THE PHARMACIST'S CONTRIBUTION TOWARDS MONITORING AND REPORTING ADVERSE DRUG REACTIONS

A thesis submitted for the Degree of DOCTOR OF PHILOSOPHY

in The University of Aston in Birmingham

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May, 1983

The University of Aston in Birmingham

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A thesis presented for the degree of Doctor of Philosophy
by J.C.C. Talbot, May 1983

Summary

The activities and function of the West Midlands Adverse Drug Reaction Study Group are described. The impact of the Group on the reporting of adverse drug reactions to the CSM by the yellow card system has been evaluated in several ways including a comparison with the Trent Region. The role of the pharmacist in the Group is highlighted. A nationwide survey of the hospital pharmacist's involvement in adverse drug reaction reporting and monitoring is described, the results are reported and discussed. The available sources of information on adverse drug reactions, both primary and secondary, are critically reviewed. A checklist of necessary details for case reports is developed and examples of problems in the literature are given. The contribution of the drug information pharmacist in answering enquiries and encouraging reporting is examined. A role for the ward pharmacist in identifying, reporting, documenting and following up adverse drug reactions is proposed. Studies conducted to support this role are described and the results discussed. The ward pharmacist's role in preventing adverse drug reactions is also outlined. The reporting of adverse drug reactions in Australia is contrasted with the U.K. and particular attention is drawn to the pharmacist's contribution in the former. The problems in evaluating drug safety are discussed and examples are given where serious reactions have only been recognised after many patients have been exposed. To remedy this situation a case is made for enhancing the CSM yellow card scheme by further devolution of reporting, increasing the involvement of pharmacists and improving arrangements at the CSM. It is proposed that pharmacists should undertake the responsibility for reporting reactions to the CSM in some instances.

Key words : adverse drug reactions
pharmacist
hospital
drug monitoring
Committee on Safety of Medicines

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ACKNOWLEDGMENTS

I wish to thank Dr. Bryan Veitch, my supervisor, for his continued encouragement, guidance and constructive criticism throughout the genesis of this thesis.

I am grateful to the many hospital pharmacists who provided me with information or data; in particular, Miss Elena Grant and Mrs. Sue Roden, Dr. Howard McNulty, Steve Baker, Mrs. Anne Everden, Steve Hudson, Mike Rogers, Dr. Jim Smith and Miss Ann Biddolph. Also the 119 Pharmaceutical Officers and other hospital pharmacists who kindly completed the questionnaire and hence contributed to Chapter 3.

I am also grateful to Dr. R. G. Penn for providing me with some figures from the CSM, Mrs. Claudia Wright for her epidemiological, data processing and statistical advice and Dr. Myles Stephens for his stimulating discussion on many aspects of adverse drug reactions but notably on postmarketing surveillance.

Finally, I wish to thank particularly Mrs. Mary Rear who typed and prepared the manuscript to her usual standards of excellence.

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CHAPTER 1

INTRODUCTION

Definitions

In the broadest sense, an adverse drug reaction is any undesirable effect produced by a drug; however, this includes factors such as deliberate drug overdoses and drug abuse and is too general for the scope of this thesis. In 1964 Cluff et al[1] in the U.S.A. defined an adverse drug reaction as "any unintended or undesired consequence of drug therapy"; the same workers in 1966 modified this to "any response to a drug in a patient that was unintended and undesired by the physician who prescribed it"[2]. These "early" definitions were further refined but perhaps one of the most widely accepted definitions is that of the World Health Organisation (WHO), "any response to a drug which is noxious, unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy"[3]. This definition clearly excludes overdoses and drug abuse but it could be interpreted as including therapeutic failures[4]. Whilst the failure of a drug to produce a desired effect is important, it is qualitatively distinct from the production of an undesirable effect[4] and many workers would not regard it as an adverse reaction. An adapted form of the WHO definition which includes this point has been proposed as "any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy, excluding therapeutic failures"[5]. This latter definition of an adverse drug reaction will apply throughout this thesis. Terms such as side effects, adverse effects, toxic effects and secondary effects have also been used by other workers, these will not be

used in the thesis except when citing these authors.

It must be remembered that the above definitions do not concern themselves with the severity of a reaction, which may vary from a minor subjective complaint to a life threatening or even fatal event, or the onset, which may be immediate or after many years. The definitions also strongly imply that the drug was responsible for the reaction whereas in reality this is usually difficult to establish, hence further terminology is needed. Schimmel[6] in 1964 referred to episodes, rather than adverse drug reactions, to include every noxious response to hospital care. Finney[7] used the description "adverse event" as any particular untoward happening experienced by a patient. This later term, as defined by Finney, will also be used at times in the thesis when the causal relationship between a drug and an adverse event is unknown.

Drug monitoring has been described as any systematic procedure for observing drugs in normal medical use, reporting instances of adverse reactions and ensuring that the records are regularly scanned and analysed[8]. The word "monitoring" has been used throughout this thesis to mean the first part of the above description, i.e. the observation and recording of drug use and adverse drug reactions.

Detection of adverse drug reactions before marketing

The primary evaluation of safety of a new drug begins with animal studies and only after extensive animal work is the compound introduced into man. However, strict rules against marketing a drug that has shown signs of danger in animal tests do not guarantee safety in man[8].

It is usual to distinguish four phases of clinical investigation, the first three before marketing and the fourth after marketing[9]. The earliest investigations in man are generally conducted under closely controlled conditions in a small number of healthy volunteers (e.g. 10 to 30 individuals) to determine the clinical pharmacology of the drug and this is known as Phase I[9,10]. The next development is to demonstrate the effectiveness and relative safety of the drug in a small number of patients, seldom more than 100 or 200, who suffer from the disease the drug is designed to treat; this is known as Phase II[9]. Full scale clinical trials (Phase III) to establish whether the beneficial effect is still evident in larger numbers and over a longer time[9] follow after effectiveness has been basically demonstrated and Phase IV is the postmarketing use of the drug[10].

Phases I and II are likely to identify adverse reactions which occur in all or nearly all subjects and which are probably due to a direct pharmacological response to the drug. Phase III should detect common adverse reactions but will probably not detect rare or idiosyncratic responses. The reasons for this are fourfold. Firstly, the number of patients treated in a clinical trial, or trial programme, is relatively small, perhaps between 500 and 5,000 depending on the drug. Small numbers limit the power of a trial to detect rarer reactions; for instance, to be 95% certain of detecting one case of an adverse reaction with an incidence of 1 in 1000 that does not occur naturally would require 3000 patients. To detect more than one case or a reaction occurring at a lower incidence would clearly require even larger numbers[11], see Figure 1. If there is a background incidence of the adverse reaction, i.e. it occurs naturally

without the drug, which is generally the case, the figures are even larger[11], see Figure 2. Secondly, clinical trials are designed primarily to test the efficacy of a new drug and inadequate attention might be paid to detecting and recording adverse reactions. This was clearly a problem with practolol where an analysis of adverse reactions experienced in over 2,000 patients treated in clinical trials showed only seven rashes and no eye complaints[12]. In the light of this and the subsequent experience with practolol, Skegg and Doll[13] advocated that doctors should record all adverse events experienced by patients and not just those regarded as adverse drug reactions; this approach has also been endorsed by others[14,15]. All reported events should be collected together for analysis and, where possible, a comparison made between active drug and placebo groups. This method might have revealed the ocular toxicity of practolol before the drug was marketed[13]. Thirdly, patients receiving a drug after marketing may differ considerably from the population in whom the drug was initially tested. For instance, patients that might be more susceptible to an adverse drug reaction are frequently excluded from many trials, e.g. children, the elderly, pregnant women, patients with renal failure, patients with other diseases, seriously ill patients, etc. Fourthly, some other characteristics of clinical trials make them artificial in comparison to the postmarketing use of the drug. For example, adverse reactions which occur only after prolonged exposure may not be detected due to limited duration of the trial, fixed doses only may be used, concurrent therapies may be restricted and only motivated clinicians keen on the drug will be the prescribers.

These considerations will also conceal the true incidence of adverse reactions in clinical practice and are likely to inhibit the revelation of factors which predispose to reactions. However, drugs are allowed onto the market on the basis of such trials. The granting of a product licence for a new drug merely means that any hazards unacceptable to the licensing authority have not been identified; it does not ensure that a medicine will be safe in subsequent prescribing practice[16]. Adverse reaction monitoring must, therefore, continue after a drug is marketed to establish its true adverse reaction profile and it will take years to detect very rare or delayed effects.

Detection of adverse drug reactions after marketing

There are several methods of detecting adverse reactions following the marketing of a drug; the role of each is different but the methods are complementary. Spontaneous reporting[17] in which a doctor observes an adverse reaction and reports the findings to his colleagues is the most basic method. The method is crude in that it lacks independent evaluation and collection of data from other sources but the publication of cases in medical journals is a valuable way of publicising the occurrence of an adverse reaction. Voluntary reporting schemes which were established in many western countries following the thalidomide tragedy are an extension of spontaneous reporting. The principle of these schemes is to centralise the spontaneous reporting of adverse reactions and this will be discussed further with particular reference to the U.K., i.e. the Committee on Safety of Medicines (CSM) yellow card system.

Another method is intensive hospital monitoring where trained monitors (doctors, nurses or pharmacists) study a defined population of patients for

possible adverse drug reactions. The best example of such a scheme is the Boston Collaborative Drug Surveillance Program (BCDSP)[18] which has made a significant contribution to our knowledge of adverse drug reactions both generally and specifically. The BCDSP extends its work worldwide and the workers have reported the results of their studies in many therapeutic areas, more than 80 papers being published between 1966 and 1977. For example the programme has established the incidence and distribution of ampicillin rashes[19] and the frequency of adverse reactions with prednisone[20], spironolactone[21] and potassium chloride[22]. Despite the value of intensive hospital monitoring there are a number of disadvantages; it is costly, only limited numbers of patients are monitored at any time, monitoring is usually only for a short period and the data cannot necessarily be extrapolated to the general population[17].

A further method of monitoring is Record Linkage in which the various medical records of an individual patient are collected together. Such a nationwide medical record linkage system exists in Finland where there are five health surveillance registries. These are all computerised and receive input from doctors and hospitals, their function includes the surveillance of drugs[23]. There is also the Oxford Record Linkage Study in the U.K. in which details of hospital discharges, some outpatient consultations, births and deaths are recorded[24]. An example of how the Oxford study could provide information about adverse drug reactions was the demonstration of a highly significant association between the use of minor tranquillisers (prescribed by general practitioners) and the risk of serious road accidents (information from hospital admissions and deaths)[25].

Another and much discussed method of monitoring is postmarketing surveillance (PMS), the primary objective of which is to identify a drug's efficacy and toxicity under conditions as near as possible to its actual clinical usage. PMS has been seen as bridging the gap between clinical trials and voluntary reporting of adverse reactions and there have been suggestions that the first few thousand patients given a new drug should undergo such monitoring. Proposals for the U.K. have included "recorded release"[26], "monitored release"[27], "restricted release"[28] and a similar scheme put forward by the Association of the British Pharmaceutical Industry (ABPI)[29]. None of these schemes as such has been implemented to date but a number of PMS schemes have been conducted by pharmaceutical companies, although unfortunately some have been little more than promotional clinical trials. A further twist is that PMS may not fulfill its objective. A recent review of 60 pharmaceutical company organised PMS schemes revealed that only one new adverse drug reaction hypothesis had been put forward as the result of the schemes[30]. However, the recently established Drug Surveillance Research Unit at the University of Southampton, directed by Dr. W. Inman, may offer some hope for the future through his Prescription Event Monitoring Scheme[31].

There are also other methods which depend entirely on epidemiological and statistical approaches and are less relevant to this thesis; however, two are worthy of a brief mention for completeness. The first started in 1966 when the Kaiser-Permanente Department of Medical Methods Research in San Francisco began to develop a system for monitoring adverse drug reactions in ambulatory patients[32]. Outpatient prescriptions dispensed by pharmacists were recorded by label typewriters connected to

the central computer and untoward events developing in users and non-users of drugs were recorded by medical staff, data being computerised and compared for large numbers of patients. Examples of possible adverse drug reactions studied using this data include Candida vaginitis in oral contraceptive users, frusemide and gout and tolbutamide and congestive heart failure[32]. The second, known as the case-control approach, is not so much a method of monitoring as a means of demonstrating a relationship between drug and event for rare adverse reactions. The technique involves comparison of the frequency of exposure to a possible aetiological agent (e.g. a drug) in a group of newly diagnosed cases and a group of suitably selected control subjects[33]. This approach is retrospective but can give rapid results although it must be appreciated that it is subject to biases. Several associations have been defined in this way; for instance, lincomycin-induced pseudomembranous colitis[34], the link between maternal stilboestrol therapy and vaginal adenocarcinoma[35] and conjugated oestrogens increasing the risk of endometrial carcinoma[36]. The BCDSP, although primarily an intensive hospital monitoring scheme, has a large body of data which can be analysed in a case-control manner, as does the Kaiser-Permanente Scheme.

Voluntary reporting of adverse drug reactions in the U.K.

In 1964 as a result of the thalidomide tragedy and with the intention of preventing further disasters the Committee on Safety of Drugs (known as the Dunlop Committee) was established. The Committee initially lacked statutory powers but this in no way hampered its work[37]. Strong legal powers were given to the Committee by the Medicines Act (1968),

although this did not become operative until late 1971, when it was renamed the Committee on Safety of Medicines (CSM). The Committee formed three sub-committees, on toxicity, on clinical trials and on adverse reactions. The remit of the latter was to assemble and assess reports about adverse effects of drugs in use and prepare information thereon which could be brought to the notice of doctors and others concerned[37]. A distinctive form (yellow card) was sent to doctors who were invited to use it for reporting suspected adverse drug reactions. Part-time medical officers were also appointed throughout the country to assist with investigation of cases and for large scale epidemiological surveys. A detailed description of the adverse reactions sub-committee and its work[38], by the former Principal Medical Officer Dr. W. Inman, is to be found in "Monitoring for Drug Safety".

The yellow card system, as with other voluntary reporting schemes, offers population-wide monitoring of adverse drug reactions and theoretically involves all doctors. The scheme is also relatively inexpensive to operate and capable of detecting both common and rare reactions. Some new adverse drug reactions have been identified through the yellow card system by comparing the patterns of reactions reported with related drugs. For instance, the reports with ibufenac rapidly showed a predominance of liver disturbances compared with other anti-inflammatory analgesics[39]; these reports led to its voluntary withdrawal from the market. Using the same approach, it was shown that skin reactions made up a larger proportion of reported reactions to protriptyline compared with other tricyclic antidepressants; the majority of skin reactions were the result of photosensitivity[40], an effect very infrequently reported with the other tricyclics. Dr. Inman, who was

responsible for the yellow card system from 1964 to 1980, has recently claimed that "literally hundreds of signals have been considered by the CSM and many problems have been quietly and efficiently attended to"[41]. However, documented evidence of this is lacking.

