, if the patient’s pain is not relieved, he or she may become distressed and exhausted and thus the patient’s life may be shortened anyway.
- 7.38 Dr Grenville explained that it was necessary, when deciding on the amount of the drug to give and the rate at which it should be delivered, to balance the need to relieve pain against the risk of depressing respiration. This is likely to be more difficult when the patient is close to death and suddenly experiences a degree of breakthrough pain, necessitating a dose of pain relief, which may reduce the patient’s respiration to the extent that he or she cannot continue. He stressed that this was likely to arise at the very end of life and that any shortening of life was likely to be by hours only.
- 7.39 Dr Grenville said that good medical practice when using opiates in these circumstances was for the doctor to ensure that the patient’s death was as pain-free as possible and that he or she was kept comfortable and did not die distressed. However, it is not lawful

to administer doses of opiates which are primarily intended to hasten death and which are more than the doctor honestly believes is required to alleviate pain.

7.40 Professor McQuay acknowledged the problem with terminally ill patients. He said that the technique in these circumstances is to titrate the dose against the response. If the patient is conscious, he or she can indicate whether the drug has had any effect in relieving pain; even if the patient is comatose, signs such as grimaces, sweating or a rise in pulse rate can indicate continuing pain. Obviously, the unconscious patient is more difficult to assess. Professor McQuay said that he could not be certain whether the giving of a dose of opiates sufficient to relieve distress in a desperately ill patient with a short time to live might also have the effect of shortening life by a brief period. In those circumstances, he would have to make a value judgement as to the appropriate dose against the background of the previous doses received by the patient.

7.41 When giving evidence about the death of Mrs Mary Ogden, Dr Grenville referred to the direct and indirect results of an intramuscular administration of opiates to a patient who was approaching death. On the one hand, the injection could have the direct effect of depressing respiration and causing death; in that event, he would expect death to occur within an hour of administration of the drug. He distinguished this situation from that of the indirect result of the injection, which he described thus:

'...in the real situation of a patient who is really ill and really needs analgesia, you could envisage the situation, and, indeed, it occurs, where they require a dose of morphine or diamorphine which is very large but may not be sufficient to cause death of itself but may be large enough to cause temporary respiratory depression which then allows, in a very debilitated patient at death's door (*sic*), to develop a terminal bronchopneumonia and to that extent one could describe the bronchopneumonia as a direct result of the morphine injection and that is a different timescale. So this really is the difference between a real-life situation of the type that I have seen and the sort of thing that happened or may have happened when Shipman was involved'.

7.42 Dr Grenville confirmed that, if the opiate were the primary cause of death, death would occur within about an hour. However, the dose of opiate might be a contributory cause of a death taking place more than an hour later.

7.43 The Inquiry has investigated a number of cases in which it has been suggested, or suspected, that Shipman administered opiates in a quantity designed to hasten death, rather than merely to relieve pain. However, in many of these cases, it has been impossible to make any assessment of the amount of medication given. Shipman's medication records were frequently inadequate, so that even when the general practitioner records are available, it is often impossible to tell from them what or how much medication was prescribed and/or administered. The exception to this is those cases of terminally ill patients on syringe drivers where the district nurses' records of drugs received and administered are still available; those records are of a generally high standard. However, Shipman's failure to record the drugs administered and the fact that he is known to have been in illicit possession of large quantities of opiates,

together with the lack of availability of any records at all in the early years, make it very difficult to assess the nature and quantity of drugs administered to some of the patients whose deaths have been considered.

Pethidine

- 7.44 In his answers to the supplementary questions put by the Inquiry, Professor McQuay explained that pethidine is a synthetic strong opioid painkiller, the effects and uses of which are similar to those of morphine. Like morphine, it acts on the receptors which transmit messages of pain to the brain. Also, like morphine, pethidine is addictive and produces various side effects, including respiratory depression, retention of urine, palpitations and convulsions. Because of the risk of these latter effects, pethidine is not generally used for the long-term relief of chronic pain. Instead, it is used to treat acute pain, usually where not more than ten doses are likely to be required.
- 7.45 Pethidine can be administered by injection or in tablet form. A usual dose would be 100mg given intramuscularly, repeated four hourly as necessary. Professor McQuay estimated a lethal dose to be of the order of 500mg for a fit opioid-naïve person. Administering a dose of that size would have considerable practical difficulties. In the 1970s, pethidine was supplied in ampoules containing 50mg of the drug in 1ml water or 100mg in 2ml water. Therefore, a lethal dose would entail the administration of five of the larger ampoules, containing a total of 10ml liquid. It seems unlikely, therefore, that Shipman can have used pethidine to kill.
- 7.46 The timing of the effects of the administration of pethidine by different routes would be similar to those for morphine and, as with morphine, the degree of effect would depend on a number of factors, including age. High or repeated doses give rise to the risk of convulsions.