The system has, however, proved inadequate in many respects; this was particularly demonstrated by its complete failure to recognise symptoms of the oculomucocutaneous syndrome caused by practolol[42]. Although four years elapsed from the marketing of practolol in the U.K. to the first warnings in the medical press (1974)[43,44] the CSM had received only one report of an eye complaint during that period[38]. However, once the association with practolol was publicised, nearly 200 reports of eye effects were notified to the CSM within a few weeks[38] and it is now known that several thousand patients probably suffered an adverse reaction due to practolol. Between 1976 and 1982 about 2,600 patients have claimed on the compensation scheme set up by ICI but the fight for compensation still goes on for a few[45]. Practolol thus illustrated the fundamental weakness of voluntary reporting systems: adverse events are never reported until doctors have a strong suspicion that they are caused by a drug.

The effectiveness of the yellow card system is dependent on what is reported and has thus been severely limited by the gross under-reporting of adverse reactions that persists. In 1968 it was found that only 8 out of 53 deaths (15%) due to thrombosis or embolism in women taking oral contraceptives were reported independently to the CSM[46]. The extent of under-reporting cannot be accurately known but it was estimated in 1972

that only between 1% and 10% of reactions were notified[40]. Other than indicating the extent of the problem, this estimate is fairly meaningless as the percentage of adverse reactions reported probably varies considerably depending on the drug and the severity of the reaction. The reasons for doctors not reporting reactions to the CSM are many and complex, some have been described by Inman[38] as the "seven deadly sins". The following is a list of possible reasons for consideration:

(a) Complacency - a mistaken belief that only safe drugs are allowed onto the market.

(b) Fear - that confidentiality may be breached, treatment may be criticised and of involvement in litigation.

(c) Guilt - because harm to patients has been caused by treatment prescribed.

(d) Ignorance - of how to report reactions and what should be reported.

(e) Lack of time - to obtain details and complete reports.

(f) Lack of achievement - a feeling that nothing is gained by reporting.

(g) Uncertainty - about the drug/reaction relationship.

(h) Diffidence - about reporting mere suspicions.

(i) Ambition - to collect and present or publish a personal series of cases which may delay the recognition of a hazard.

Apart from under-reporting, the yellow card system has other defects. The quality of reports is frequently poor and inadequate to make an assessment of the causal relationship between drug and reaction. The reasons for this are twofold; firstly, the details requested on a yellow card (see Appendix 1) are barely sufficient for the assessment of an adverse reaction and there is virtually no space for the doctor to provide additional data. Secondly, doctors are generally not very good at completing yellow cards and frequently omit vital facts, such as dates, doses, concurrent therapies, etc.

Another problem is communication between the CSM and practitioners. The small staff at the CSM is unable to deal with many enquiries from outside. Feedback in response to a report consists mainly of providing a current computer print-out for the drug from the Register of Adverse Reactions and even this is not now generally provided. There are also communications, such as Chairman's letters, "Current Problems" and the "Adverse Reactions" series - these are interesting but often late. First warnings of a new adverse reaction generally appear in the medical literature; the time between a reaction becoming well established in the literature and a warning from the CSM has been described as the "information lag" and varies between zero and eight years[47]. The CSM clearly has a problem regarding when to notify practitioners of a hazard, since unsubstantiated and premature warning could unjustly condemn a drug, whilst waiting for more evidence and final proof could be hazardous to patients. This dilemma has been demonstrated recently by the suspension of the product licence for Opren (benoxaprofen) on 3rd August 1982. On one hand, certain politicians criticised the CSM for

not acting earlier as more than 3,500 reports had been received, including 61 deaths, by the time of the suspension[48]. On the other hand, some rheumatologists felt that the suspension was a hasty decision and they had lost a potentially valuable drug[49]. Both are valid points but time will be needed before a more objective view can be taken of benoxaprofen and its withdrawal; however, it is bound to have a wider impact on adverse reaction monitoring.

There have been a number of suggestions as to how the yellow card system could be improved. Firstly, there is a case for some devolution of the reporting system as suggested by Rawlins[42] and echoed in a British Medical Journal leading article[50]. Being based solely in London, the reporting agency is remote, both physically and psychologically, from most doctors and is seen by many to represent an "arm" of government with little chance of any form of dialogue[42]. Rawlins suggests that the responsibility for the initial collection and collation of yellow cards should be devolved to the Regions with copies being forwarded to the CSM for national collation and review by the Adverse Drug Reaction Sub-committee[42]. This has been done in the West Midlands Region since 1973 with some measure of success, see Chapter 2. Secondly, reporting could be made easier by offering a telephone reporting system for doctors who had not a yellow card to hand or wanted to discuss the problem before making a report[42]. All information transmitted could be transferred to a yellow card and other pertinent questions could be asked. Thirdly, there is a clear need to provide regular and useful feedback to doctors to maintain their interest in reporting; Rawlins proposes that analyses of data collected, together with appropriate commentaries on significance,

should be circulated to doctors[42]. This has also been done in the West Midlands by distributing bulletins at six-monthly intervals since 1976, see Chapter 2.

Adverse drug reactions in the hospital setting

The incidence of adverse drug reactions as the reason for a patient's admission to hospital has been consistently reported as being around 3 to 5%. In the U.K., Hurwitz[51] found that 2.9% of 1,268 patients were admitted because of adverse reactions and 2.1% were admitted because of self-poisoning. More recently Hutcheon et al[52] reported that out of 2,580 consecutive admissions 3.3% were attributed to drugs taken in normal doses and 2.6% were attributed to drug overdoses. Rather more studies have been conducted in the U.S.A.; Seidl et al[53] at The John Hopkins Hospital, Baltimore, estimated that about 5% of all admissions were directly caused by drug reactions. Gardner and Watson[54] reported that 5.1% of 939 patients had adverse drug reactions on admission to hospital and Caranasos et al[55] recorded that drug-induced illness, excluding suicide attempts and drug abuse, accounted for 2.9% of 6,063 admissions over a three-year period. Miller[56] in a report from the BCDSP of a study involving 7,017 hospitalised medical patients in the U.S.A., Canada and Israel reported that 3.7% were admitted because of adverse drug reactions.

Other workers outside the U.K. and U.S.A. have also found a similar incidence. An early study in Canada[57] reported that 6.6% of 731 patients were admitted with an adverse effect from drug therapy and a recent Swedish study[58] noted adverse drug reactions in 5.6% of 285 patients on

admission to hospital. There is also some general agreement on the offending drugs from these studies, digoxin, aspirin, corticosteroids, warfarin and phenylbutazone being notable examples. Adverse reactions to drugs clearly make a significant contribution to hospital admissions but it should be noted that all of these studies were conducted mainly or exclusively on medical wards where the likelihood of such admissions is probably highest.

There is considerably less agreement about the incidence of patients experiencing an adverse drug reaction once they are in hospital. Many such studies have been conducted, and quoted incidences vary from 10.2%[59] to 36%[60]. Hurwitz and Wade[59] in Belfast found drug reactions in 10.2% of 1,160 inpatients who received drug therapy, the definition of an adverse drug reaction used being that proposed by Cluff et al[1]. Most of the recorded reactions were due to known pharmacological actions of the drugs, digitalis preparations, ampicillin and bronchodilators (theophylline and its derivatives and orciprenaline) having the highest reaction rates. Using the same definition, Seidl et al[53] recorded that 15% of all patients acquired an adverse drug reaction whilst hospitalised, the majority of reactions occurring within the first four days. Some Canadian workers[57], also using the same definition, reported an incidence of 18% in a study involving 731 patients; digitalis, antibacterial drugs, insulin and diuretics accounting for 60% of the reactions. Gardner and Watson[54], using a slight modification of the Cluff definition, showed that 10.5% of patients developed drug reactions whilst in hospital. More recently, Steel et al[60] found that 36% of 815 general medical patients experienced at least one iatrogenic illness during their hospital stay. This apparently

higher incidence probably results from their fairly broad definition of iatrogenic events, which included falls, decubitus ulcers and adverse events associated with diagnostic procedures. However, the authors suggest that the high incidence is due to the nature of the patients studied, i.e. seriously ill patients, and the high-risk procedures now used.

Apart from attempting to identify the frequency of adverse drug reactions in hospitalised patients, these studies have provided other valuable data. Firstly, all have shown that only a small proportion of adverse drug reactions are fatal or life-threatening. However, if these findings are extrapolated, this fact is not so comforting. For instance, considering the total number of acute general hospital admissions in the U.S.A., the number of fatal adverse drug reactions has been estimated to range from 60,000 to 140,000 per annum[61]. Secondly, they have shown that adverse reactions to drugs tend to occur soon after treatment has started and early during the patient's stay in hospital. Thirdly, some have shown that more elderly patients develop adverse drug reactions and women appear to be more susceptible[53,59], whereas others have related the increased frequency to severity of illness and complications, age being secondary[57,60]. Fourthly, there is a consensus about which drugs cause the most problems, digoxin and other digitalis preparations being the most notable, with antibiotics, anticoagulants, diuretics and quinidine also deserving mentions.

The Hospital Pharmacist's Contribution

The yellow card system, despite its shortcomings, still provides the most effective post-marketing surveillance now available, but it will fail unless

doctors play their part[62]. However, the CSM has in the past made it clear that only medical practitioners and dentists, not pharmacists, may report adverse reactions on the yellow cards, although pharmacists can report reactions in other countries, e.g. Australia (see Chapter 6) and Eire. The pharmacist's role in the U.K., therefore, appears to be restricted to encouraging reporting. However, this may be interpreted in various ways and does not preclude the pharmacist's involvement in adverse reaction monitoring.

The majority of the published work describing the pharmacist's contribution to drug monitoring has come from groups in the U.S.A., and some of this work was reviewed in 1973 by the Geigy Travelling Fellow from the U.K.[63]. As early as 1954 the American Society of Hospital Pharmacists participated in informal discussions with the Food & Drug Administration (FDA) concerning the establishment of an adverse drug reaction reporting system[64]. A pilot study was set up and the FDA recognised the need for a reporting programme but there was little progress over the next decade. At an FDA Adverse Reaction Reporting Seminar in 1966, Cleveland[64] stated that this delay was because the responsibility for data collection and drug surveillance was not assigned to an individual who would give it full-time attention and could supply continuity to the effort. Furthermore, to the physician, the act of reporting was secondary to the well-being of the patient and a system that relies entirely on him is not realistic. It was suggested at the Seminar that the hospital pharmacist could be responsible for administrative implementation of adverse drug reaction reporting programmes. An effective adverse drug reaction reporting programme was also seen as

only one phase of promoting rational drug therapy and better patient care. Feedback of information through drug communication centres was an equally important consideration[64].

In 1970 workers at Shands Teaching Hospital, University of Florida, described a pharmacist-based system which monitored drug discontinuation or dosage reduction as a means of discovering adverse drug reactions[54]. These were found to result in 7.3% of drug discontinuations or dosage reductions and in comparison with a physician-based system of daily monitoring the pharmacists detected more reactions and provided a more uniform method of study[54]. The same pharmacist-based method of surveillance was later used in the paediatric medicine service at Shands to determine the incidence, morbidity, mortality and predisposing factors of adverse drug reactions in children[65]. Following a change in drug therapy possible adverse reactions were identified by reviewing the patient's notes, charts, laboratory results, etc. Of 658 consecutive patients, 53 (8.1%) were admitted with an adverse drug reaction and a further 70 (10.6%) developed at least one reaction whilst in hospital[65]. Several other interesting points emerged from this study, e.g. children experiencing adverse reactions stayed in hospital twice as long as others, and as the numbers of drugs increased so did the incidence and severity of adverse reactions. Among reactions detected 63% were caused by exaggeration of expected pharmacological effects and allergic reactions accounted for most of the mild reactions. Clearly, the pharmacist-based monitoring system had proved successful in identifying and quantifying reactions.

In 1971, workers at Iowa described another pharmacist intensive monitoring scheme[66]. Patients were randomly assigned to two groups, one group was interviewed daily by a pharmacist who tabulated the symptoms of each patient, and the other was interviewed by a physician who then reported suspected adverse drug reactions to the pharmacist. Patients with a suspected adverse drug reaction were evaluated by a clinical pharmacologist and a reaction record was completed. The pharmacist was shown to be more effective at detecting reactions in comparison to the physician reporting them to him[66]. This is perhaps not surprising since it is unfair to compare a researcher taking an active interest in the subject with a busy physician. However, the study did show the pharmacist to be capable of detecting and evaluating adverse drug reactions.

Other workers, from the University of North Carolina[67], suggested that clinical pharmacists should establish a comprehensive adverse drug reaction programme for the detection, validation, reporting and prediction of reactions. This should run alongside programmes to encourage the proper utilisation of drugs and counselling of patients regarding their drug therapy. The authors detail the pharmacist's role in each area, some of which are relevant here;

Detection - the pharmacist should:

i) Monitor drug orders for discontinuation or reduction of drug dosage or drug orders for antidotes and other medications commonly used for treating adverse drug reactions.

ii) Participate in intensive surveillance of patients by daily questioning the medical team physicians and nurses concerning possible drug reactions noted during hospitalization and daily questioning patients concerning possible adverse drug reaction signs and symptoms.

iii) Concern himself with additional forms of adverse drug reactions including: drug interactions, lack of drug efficacy, teratogenicity, overdosage, superinfections, laboratory test-drug interference, drug dependence and long-term toxicity.

Validation - the pharmacist should:

i) Gather information concerning past adverse reactions caused by the drug in question.

ii) Gather all appropriate patient data including predisposing factors.

iii) Develop a chronological table of the dates the patient received his drugs in relation to development of possible adverse drug reactions.

iv) Review other possible causes of the adverse reaction including: drugs not initially considered, the combined action of several drugs, the disease being treated, the results of previous operations or diagnostic procedures, other methods of therapy used, a placebo reaction or a combination of factors.

v) Review the gathered data to determine the probability of an adverse drug reaction.

Reporting - the pharmacist should:

i) Report drug reactions noted in the hospital or in the literature through pharmacy bulletins, seminars and patients rounds.

ii) Report validated reactions to the FDA and to the pharmaceutical manufacturers involved.

iii) Publish significant findings in the medical and pharmaceutical literature.

iv) Place special emphasis on the feedback of useful information to the pharmacists and health care team who will be using the data.

Prediction and prevention - the pharmacist should:

i) Use developed information of incidence of adverse drug reactions due to specific drugs or patient predisposing factors to predict reactions.

ii) Determine the incidence of adverse reactions due to other drugs.

iii) Determine the clinical significance of possible additional patient predisposing factors.

iv) Undertake studies to determine which patient predisposing factors are more important in causing adverse drug reactions and determine possible inter-relationships of predisposing factors in causing adverse drug reactions.

v) Undertake studies and co-operate with other hospitals in collecting the incidence data for adverse drug reactions which are needed to develop newer prediction techniques based upon the parameters of patient predisposing factors and drugs.

Several descriptions of adverse reaction reporting schemes also appear in the literature. Methods of recording drug utilisation data and an adverse drug reaction reporting programme which involved physicians and pharmacists at Jefferson Medical Centre, Philadelphia, have been described[68,69]. In the programme hospital admissions directly caused by adverse drug reactions were reported to the FDA; also dosage reductions, drug discontinuations, prolongations of hospital stay and complications of diagnosis were monitored to see whether they were the result of adverse reactions and, if so, they were also reported[69]. The potential role of the pharmacist was outlined in the light of experience in the programme[69]. O'Brien and McManus[70] described a small hospital scheme where adverse drug reactions reported to the department of pharmacy were forwarded to the FDA and listed in a monthly pharmacy bulletin. In 1978, Farkas[71] described a scheme involving nine hospitals in Hamilton, Canada, where reports were requested only on a small selected list of drugs. A two phase approach was adopted; phase one requested the nurse or doctor to report on a form any unwanted drug effect and the second phase was an evaluation by a pharmacist which, if necessary, included further documentation.

Other references to the involvement of North American pharmacists in adverse drug reaction monitoring and reporting schemes include a study

where a pharmacist effectively co-ordinated a programme to detect and evaluate reactions occurring in paediatric patients in a haematology/oncology unit[72]. The detection and reporting of reactions was greatly improved and specific patient and drug factors which appeared to be related to the incidence of adverse drug reactions were identified. The training and specialised function of pharmacist monitors in the BCDSP (see earlier) has also been described[73]. More recently, descriptions of hospital pharmacy based programmes for monitoring and reporting adverse drug reactions continued to appear in the American Journal of Hospital Pharmacy[74,75].

Unfortunately, there are rather less schemes involving pharmacists in the U.K. (see Chapter 3) compared with both the U.S.A., as described above, and Australia, see Chapter 6. Even more apparent is the lack of publications describing adverse reaction work done by U.K. pharmacists, much of which is described herein. An exception to this is some of the work conducted as part of the Hereford Hospital Prescribing Study, the aim of which was to link information about drug usage to diagnostic data[76,77]. Using the Hereford data, pharmacists in collaboration with physicians have investigated methods of identifying adverse drug reactions. The discontinuation of drug therapy was shown to identify possible adverse drug reactions using indomethacin as a model, whereas referrals to other consultants failed to identify any reactions with the drug[78]. The co-prescription of other drugs that could possibly be used to treat adverse reactions due to indomethacin was also studied. Prescriptions for antacids were significantly greater in patients taking indomethacin in comparison with all patients[78]. This was presumably due

to the high incidence of dyspepsia associated with the drug. Another study using the Hereford data identified possible adverse reactions due to cimetidine and cases of upper gastro-intestinal cancer occurring in patients who had taken the drug[79].

There is one recent U.K. publication describing a monitoring scheme conducted over five weeks at Lincoln County Hospital[80]. Ward pharmacists reviewed prescriptions for drugs which might be used to treat possible adverse drug reactions and confirmed these suspicions by checking the patients' notes and in discussion with ward staff. An audit of anti-rheumatic drug use by a hospital pharmacist in which all adverse drug reactions were recorded for a number of such drugs has also recently been reported[81]. The pharmacist was effective in obtaining such data from notes and by interviewing patients and was able to collate adverse drug reaction profiles which were of value to the rheumatologists. All unusual adverse reactions detected were reported to the CSM and it was considered that this would not have occurred in the absence of the audit and the pharmacist's encouragement.

The pharmacist's role, therefore, appears to vary from an almost disinterested party to a central figure in adverse drug reaction monitoring and reporting. Pharmacists in some American hospitals have clearly taken the initiative often as part of a wider clinical pharmacy programme. The developments in the U.S.A. cannot be directly extrapolated to the U.K. because of different practices in medicine, hospital organisation and manpower, etc., etc. However, some of the American ideas are sound and could be adopted. This thesis is in part

devoted to the application of some of these ideas in the U.K. hospital environment. Evidence will be presented to demonstrate that there is a significant role for U.K. hospital pharmacists in the monitoring and reporting of adverse drug reactions.

Figure 1 : Number of patients required to be 95% certain of detecting one, two and three cases of an adverse reaction

Incidence of adverse reaction	No. of patients required No. of adverse reactions detected		
	One Case	Two Cases	Three Cases
1 in 100	300	480	650
1 in 200	600	960	1,300
1 in 1,000	3,000	4,800	6,500
1 in 2,000	6,000	9,600	13,000
1 in 10,000	30,000	48,000	65,000

Figure 2 : **Number of patients required to be 95% certain of detecting an additional incidence of an adverse drug reaction**

Known background incidence of adverse reaction	Additional incidence of adverse reaction on drug		
	1 in 100	1 in 1,000	1 in 10,000
1 in 10	10,000	980,000	98,000,000
1 in 100	1,600	110,000	11,000,000
1 in 1,000	500	16,000	1,100,000

CHAPTER 2

THE WEST MIDLANDS ADVERSE DRUG REACTION STUDY GROUP

History, objectives and function

The West Midlands Adverse Drug Reaction Study Group was formed in 1973 following discussions between the Professor of Therapeutics at the University of Birmingham and the then Regional Pharmacist. The aim was to improve the reporting of adverse drug reactions from hospitals in the Region by acting as an intermediary between the doctor reporting a reaction and the CSM. The Group naturally developed over the years and the description here is mainly of its activities in late 1980/early 1981. In 1982 the Group was renamed the West Midlands Centre for Adverse Drug Reaction Reporting and has been referred to as the West Midlands Regional Reporting Scheme in a recent article describing its activities[82].

The Group has about forty members with an interest in adverse reactions, the number being divided equally between the medical and pharmaceutical professions. In the early years of the Group the pharmacist members were mainly Area Pharmacists, who later became Area and District Pharmaceutical Officers, and the medical members were consultants in various specialities. However, this gradually changed over the years and now the pharmacists are mainly the drug information pharmacists in the Region and the medical members are from varied grades. The Group is co-ordinated by a Consultant Clinical Pharmacologist and a Staff Pharmacist at the Queen Elizabeth Hospital, both having commitments other than the adverse reaction work. However, a second Staff Pharmacist devoted full-time to the Group joined in early 1982.

With the agreement of the CSM, their yellow cards with an adhesive address label over the CSM address are distributed to the Group members who try to ensure they are available to any doctor wishing to report an adverse reaction. Completed reports are returned to the co-ordinators who assess each one within a few days of its arrival and, if necessary, obtain further information by referring back to the reporting doctor, either directly or through the local Group member. A letter is sent to each doctor reporting a reaction, thanking him for the report and supplying a further re-addressed yellow card. Details of similar reports, generally from the literature, are also sent, where appropriate, in an attempt to stimulate interest and encourage more reporting in the future. Each report is photocopied and all the original reports, together with any additional information obtained, are sent on to the CSM in batches. Details of reports are passed to a third party only with the permission of the reporting doctor and confidentiality of patients' names is always maintained and only passed on to the CSM.

Every six months a bulletin is produced which summarises the reports received in that period; the bulletin was modelled on those produced by the Dutch and Swedish drug monitoring centres (see also Chapter 4). Drugs are listed in the bulletin under body systems; each drug included is followed by a description of the reaction(s) reported, other drugs possibly responsible, any contributing factors and the source of the report - see sample page from Bulletin No. 14, January 1982 in Appendix 2. An assessment of the causality of each reaction is also included and this is explained further in Appendix 3 - Key to table of reported reactions. The bulletin also contains short editorial comments on adverse reactions of

current interest and may appeal for reports on particular drugs and reactions. The bulletin provides readers with a description and assessment of all reactions reported and this feedback hopefully stimulates further reporting; it would not be available if reports went directly to the CSM. The bulletin is distributed throughout the West Midlands, to some doctors and pharmacists in other Regions, to the CSM and a few overseas drug monitoring centres and to some pharmaceutical companies. When the first three bulletins were published there was evidence that reporting increased in the following two months[83] but more recently, although the number of reports has increased, they have shown less variation from month to month.

The Group also holds meetings three or four times a year at different Postgraduate Medical Centres in the Region. At these meetings adverse reaction topics are presented by researchers, or speakers present cases illustrating adverse reactions to a particular drug or group of drugs and these are discussed, together with similar reactions reported to the Group. The meetings are open and it is hoped thereby to interest more doctors and pharmacists in adverse reaction reporting.

The Group co-ordinators are frequently consulted about adverse drug reactions and provide a service from the wealth of information sources and reports available to them. The supply of information frequently leads to the reporting of a suspected reaction and it is a key function of the Group.

The co-ordinators have also acted as a link between doctors reporting certain reactions and centres conducting research on those reactions. Group members are kept informed of these projects and asked to help by making a particular effort to report or encourage the reporting of such reactions. There are several examples where the Group has been of value to others in this way, two of which will be briefly described. Firstly, Dr. April Kay of the Arthritis and Rheumatism Council as part of a research project on adverse reactions to antirheumatic drugs was compiling a register of reactions. Her work was outlined in bulletin No. 7 (July 1978) and subsequently copies of all reports of reactions to antirheumatic compounds, with the patient's name removed, were forwarded to her. Secondly, Dr. Rashmi Shah of St. Mary's Hospital Medical School wished to investigate the oxidative phenotype of patients who had experienced adverse reactions to certain drugs; a list of the reactions and drugs he was interested in appears in Figure 3. To determine the oxidative phenotype of a patient is a simple procedure which involves giving a single dose of debrisoquine and measuring the amounts of 4-hydroxydebrisoquine and unchanged drug appearing in the urine[84]. Dr. Shah's problem was locating patients who had experienced one of the adverse reactions which was thought might result from impaired oxidative metabolism. Whenever such a reaction was reported to the Group, the co-ordinators acted as a link between Dr. Shah and the reporter in an attempt to facilitate the oxidative phenotyping of the patient. Part of Dr. Shah's work subsequently showed that patients who developed neuropathy with perhexiline frequently had an impaired ability to effect metabolic drug oxidation[85].

Evaluation of West Midlands Group

The source of reports received by the West Midlands Group, and hence passed on to the CSM, from 1976 to 1981 inclusive is shown in Figure 4. A fair proportion of the reports (63% in 1976 declining to 21% in 1981, mean 41%) have come from only three Birmingham hospitals - Good Hope Hospital, Selly Oak Hospital and the Queen Elizabeth Hospital. All other hospitals in Birmingham AHA(T) have contributed a fairly consistent but much smaller proportion of reports, 16% (range 12 - 23%). The proportion of reports from the remainder of hospitals in the Region, i.e. those not in Birmingham AHA(T), has been steadily increasing from 18% in 1976 to 42% in 1980, although this fell to 28% in 1981. This increase reflects a greater effort in recent years to spread the Group's activities beyond Birmingham. Prior to 1980 the proportion of reports from general practitioners was small (mean 6%, range 5 - 9% for 1976 to 1979 inclusive), despite the fact that about 60% of reports received by the CSM are from general practice. This emphasises the hospital-based nature of the Group in the past. However, as efforts to interest general practitioners have intensified, the proportion rose to 17% of reports in 1980, 27% in 1981 and a provisional analysis of figures for 1982 showed that there has been a considerable further increase with over 200 reports (around 46% of the total number received) coming from general practice. Unfortunately, it was not possible to calculate accurately the figures for the source of reports for 1974 and 1975 but at that time the majority came from hospitals in Birmingham as in 1976, see Figure 4.

A more thorough analysis of reports received between January 1978 and January 1979 has been undertaken[86]. Two hundred and thirty seven

reports were received in this period, 94 (40%) came from the three Birmingham hospitals previously mentioned: Good Hope, Selly Oak and the Queen Elizabeth. These are compared with the small numbers of reports received from comparable size hospitals A, B and C (two in Birmingham and one outside Birmingham) over the same period, see Figure 5. The higher number of reports from the three hospitals can be attributed to the efforts of the drug information pharmacists at Good Hope and Selly Oak Hospitals and the Group co-ordinators being based at the Queen Elizabeth Hospital. These two drug information pharmacists and the Group co-ordinators were particularly active in encouraging doctors in their respective hospitals to complete yellow cards, see below. At hospitals A, B and C there was only very limited involvement of pharmacists in adverse reaction reporting.

A sample of 120 reports from Good Hope, Selly Oak and the Queen Elizabeth Hospitals was also examined[86]. The pharmacists' contribution to each report was assessed at the first two hospitals by interviewing the drug information pharmacist and reviewing their records. The author made his own assessment of reports received from the third hospital. The assessment covered the previous 18 months at Good Hope and Selly Oak Hospitals and the previous 12 months at the Queen Elizabeth, see Figure 6. Twenty-nine of the 120 yellow cards (24%) were completed by a pharmacist and then signed by the doctor, 40 (33%) followed requests for information and a further 27 (23%) came after a pharmacist had recommended that a report should be sent, see also Figure 6. A pharmacist was thus involved in 80% of the reports coming to the Group from the three hospitals; in many cases these reactions would not

otherwise have been reported to the CSM. For only 24 reports (20%) was a pharmacist not actively involved, but the two drug information pharmacists were also aware of most of these cases. This level of reporting where the pharmacist was not actively involved was similar to the level from hospitals A, B and C, where pharmacists made only a very limited contribution.

It thus appeared that pharmacists in three Birmingham Hospitals were having a significant effect on the number of yellow cards completed. However, because the number of reports going directly to the CSM from the West Midlands was unknown, it has not previously been possible to confirm that the Group had improved reporting of reactions and that there really were more reports coming from Good Hope, Selly Oak and the Queen Elizabeth Hospitals. Dr. R. G. Penn, Principal Medical Officer at the Medicines Division, has kindly provided some figures up to mid 1980 which have enabled clarification of this. However, requests for further data could not be met.