Chlorpromazine

- 7.47 The proprietary name for chlorpromazine is Largactil. Chlorpromazine is an anti-psychotic or neuroleptic drug, which has been in use for more than 25 years. It can be used to manage agitated states in the elderly and, since it suppresses nausea and potentiates the effects of other centrally acting depressant drugs, it has been much used in the treatment of the pain of terminal illness. It exists in tablet, elixir and injectable forms.
- 7.48 Dr Grieve, one of Shipman's partners in Todmorden, confirmed to the Inquiry that the doctors there used injectable chlorpromazine in the treatment of terminally ill patients, such as Mrs Lily Crossley, and there are references also to its use by Shipman during the Hyde years.
- 7.49 In 1974 to 1976, ampoules of chlorpromazine for injection contained either 25mg in 1ml of solution or 50mg in either 2ml or 5ml of solution. The recommended dosage was 25 to 50mg, to be repeated every 6 to 8 hours. Smaller dosages would be appropriate in the case of small, elderly or frail patients. The March 2001 British National Formulary refers to ampoules containing 25mg chlorpromazine in 2ml of solution.

- 7.50 The solution is given by deep intramuscular injection, into either the buttock or upper arm. It has irritant properties which would make intravenous injection painful and, to all intents and purposes, impracticable. While a massive overdose of chlorpromazine might be capable of directly causing death (for example, by inducing fatal cardiac arrhythmia), such an overdose would involve the injection of a substantial volume of fluid and I do not think that Shipman would ever have chosen to kill a patient by this method.
- 7.51 On the other hand, a smaller overdose of chlorpromazine could have an indirect lethal effect in very much the same way as might be achieved by a sublethal dose of morphine or diamorphine. A dose of 100mg chlorpromazine is not a lethal dose, but could contribute to a patient's death. The mechanism would be by suppression of the respiration, or of the protective cough reflex, of a frail person, especially where that person already had a chest infection or history of chronic obstructive pulmonary disease. Depending on the circumstances of the individual and the dosage given, death might ensue by this indirect mechanism after anything between a small number of hours and several days. The patient would go into a deep sleep quite soon after the giving of the injection, a sleep from which he or she might well not wake if death followed as an indirect result of the injection.
- 7.52 Other drugs exerting a comparable depressant effect on the respiration or central nervous system would include the anxiolytics, hypnotics and some of the more sedating anti-depressants and anti-histamines.

Other Types of Treatment by Injection

- 7.53 In the course of considering individual cases, I have come across other suggested types of treatment by injection. When giving evidence in the case of Mrs Hannah Jones, Dr Grenville said that, in 1985, the best treatment available for a severe asthma attack was an intravenous injection of aminophylline or terbutaline, and it is quite possible that Shipman legitimately treated Mrs Jones with such injections some months before she died. Both drugs carried a risk of causing fatal irregularities of the heartbeat, but such problems, if they occurred at all, would follow immediately after the injection, when the patient would go into cardiac arrest. Dr Grenville also alluded in that case to the giving of an intramuscular injection of a steroid. In considering the case of Miss Florence Taylor, Dr Esmail told me that, in the early 1980s, intravenous injections of salbutamol might have been given in similar circumstances and with similar possible side effects.
- 7.54 I should mention, for the sake of completeness, that there were undoubtedly occasions on which Shipman gave a lethal injection of diamorphine but purported to have given something else. So, in the case of Mrs Eileen Crompton, Shipman purported to give an intravenous injection of benzylpenicillin, whereas I am sure that he gave a lethal injection of morphine or diamorphine.
- 7.55 In the next Chapter, I will consider the means by which Shipman was able to acquire controlled drugs.