Figure 7 shows the total number of reports from hospitals sent to the CSM from Birmingham AHA(T), thus combining the reports that went via the West Midlands Group with those that had gone direct. Unfortunately, there was a misunderstanding at the CSM about coding the source of reports when the Group began using re-addressed yellow cards in 1978; prior to which special yellow forms were used. Thus, the figures for reports going direct to the CSM for 1978 and 1979 are estimates; the 1980 figure has also been estimated from the numbers half-way through that year. Over the five years examined a mean of 72% of hospital reports

from Birmingham AHA(T) had come via the West Midlands Group (range 66% in 1977 to 76% in 1979). The 24-34% of reports going directly to the CSM could have come from any Birmingham hospital, including Good Hope, Selly Oak and the Queen Elizabeth. These three hospitals accounted for a high proportion of reports coming from all Birmingham hospitals, the mean figure being at least 53% (range at least 43% in 1980 to at least 62% in 1976).

The reporting of adverse reactions to the CSM thus appears to be improved in three Birmingham hospitals but has the West Midlands Group really improved the level of reporting from the Region? An improvement could be measured by comparing reporting from the West Midlands with another Region. The Trent Region has been selected for comparison because it is adjacent to the West Midlands Region, the populations of the two Regions have very similar age and sex distributions and the mortality rates for most diseases are also comparable[87]. Figure 8 shows the number of hospital reports received by the CSM as a proportion of the total U.K. reports for 1973 to 1979 inclusive. The proportion of hospital reports for the Trent Region over this seven year period was 32.4% which is very similar to the national figure (31.5%) whereas the proportion from the West Midlands was higher at 36.9%. Figure 9 shows the numbers of reports received by the CSM from hospitals in the two Regions. The numbers have to be corrected for the difference in populations, as the West Midlands has a larger population than Trent: 5.1511 million compared with 4.515 million (1979 figures)[88]. The reports in Figure 9 are thus presented as number per 1,000 occupied hospital beds for the two Regions, as indicated in the 1978 Hospitals and Health Services Year

Book[89]. The two Regions had virtually the same number of reports coming from hospitals in 1973, the year in which the West Midlands Group was formed, but in each subsequent year the numbers from the West Midlands were greater than from Trent; this difference is significant ($P < 0.01$). Figure 10 shows the number of reports from general practitioners in the same two Regions; the numbers are expressed as reports per million population to allow for the difference between the Regions. Although reporting from general practitioners in the West Midlands was slightly better than from Trent in 1973, there is no statistically significant difference between the two Regions in the level of reporting from general practitioners over the eight years studied.

The level of adverse reaction reporting from hospitals in the West Midlands was, therefore, higher when compared with Trent Region, whereas there was no difference in the level of reporting from general practitioners. This could be accounted for in a number of ways. First, more patients experience adverse drug reactions in West Midlands hospitals than those in Trent; this is unlikely but very difficult to disprove. Second, reporting from hospitals in the Trent Region has been inhibited, but Figure 8 shows that the mean proportion of hospital reports from Trent is almost identical to the national average. Third, reporting from hospitals in the West Midlands Region has been stimulated; this final option is naturally the most attractive to the author.

In a further attempt to establish whether the West Midlands Group has increased reporting, the number of reports from hospitals in Stoke- on-Trent has been investigated. Stoke-on-Trent was chosen because no

specific attempt was made by the West Midlands Group to stimulate reporting until August 1978; data is thus available both before and after this time. In August 1978 the Pharmaceutical Officers and drug information pharmacist at Stoke were approached by the author regarding the apparently poor level of adverse reaction reporting from hospitals in the City. Re-addressed yellow cards and West Midlands Group bulletins were subsequently distributed and a seminar on reporting was held for the hospital pharmacists. In 1979, a consultant clinical pharmacologist was appointed at the City General Hospital, Stoke-on-Trent; he expressed interest in the West Midlands Group and joined forces with the pharmacists involved. Figure 11 shows how the number of reports that were sent to the West Midlands Group increased from zero in 1973 to 1976, to a significant number by 1979. Although some reports were already going directly to the CSM, the numbers were small, only between 4 and 14 a year. The influence of the West Midlands Group was not simply a re-routing of reports through the Group but an increase in the overall numbers to 31 in 1980. Unfortunately, figures for the total number of reports received by the CSM from Stoke-on-Trent for 1981 and 1982 are not available, but there does appear to have been an increase in reporting of adverse reactions from Stoke hospitals.

However, the number of reports going to the CSM is not the only factor that should be considered. The type of reactions reported and the drugs concerned should also be examined. On the yellow card practitioners are asked to report "all reactions to recently introduced drugs and serious or unusual reactions to other drugs". To determine what type of reactions were reported and to which drugs, 812 reports received by the West

Midlands Group over a three-and-a-half year period (July 1978 to December 1981) were reviewed. 249 reports (31%) concerned recently marketed drugs, i.e. those marked by the black triangle symbol (▼), see page 101. 287 (35%) concerned serious reactions, see also later, or adverse events that were not well established or documented with older drugs, see Figure 12. These 812 reports are further broken down by drug groups (Figure 13) and types of reactions reported (Figure 14). The groups of drugs to which adverse reactions were most frequently reported were anti-rheumatic and anti-inflammatory agents and central nervous system drugs, these two groups accounting for nearly half of the reports received. Under-reporting was clearly evident with cytotoxic drugs, vaccines and anaesthetic agents, all of which are associated with a high incidence of reactions but of which only a few reports were received, see Figure 13. The most common type of reactions reported were cutaneous which accounted for nearly a quarter of all reports. Other commonly reported reactions included CNS effects, gastrointestinal bleeds, hepatitis/jaundice, allergic reactions and blood dyscrasias; the remainder were a wide range of different events, see Figure 14. Drug interactions accounted for only 2% of adverse reactions reported. Unfortunately, it was not possible to undertake a comparative review of reports from another Region.

The quality of reports is also an important consideration but, again, it was not possible to compare the quality of reports in the West Midlands with those from another Region as the latter were not available for study. However, a system in which Group members who know what information is required and who can assist in completing the report and with any follow-up must be of value in this respect.

The group has also attempted to increase awareness of certain adverse drug reactions; for instance by the publication of letters or reports on current problems. Examples of this include the publication of a letter in The Lancet, briefly describing four patients who experienced an exacerbation of their angina when starting on nifedipine[90] and a similar letter reviewing six cases of jaundice reported with Fucidin[91]. Brief details of some reactions reported to the Group have also been included in recent annuals of Meylers Side Effects of Drugs, see below, e.g. obstructive jaundice and melaena and duodenal ulcer with feprazone and a case of neurological disturbance, abnormal liver function tests and diffuse pulmonary infiltration with perhexiline[92].

Although the West Midlands Group has been successful in some respects, as described, its overall contribution to monitoring adverse drug reactions has been limited in the past, notably by lack of resources. A further limitation is the isolation of its role, as until recently it was the only group through which reports to the CSM were channelled. Two other centres are now established, one in Leicester based on the local Drug Information Centre and the other in the Northern RHA based on the Wolfson Unit of Clinical Pharmacology, Newcastle-upon-Tyne; these are described in Appendices 4 and 5 respectively. A third scheme was also established on 1st March 1983 to encourage the reporting of adverse drug reactions within Wales[93]. A joint approach was planned between the Welsh drug information centre and the department of pharmacology and therapeutics along similar lines to the West Midlands Group.

Figure 3 : Adverse drug reactions with metabolic basis and probably related to oxidative phenotype

Adverse Reaction	Drugs concerned
Lactic acidosis	Phenformin Metformin
Agranulocytosis	Carbimazole Phenylbutazone Chlorpromazine Nortriptyline Imipramine Thioridazine Captopril
Neuropathy and sensory disturbances	Perhexiline Phenytoin
Hepatic adenomas	Oral contra-ceptives
Cerebellar signs	Perhexiline Phenytoin
Cirrhosis	Perhexiline
Vitamin D deficiency-like state	Phenytoin Phenobarbitone
Folate deficiency-like state	Phenytoin Phenobarbitone
Syncope	Prazosin
Malignant ventricular arrhythmias	Mexiletine Disopyramide Prenylamine Perhexiline

Figure 4 : Source of reports received by the West Midlands Group

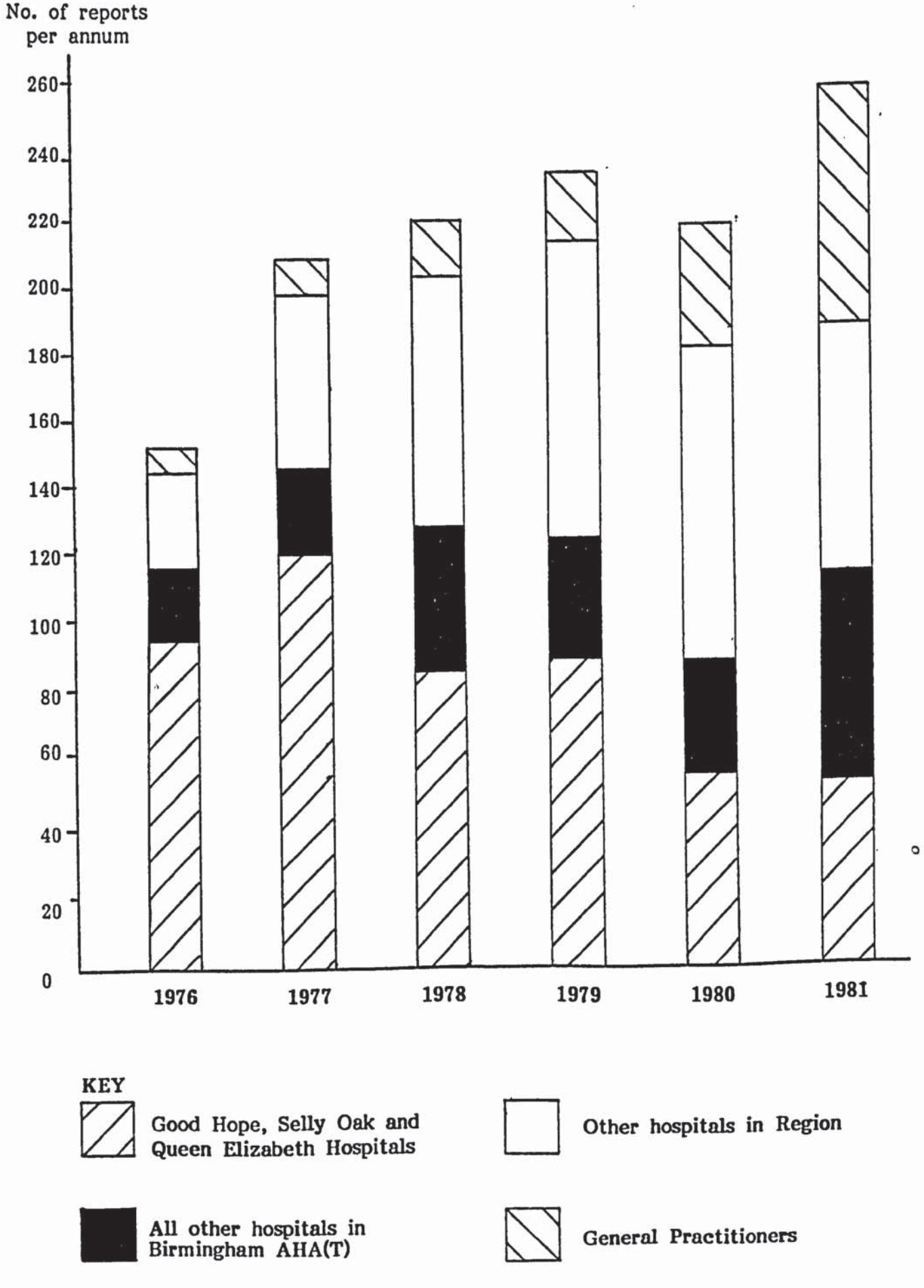


Figure 5 : Source of adverse reaction reports received by West Midlands Group: January 1978 - January 1979

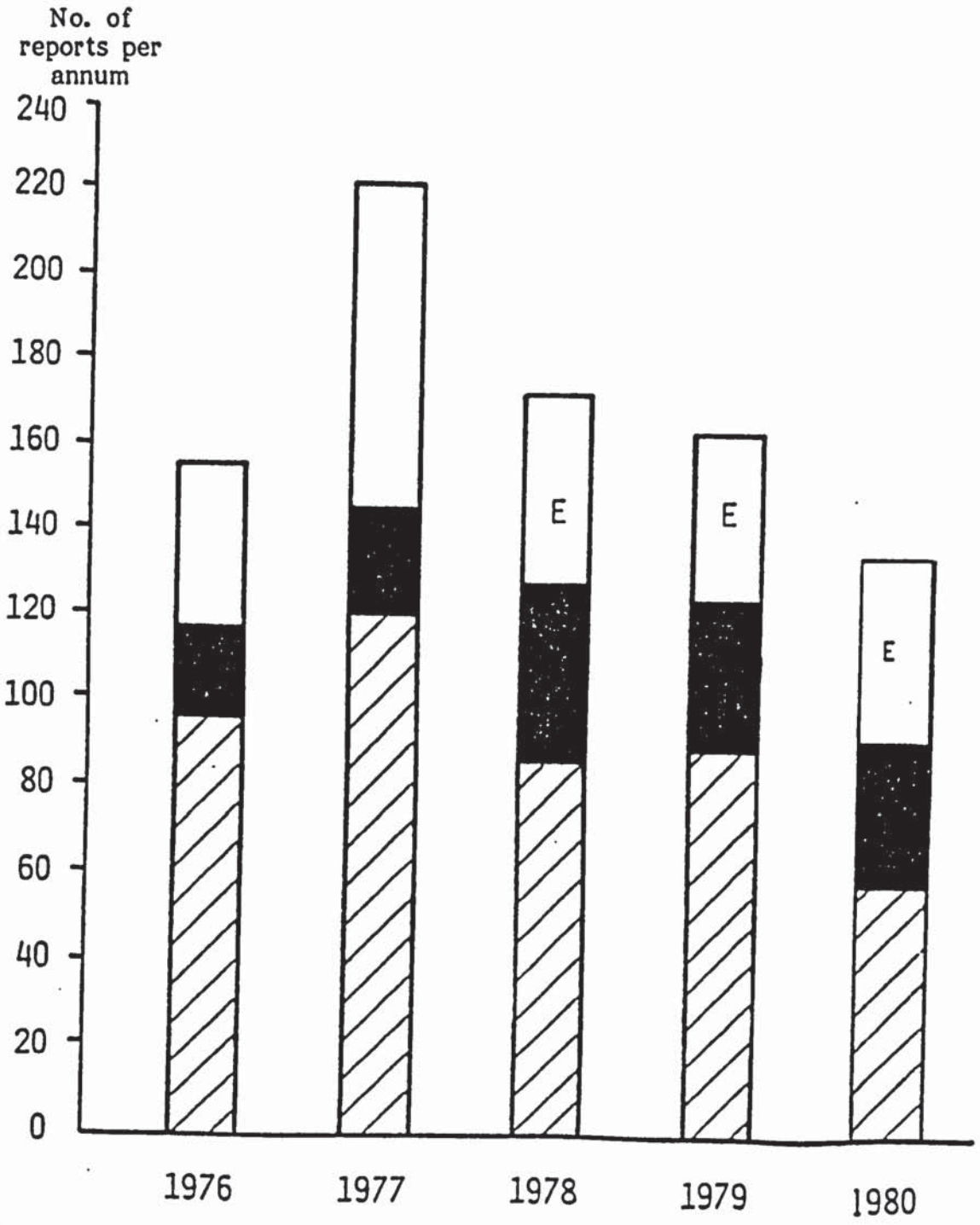
Hospital	No. of reports		% of total	
Queen Elizabeth Medical Centre	30)		13%)	
Selly Oak Hospital	23)	94	10%)	40%
Good Hope General Hospital	41)		17%)	
Hospital A (Birmingham)	11)		5%)	
Hospital B (Birmingham)	5)	19	2%)	8%
Hospital C (outside Birmingham)	3)		1%)	
All other sources (34 hospitals and general practitioners)	124		52%	
Total number of reports	237		100%	

Figure 6: Pharmacists' involvement in adverse reaction reporting:

Queen Elizabeth Medical Centre July 1978 to July 1979
Selly Oak Hospital January 1978 to July 1979
Good Hope General Hospital January 1978 to July 1979

Pharmacist's involvement	Queen Elizabeth	Selly Oak	Good Hope	Totals
Pharmacist completed yellow card, then signed by doctor	8	14	7	29 (24%)
Pharmacist provided information, recommended report should be sent	10	4	26	40 (33%)
Pharmacist recommended a report should be sent	3	12	12	27 (23%)
Pharmacist not actively involved in reporting process	10	6	8	24 (20%)
Total	31	36	53	120 (100%)

Figure 7 : Number of reports received by the CSM from Birmingham AHA(T)



Reports sent direct to the C.S.M. from all hospitals in Birmingham AHA(T)

Reports sent via the West Midlands Group from other hospitals in Birmingham AHA(T)

Reports sent via the West Midlands Group from Good Hope, Selly Oak and Queen Elizabeth Hospitals

E Estimate

Figure 8 : Total numbers of reports and numbers of hospital reports received by the CSM from the West Midlands and Trent Regions plus U.K. totals (complete years 1973-1979 inclusive)

	West Midlands			Trent			U.K. Totals		
Year	Total No. Reports*	Hospital Reports		Total No. Reports*	Hospital Reports		Total No. Reports*	Hospital Reports	
		No.	% of total		No.	% of total		No.	% of total
1973	338	105	(31.1%)	239	88	(36.8%)	3525	1478	(41.9%)
1974	511	252	(49.3%)	318	153	(48.1%)	4738	2219	(46.8%)
1975	450	203	(45.1%)	309	122	(39.5%)	4748	1931	(40.7%)
1976	648	245	(37.8%)	408	149	(36.5%)	6346	2048	(32.3%)
1977	1023	365	(35.7%)	827	214	(25.9%)	11213	3078	(27.5%)
1978	1097	375	(34.2%)	831	211	(25.4%)	11628	3164	(27.2%)
1979	1014	331	(32.6%)	783	265	(33.8%)	10534	2699	(25.6%)
Totals	5081	1876	(36.9%)	3715	1202	(32.4%)	52732	16617	(31.5%)

*Note:

Includes reports from general practitioners, hospitals, medical officers of health, FPA clinics, dentists, coroners, blood transfusion centres and epidemiological research

Figure 9 : Number of reports received by the CSM from hospitals in the West Midlands and Trent Regions

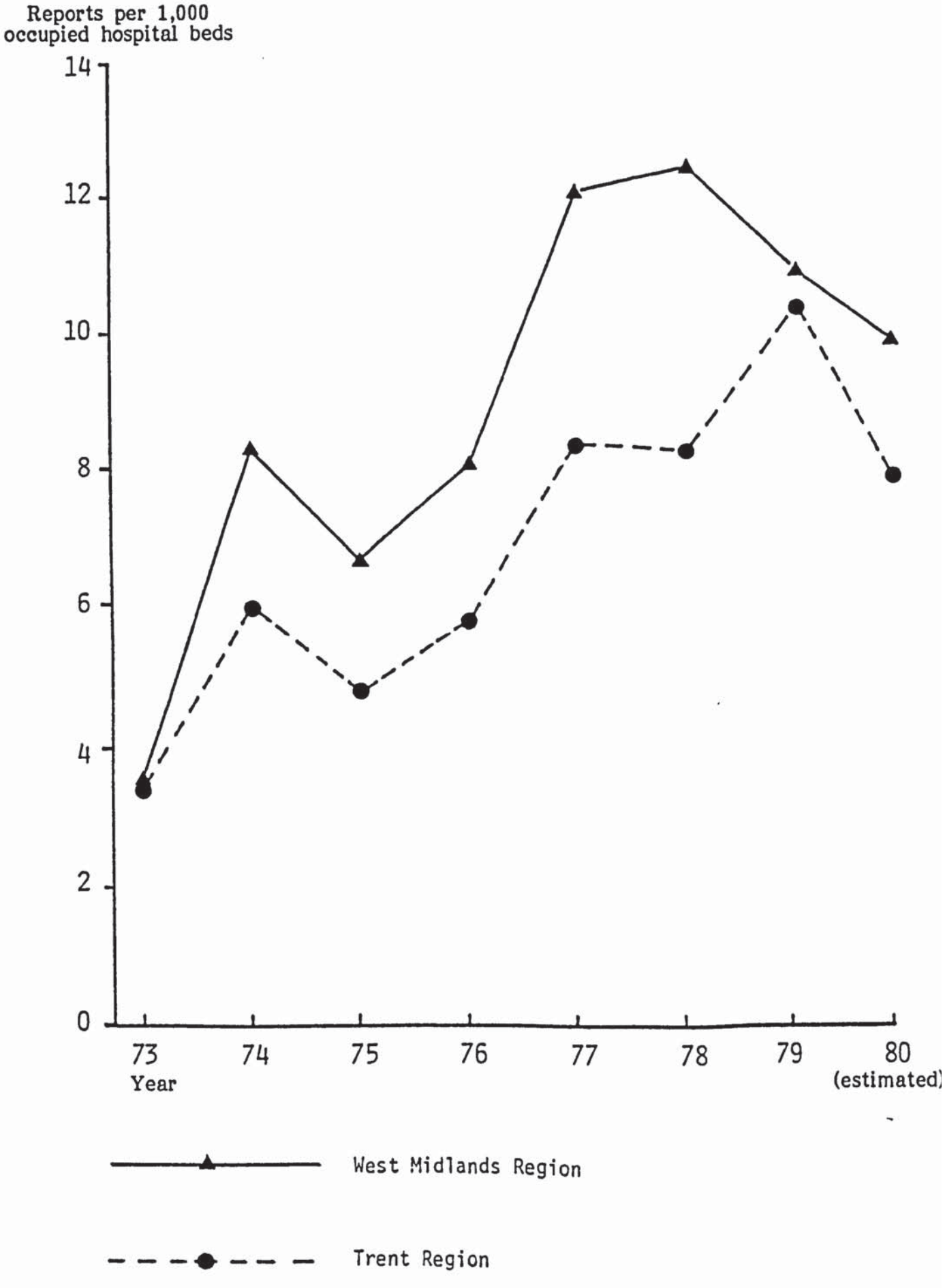


Figure 9 : Number of reports received by the CSM from hospitals in the West Midlands and Trent Regions

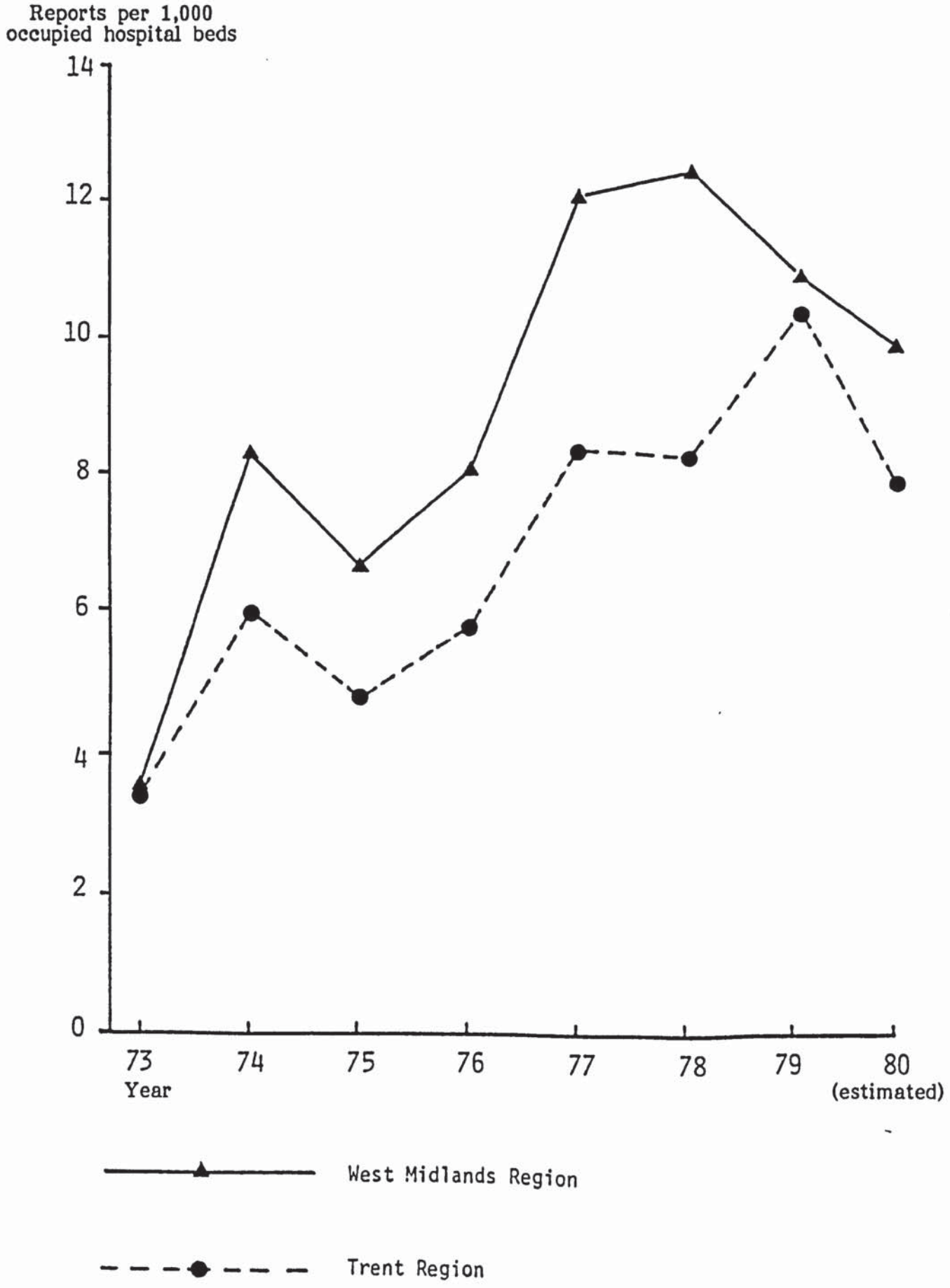


Figure 10 : Number of reports received by the CSM from G.P.s in the West Midlands and Trent Regions

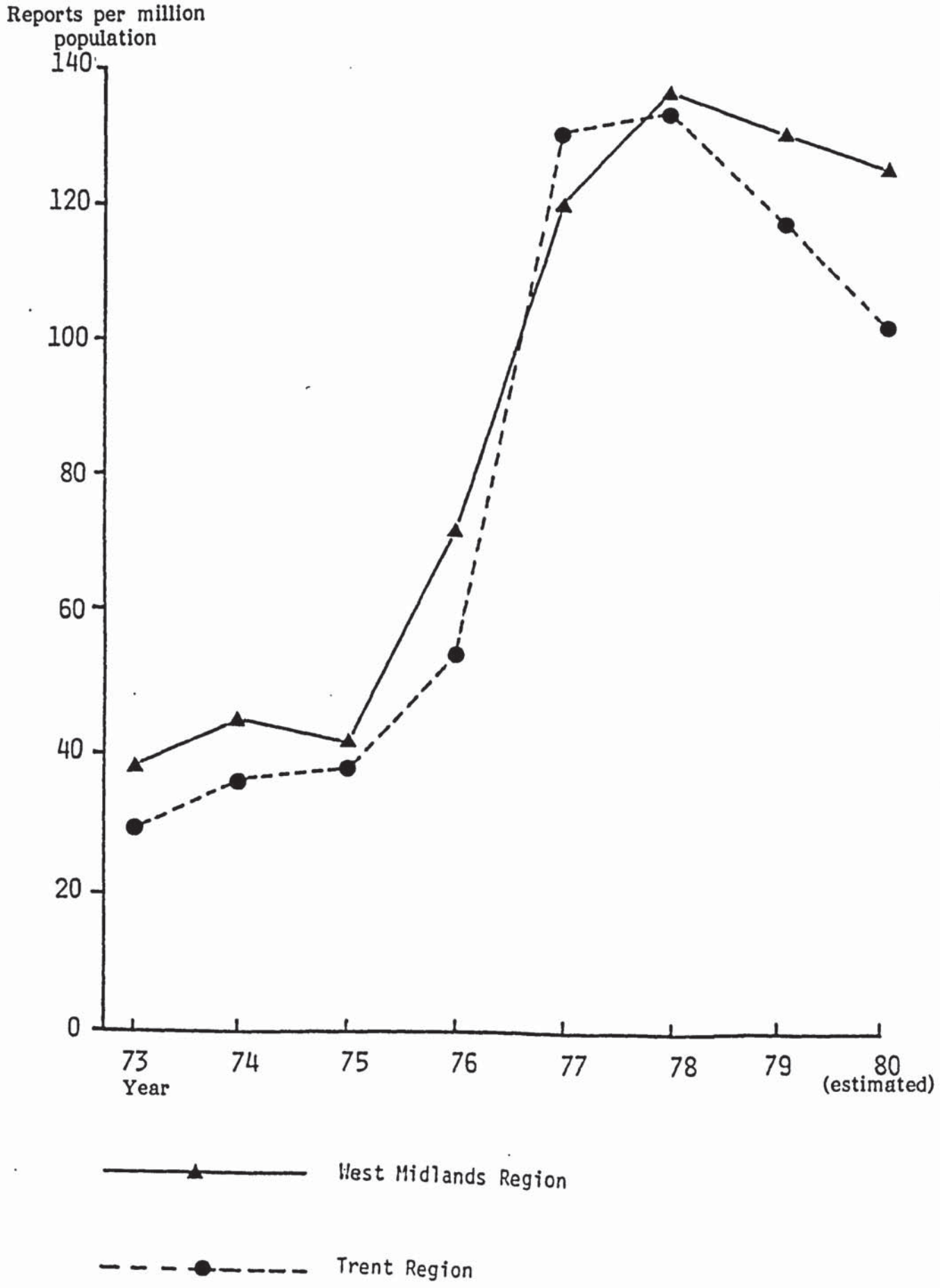


Figure 11 : Reporting from Stoke-on-Trent

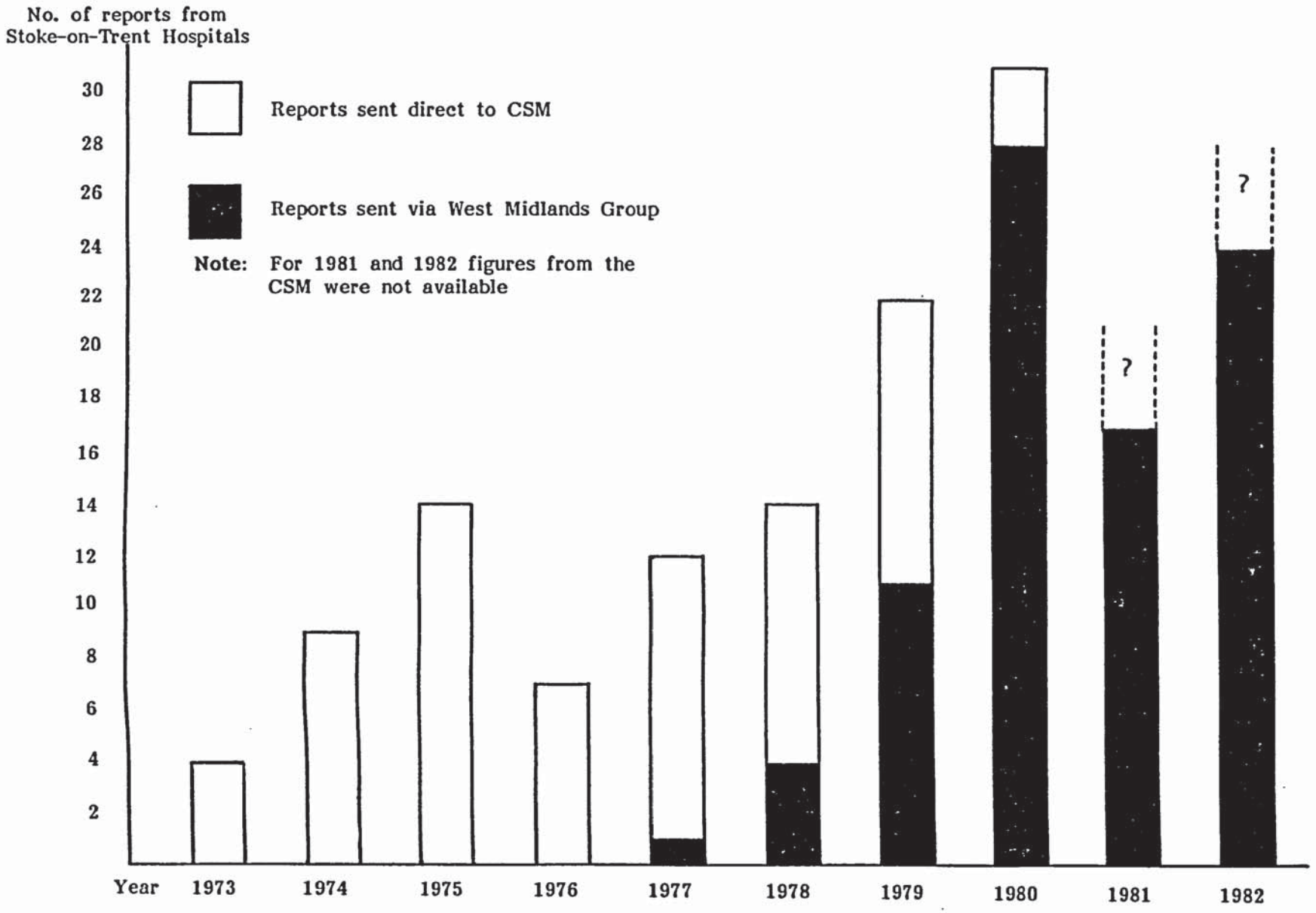


Figure 12 : Classification of Adverse Reactions reported to The West Midlands Group July 1978 to December 1981 (Bulletins 8 - 14 inclusive)

Classification of reports	Number of reports	%
New drug*	249	31%
Unusual or serious reaction with established drug	287	35%
Not as either above	276	34%
Total	812	100%

*New drug means one marked by the black triangle symbol or a drug not yet on the market, e.g. clinical trial drugs, levamisole, etc.

Figure 13 : Groups of drugs associated with Adverse Reaction Reports to the West Midlands Group July 1978 to December 1981 (Bulletins 8 - 14 inclusive)

Drug Group	No. of Reports	%
Anti-rheumatic and anti-inflammatory drugs	191	24%
Central nervous system drugs	189	23%
Cardiovascular drugs	128	16%
Antibacterials	75	9%
Endocrine and metabolism drugs	62	8%
Alimentary tract drugs	48	6%
X-ray contrast media	22	3%
Cytotoxic agents	18	2%
Vaccines	16	2%
Anaesthetic agents	10	1%
Topical preparations	7	1%
Others*	46	6%
Total	812	(100%)

*Others includes antihistamines, intravenous fluids, IUCDs, iron preparations, etc.

Figure 14 : Types of adverse reactions reported to the West Midlands Group July 1978 to December 1981 (Bulletins 8-14 inclusive)

Type of Reaction Reported	No. of Reports	%
Skin reactions	193	23%
CNS (including psychiatric)	89	11%
GI haemorrhage/ulceration	57	7%
Blood dyscrasias/anaemias	56	7%
Anaphylactoid/other allergic	55	7%
Hepatitis/jaundice	49	6%
Cardiovascular (arrhythmias, cardiac arrest, blood pressure)	38	5%
Ophthalmic	23	3%
Convulsions	16	2%
Diarrhoea/pseudomembranous colitis	17	2%
Renal/urinary	17	2%
Congenital malformations	16	2%
Drug interactions	18	2%
Others*	178	22%
Total	822	(100%)

*includes : alopecia, apthous ulcers, arthropathy, cramps, galactorrhoea, deafness, impotence, lactic acidosis, localised injection reactions, myopathy, neuropathy, pregnancy with IUCDs and oral contraceptives, Raynauds, thromboembolism, etc.

Note:

The number of reactions (822) is greater than the number of reports (812) as in ten cases there were major events affecting more than one classification group.

CHAPTER 3

NATIONAL SURVEY OF HOSPITAL PHARMACISTS' INVOLVEMENT IN ADVERSE DRUG REACTION REPORTING AND MONITORING

Introduction and Methods

Although a subjective assessment could be made, there was no hard data available which identified the extent and limitation of the hospital pharmacist's involvement with adverse drug reactions in the U.K. It was thus decided to undertake a nationwide survey to determine the hospital pharmacist's role. The aim of the survey was to establish the current level of involvement and interest in adverse drug reaction reporting and monitoring amongst hospital pharmacists. The simplest and most effective way to determine this was considered to be through the managers of the hospital pharmaceutical service, namely the Area Pharmaceutical Officers (England and Wales) and the Chief Administrative Pharmaceutical Officers (Scotland).

A questionnaire (see Appendix 6) was sent with a covering letter to the 82 Area Pharmaceutical Officers and the 12 Chief Administrative Pharmaceutical Officers on the 3rd September 1979. The questionnaire was devised to answer the following:

i) To what extent are hospital pharmacists involved in adverse reaction reporting to the CSM?

ii) Are hospital pharmacists involved in adverse reaction monitoring schemes?

iii) What developments in these fields are plannned?

iv) Who are the pharmacists that are active or interested?

v) How well-known is the West Midlands Adverse Drug Reaction Study Group?

Results and Discussion

Seven weeks after sending the questionnaire 61 of the 94 officers (65%) had responded with 82 replies. The number of replies was larger because several officers had passed copies of the questionnaire to the Districts or large hospitals in their Area. A further letter was sent to the 33 officers who had not replied by that time, asking them to complete the questionnaire as soon as possible. Twelve weeks after first sending the questionnaire a further 23 officers had responded, 37 more replies being received. The total number of replies was, hence, 119 and these came from 84 of the 94 originally circulated; the response was, therefore, 89%. Each Pharmaceutical Officer who had replied was written to during December and thanked for their co-operation.

Each returned questionnaire was allocated a form number; a code to indicate Area, District, hospital or Health Board (Scotland) and a further code to identify which Region it came from. The data from each reply was punched on to a computer card and transferred in a batch operation to magnetic tape. The whole data was then analysed using SPSS (Statistical Package for the Social Sciences), a program designed to handle questionnaires. A further four replies were received after the data

analysis had been completed but unfortunately it was not practical for these to be included.

The source of the 119 replies is shown in Figure 15, 76 returned questionnaires (64%) representing an Area (England and Wales) or a Health Board (Scotland) and 43 (36%) coming from a District or individual hospital. The raw data from returned questionnaires is included in Appendix 7 but replies from all the sources are presented together for simplicity in histograms (see Figures 16, 17, 19, 20 and 21), any significant differences between Areas/Health Boards and Districts/hospitals being noted. Generally, the replies from Areas/Health Boards were more encouraging, presumably because, if pharmacists in any one hospital in the Area were actively involved, the reply would be positive, whereas the reply from a single hospital was often negative. Where a question was not answered, the reply was assumed to be "no" or "none". This was infrequently the case, usually only one or two per question, except with the questions relating to the West Midlands Group where "no answer" is also included, see Figure 21 and Table 5, Appendix 7.

One possible reason for not reporting an adverse drug reaction to the CSM is that the doctor does not have a yellow card to hand. Figure 16 and Table 1, Appendix 7, show that most Pharmacy Departments kept a supply of yellow cards but only some distribute them to the hospital wards. Only a small proportion of ward pharmacists actually carried yellow cards and would, therefore, have one immediately available when they learned of an adverse drug reaction on their wards. The practice of ward pharmacists carrying yellow cards is commendable, as there is sometimes no substitute

for capitalising on the doctor's initial enthusiasm when he first asks the pharmacist whether an event could be drug-induced. One Area Pharmaceutical Officer, after answering that his ward pharmacists did not carry a small supply of yellow cards, noted "they will now!". Only two replies indicated that they did not provide a ward pharmacy service.

Pharmacists have recommended that adverse drug reactions should be reported to the CSM according to 104 replies (88%), see Figure 17 and Table 2, Appendix 7; however, this was a frequent practice in only 21 (18%) respondents. Pharmacists were told about reports already sent by their medical colleagues according to 81 replies (68%) but again this was a frequent practice in only 12 (10%). However, few pharmacists took the initiative by completing a yellow card themselves and then obtaining the doctor's approval and signature as in some Birmingham hospitals[86] (see Chapter 2). Possible explanations for the low frequency of this practice are that pharmacists were unaware of the approach or lacked the confidence,experience or skill to carry it through.

Forty-two replies (35%) indicated that attempts were made to channel reports to the CSM via a Pharmacy Department or Drug Information Centre in a manner similar to the West Midlands Group. However, of these 42 only a few had been successful, see Figure 18. In 12 cases the estimated number of reports per month was either zero or left blank and in a further 14 another answer indicating the lack of success was given; for instance "less than one", "practically none", "none so far", "4 a year" and "occasionally". It was apparent that only a small number of Pharmacy Departments or Drug Information Centres had made any real contribution to adverse reaction reporting in this way.

If hospital pharmacists were involved in any adverse drug reaction schemes, it was most likely to be in encouraging the reporting of reactions to the CSM; this was indicated in 36 replies (30%), see Figure 19 and Table 3, Appendix 7. Nearly half of these commented that this was an integral part of ward or clinical pharmacy and four considered that Drug Information Centres played an important role. Twenty respondents (17%) stated that pharmacists monitor patients on a particular drug or drugs; examples cited included aminoglycoside antibiotics, digoxin and anticoagulants and also total parenteral nutrition. This was not so much monitoring for adverse reactions but rather monitoring to prevent reactions and this is discussed further in Chapter 5. A scheme was also described in which prescriptions for drugs requiring special monitoring (e.g. new drugs) were flagged with a red triangle to alert medical and nursing staff. Another reply stated that a study of pentazocine side effects had been conducted and a record of out-patient prescriptions for atenolol and cimetidine was kept. Eight replies (7%) indicated other monitoring schemes but details were not given in every case. This group included the Hereford Hospital Prescribing Study which is described elsewhere[76,77] (see also Chapter 1) and a proposed scheme for general practice pharmacists to report information provided by customers on their experiences with over the counter and prescribed medicines. Clearly, the hospital pharmacist's involvement in adverse drug reaction reporting and monitoring schemes was limited, any such involvement was generally achieved through ward pharmacy.

In contrast with the relatively low level of current involvement, 84 replies (71%) indicated that they would like to see pharmacists more involved in

reporting to the CSM and 69 (58%) wished to see more involvement in other adverse reaction monitoring schemes (see Figure 20 and Table 4, Appendix 7). Many thought that increased involvement could be achieved by further development of ward pharmacy and by setting up local reporting schemes based on Drug Information Centres. Others considered that co-operation with clinical pharmacologists and working through local Drug and Therapeutics Committees were important steps. Despite this enthusiasm, only a limited number of monitoring schemes involving pharmacists were planned, in 79 replies (66%) there was no indication that schemes were planned, even in the next five years.

It was gratifying to see that 81 respondents (68%) were aware of the West Midlands Group, see Figure 21 and Table 5, Appendix 7. More replies from Areas/Health Boards indicated awareness of the Group in comparison with Districts/hospitals, 56 out of 76 (74%) and 25 out of 43 (58%) respectively. Most of those who were not aware were geographically remote from the Midlands. Further information regarding the Group was requested in 82 replies (69%), most of those who did not require this were from the West Midlands Region or were already in contact with the Group. More replies from Districts/hospitals, 36 (84%), requested further information compared with Areas/Health Boards, 46 (61%). A request to receive the bulletin of the West Midlands Group was included in 88 replies (74%) and again a larger proportion of these requests came from Districts/hospitals, 38 (88%), rather than Areas/Health Boards, 50 (66%). Presumably, further information and bulletins were thought to be of more practical value at that level. Many of those who did not require the bulletin were already on the mailing list. The response to this final

section of the questionnaire indicated a general awareness of the West Midlands Group and a high level of further interest.

In addition to the answers given for each question a number of comments and additional facts or opinions were provided by respondents. From these, four possible factors were identified which could conceivably limit the pharmacist's involvement in adverse drug reaction reporting and monitoring. Firstly, many replies mentioned a lack of the necessary resources which would enable more pharmacists to undertake the work. While this may be the case, the employment of more pharmacists for this role cannot be justified until they have first shown themselves capable of making a valuable contribution in this respect. Secondly, some felt that many pharmacists lacked the training and knowledge to fulfil an active reporting and monitoring role. This may be true in some cases but the large number of postgraduate courses and in-service training programmes that have started in recent years should soon rectify the situation. Perhaps more attention should be paid to adverse drug reactions on these courses. Thirdly, it was thought by some that medical staff would be resistant to greater involvement on the part of pharmacists. Two of those who replied went as far as saying that it was the doctor's and not the pharmacist's job anyhow! Lack of time or laziness of doctors is a likely cause of under-reporting of adverse drug reactions[38] and, if experience in the West Midlands is a guide, medical staff, providing they are approached with confidence and tact, welcome assistance in completing reports. Fourthly, a number of replies considered that the CSM was very reluctant to accept that pharmacists had a contribution to make. There was certainly an impression that formal recognition of the

pharmacist's role by the CSM would be an encouragement. Once again this is an area where pharmacists need to demonstrate their capabilities and show what they can achieve before their role will be fully recognised.

Conclusions from national survey

Hospital pharmacists have a high level of interest in the reporting and monitoring of adverse drug reactions but their current involvement is limited. There was a desire for increased involvement but few had made formalised plans. Lack of resources and inadequate training and knowledge, coupled with resistance from doctors and the CSM, were seen as obstacles to developing the pharmacist's role. This development will come through ward and clinical pharmacy with the necessary support from Drug Information Centres, possibly acting as local reporting centres. Hospital pharmacists must show themselves capable of making a valuable contribution to reporting and monitoring adverse drug reactions before more formal recognition of their role and additional resources will be obtained. To this effect, Pharmaceutical Officers should consider establishing pilot schemes involving one or two pharmacists, in order to gain experience and confidence, and then evaluate their contribution locally.

Figure 15 : Source of replies to questionnaire

Regions	No. of questionnaires sent	Replies received from Areas	Districts or Hospitals
West Midlands	8	9	0
East Anglia	3	3	0
Mersey	6	5	1
Northern	6	4	0
Oxford	4	3	1
North East Thames	6	5	4
North West Thames	7	3	14
South East Thames	5	4	3
South West Thames	5	5	0
North Western	5	6	4
South Western	5	4	4
Trent	6	5	5
Wessex	3	2	0
Yorkshire	6	5	0
Wales	7	5	0
Total for England and Wales	82	68	36
		Health Boards	
Scotland	12	8	7
Totals	94	76	43
Grand total		119 (from 84 Areas/Health Boards)	

Figure 16 : Availability of yellow cards

Replies to questions 1.1, 1.2 and 1.3

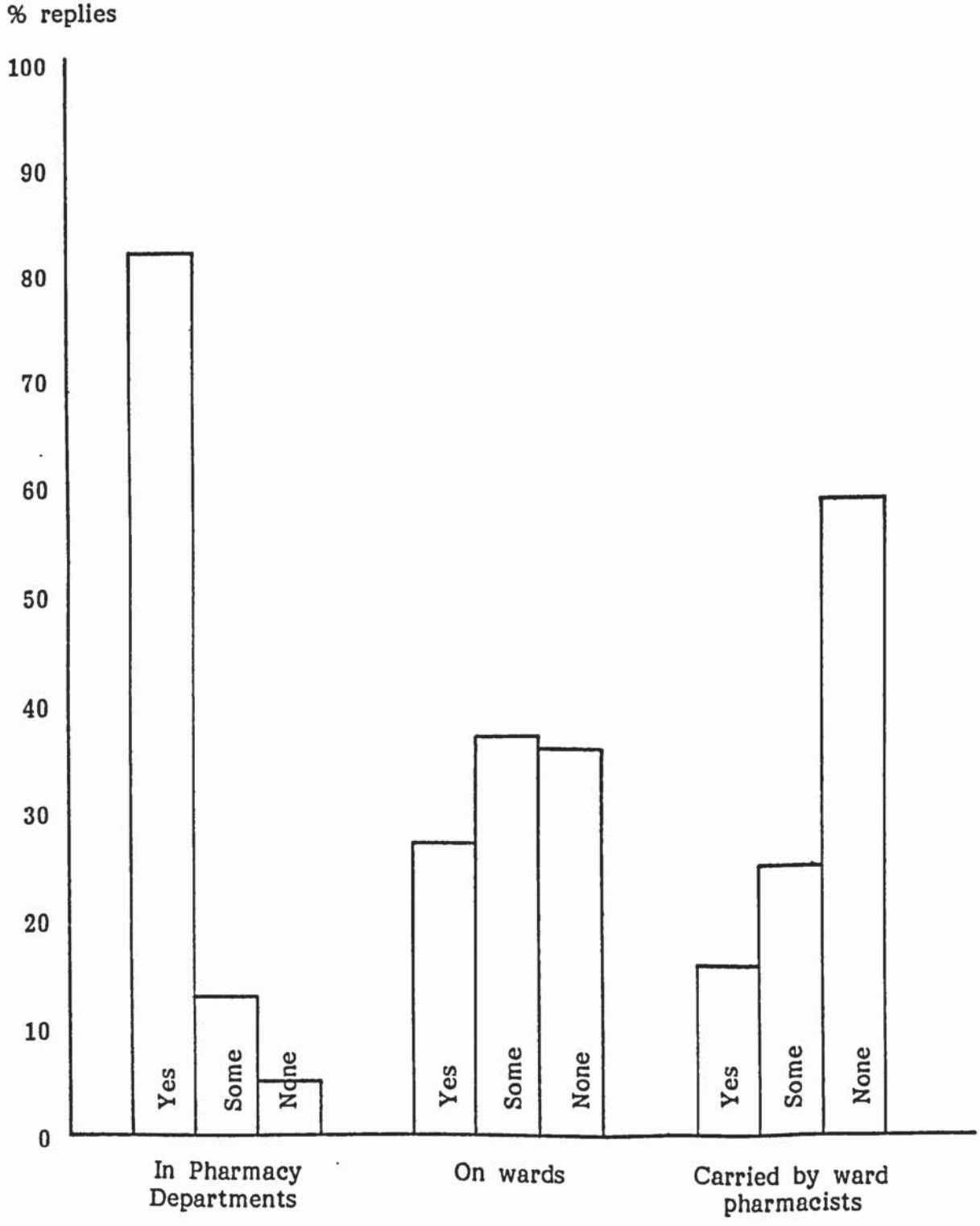


Figure 17 : Completion of yellow cards

Replies to questions 2.1, 2.2 and 2.3

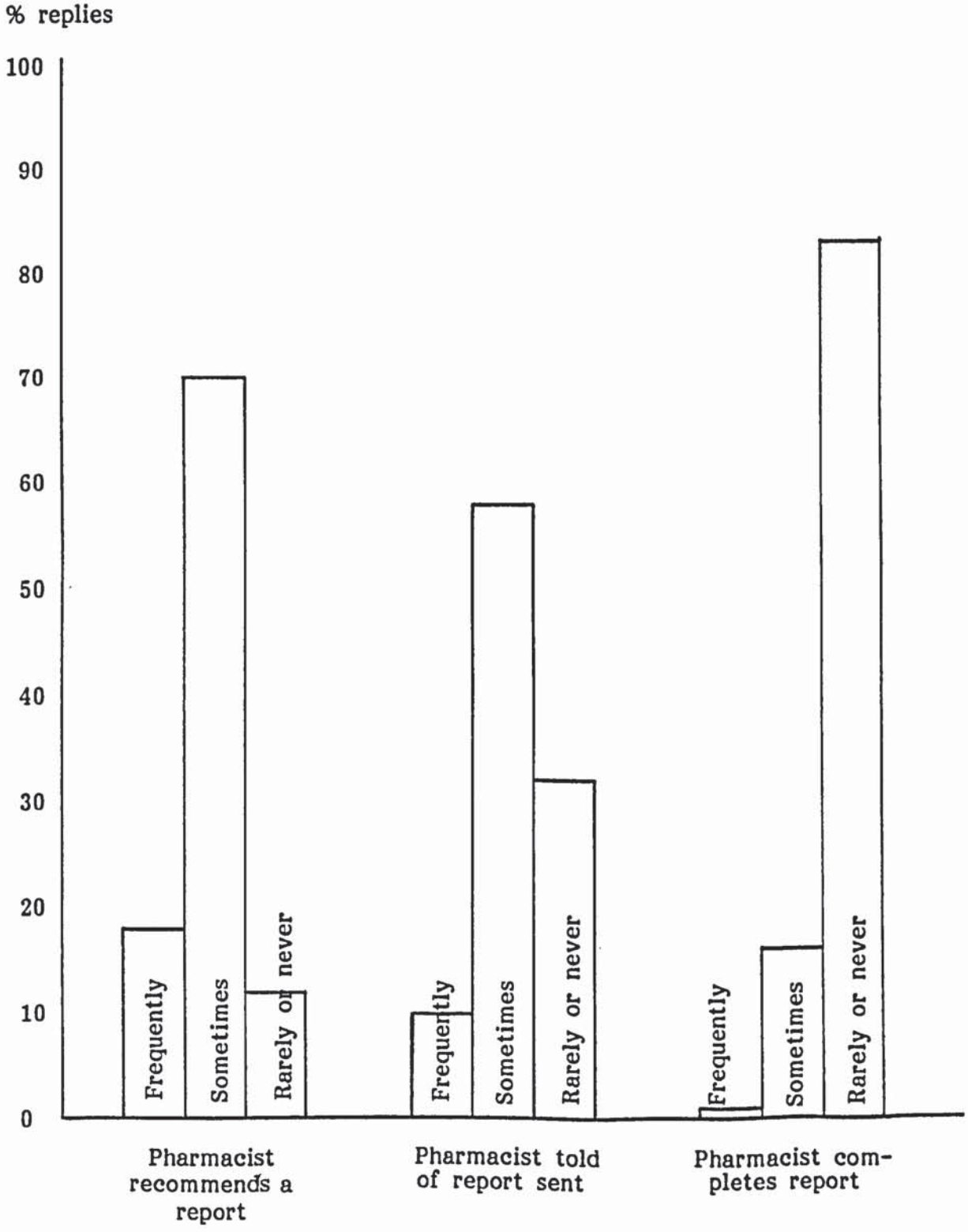


Figure 18 : Estimated number of reports per month going to the CSM via a Pharmacy Dept. or Drug Information Centre

No. of reports going to CSM per month	No. of Pharmacy Depts. or Drug Information Centres attempting to channel reports
Zero or left blank	12
1	5
2	4
3	2
4	2
5	1
11	1
12	1
Other answer	14
Totals 38	42

Figure 19 : Pharmacists' current involvement in reporting and monitoring schemes

Replies to questions 3.1 (a), (b) and (c)

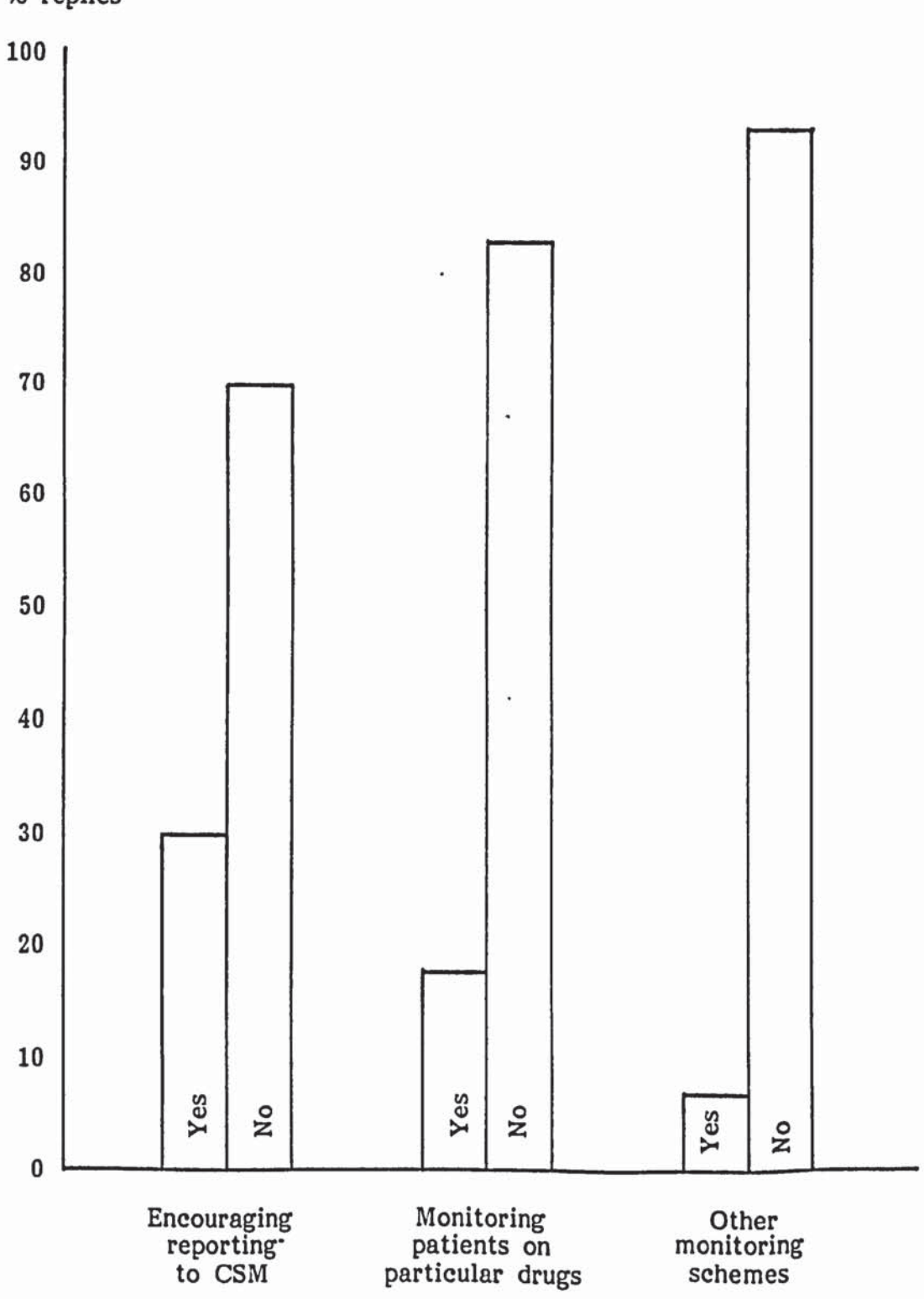


Figure 20 : Pharmacists' future involvement in adverse drug reaction reporting and monitoring schemes

Replies to questions 3.2 and 3.3

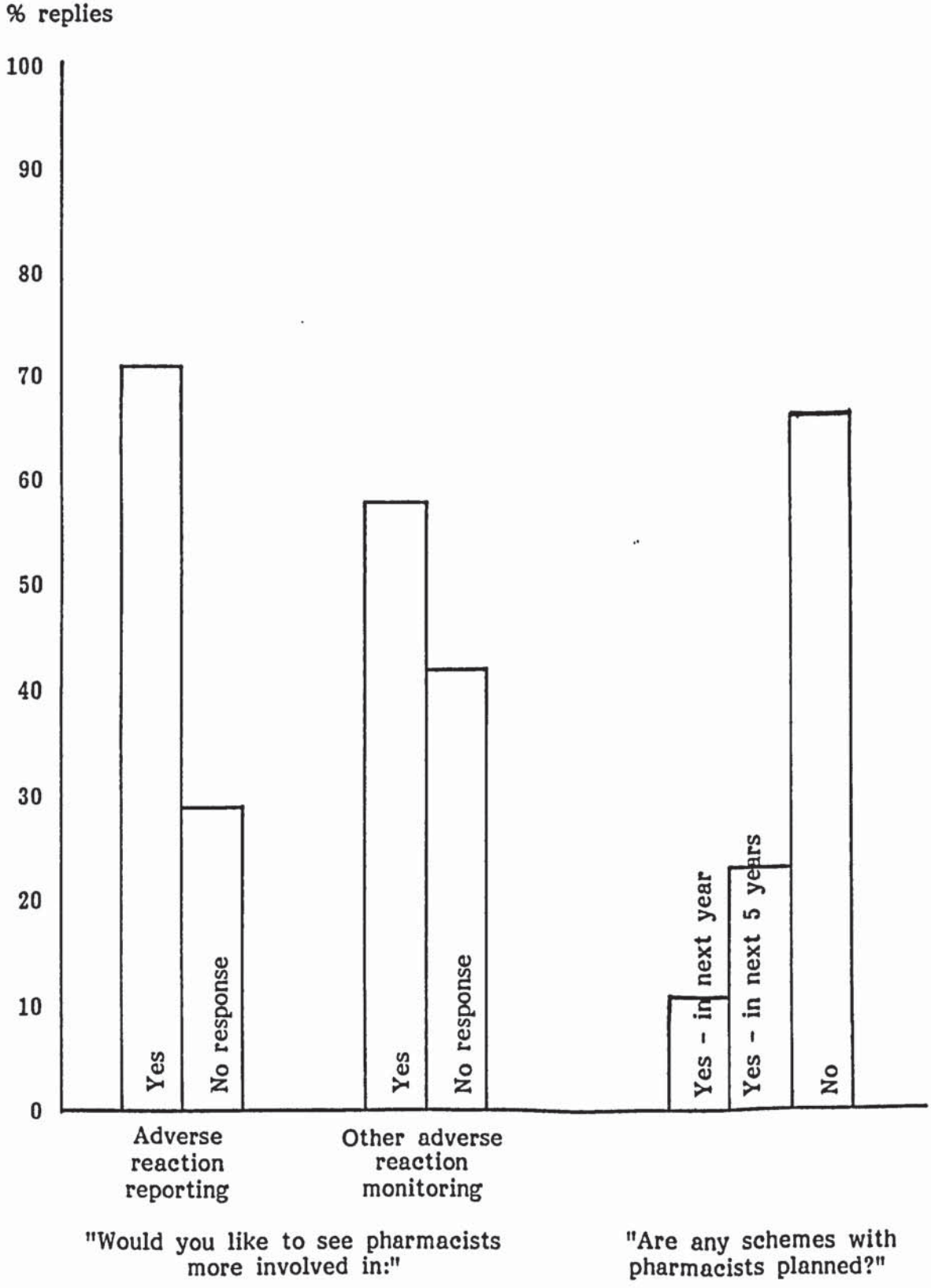
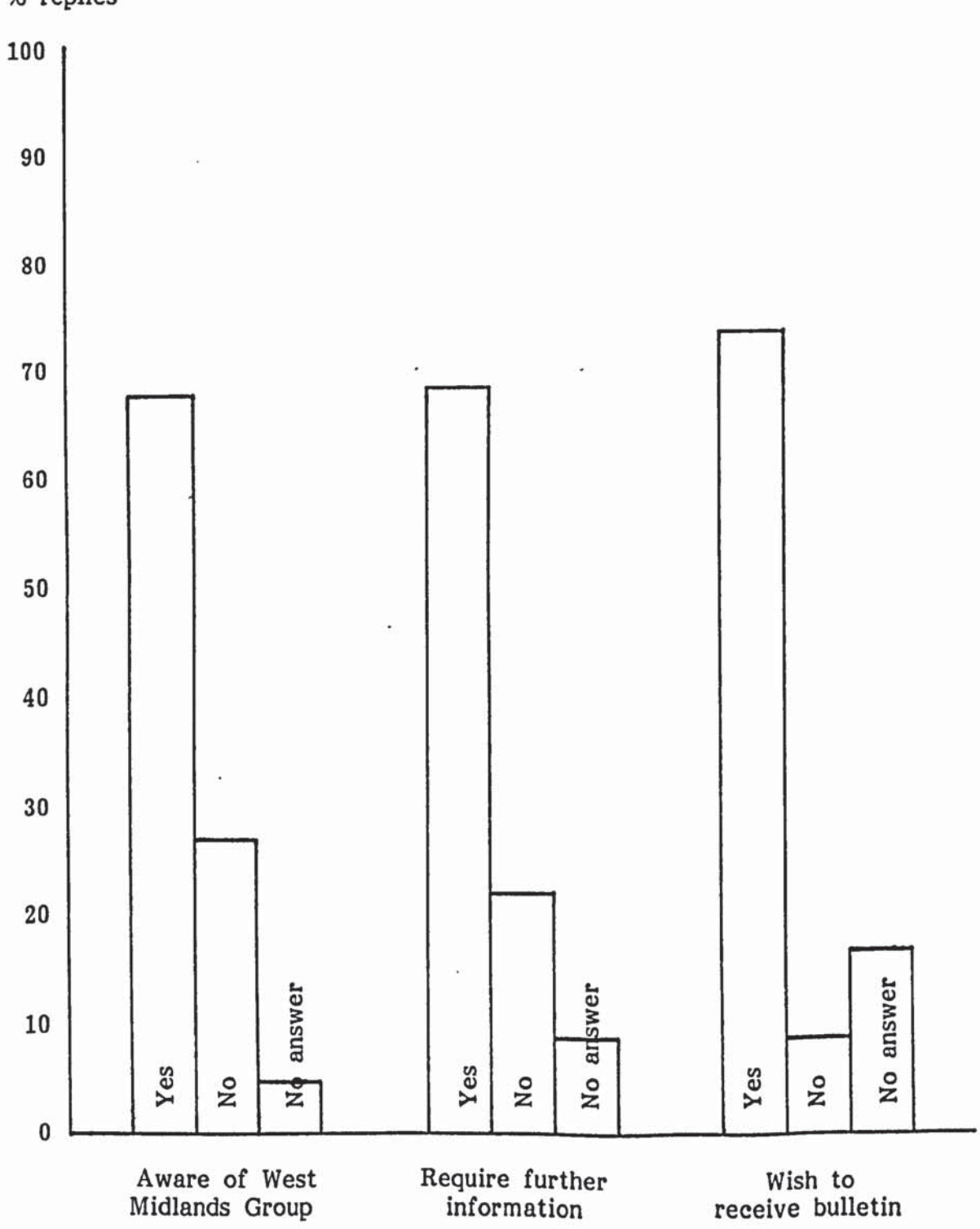


Figure 21 : Answers relating to the West Midlands Group

Replies to questions 4.1, 4.2 and 4.3



CHAPTER 4

LITERATURE AND DRUG INFORMATION

The Problem

For many drugs there are now a vast number of publications; for example, there are some 2,500 papers concerning salbutamol and 1,100 concerning labetalol. These quoted figures are for the total number of publications and include papers where the drug is only briefly mentioned and others dealing with chemical and analytical aspects as well as clinical work. However, a fairly high proportion are clinically orientated and some of these describe adverse drug reactions either in passing or in considerable detail. These large numbers of papers are spread throughout the ever-increasing number of scientific and biomedical journals now published. On the other hand, for some drugs, particularly recently marketed compounds, there is a scarcity of clinical publications and frequently there is an inadequate account of the adverse reaction profile. Clearly, even for adverse drug reactions alone, it is only feasible for a practitioner to keep abreast with a limited number of journals, or papers on a very small group of drugs. The development of drug information as a speciality within pharmacy in the U.K. and elsewhere is, in part, a response to the problem.

Sources of information

The primary source of information on adverse drug reactions is the publication of case reports in medical or scientific journals. A reaction may later be confirmed by further reports or specific studies, but how

reliable are these reports? Venning[94] has recently analysed 52 suspected adverse drug reactions first reported in four key medical journals in 1963. Of the 52 articles five were deliberate investigations into potential or predictable problems and the other 47 were essentially anecdotal reports. Validity was satisfactorily established in 28 of these 47 articles but of the remaining 19 only seven were later verified by subsequent reports. Thus 12 out of 53 reports (23%) have not been verified even after nearly 20 years, 7 of these possible false alarms were haematological problems. Venulet et al[95] have investigated the quality and completeness of articles on adverse drug reactions; 5,737 papers from 80 countries, published between 1972 and 1979, were studied. Only publications describing experiences with many patients were included but the incidence of a particular adverse drug reaction could only be calculated in 55%. Furthermore, only 19% of papers contained information on the age of patients, dosage, formulation and duration of treatment, in addition to the data necessary to calculate incidence. O'Connor et al[96] analysed 614 articles, from three key medical journals, which contained reports of adverse drug reactions. Case reports accounted for 43% of papers, the rest being reviews and specific studies. The authors divided the 614 articles into major and minor, the latter comprising mainly letters to the editor. Only 29% of the major articles had some form of recognisable research strategy whereby the problems of bias, confounding factors and random occurrences could be partially evaluated. The value of publishing case reports was recognised but attention was drawn to the danger of ascribing excessive weight to unsubstantiated reports. It was suggested that case reports of suspected adverse drug reactions should be published only in specific areas of medical journals where the anecdotal nature of the report and its implications were understood.

Judith Jones of the FDA has recently proposed minimal information elements that are required to draw any conclusion about the possible relationship between a drug and an adverse event[97]. She suggests that adherence to such criteria would greatly enhance the usefulness of anecdotal reports of adverse reactions in the literature[97]. The criteria for these basic data elements in reports are closely related to those for adverse drug reaction causality assessment using algorithms or scoring lists[98,99,100], but some of these are probably over complex for day to day use. The following points, considered to be essential by Jones[97], have been adapted and developed for a potential checklist, as follows:

1. Timing

    1.1 How long had the patient been receiving the suspected drug before the adverse event?

    1.2 What other drugs had been taken and how long for?

    1.3 Were there other relevant factors, e.g. diet, occupational exposure, etc.

2. Dechallenge

    2.1 Was the suspected drug stopped or continued?

    2.2 If stopped, did the adverse event disappear or improve?

    2.3 What was the time course of the above?

    2.4 Was the time course consistent with the drug's kinetics and the dynamics of the disease process?

3. Rechallenge

3.1 Was the patient rechallenged with the suspected drug?

3.2 Did the adverse event recur in a reasonable time course?

4. Alternative causes

4.1 What other conditions or factors were present or possibly present that could have accounted for the adverse event?

5. Patient details

5.1 Age, sex, race, body weight, etc.

5.2 Previous medical history.

The proposals by Jones were commended to potential authors in a "Clinical Pharmacy" editorial[101] and they would indeed serve as a useful guide for pharmacists preparing adverse drug reaction case descriptions whether or not for publication. Furthermore, they could also prove helpful to pharmacists when assessing the validity of such case reports in the literature.

Despite the above limitations, publication of case reports in journals still remains one of the most useful primary sources of information on adverse drug reactions. Journals should continue to publish such reports although there is always the risk of false alarms; however, this problem is recognised, the British Medical Journal now "aims at steering a path between the extremes of crying wolf too often and insisting on near

certain evidence"[102]. Pharmacists must be aware of the possible flaws in adverse reaction case reports and need to adopt a critical approach to the literature.

The available secondary information sources for adverse drug reactions will be critically, but not comprehensively, reviewed in brief. The most basic secondary sources of information which should be available to all pharmacists are Martindale's Extra Pharmacopoeia[103], the British National Formulary (BNF)[104] and the Data Sheet Compendium[105]; all three are useful but each has its limitations. Martindale is sometimes deservedly referred to as the "pharmacist's bible" but, because it is only published every five years, it can be out of date and may be useless for new drugs. It also simply lists all adverse drug reactions under the monograph heading "Toxic Effects", giving little indication of incidence or severity and failing to identify reactions of the greatest clinical importance. However, it does cite original papers and reviews relating to some adverse drug reactions and this can be useful if further information is required. Martindale Online should be available later in 1983 and hence users with "on-line" facilities will gain access to the more recent additions.

The new style BNF, first published in February 1981, is a considerable improvement on its predecessors but still tends to deal with adverse drug reactions in a fairly general and superficial manner. This is not surprising, as the BNF is intended as an aid to prescribing and not as an adverse reactions reference book. However, it is updated every six months so newly reported adverse drug reactions may be easily included and it does indicate the common and clinically important reactions.

The Data Sheet Compendium[105] is a book of the data sheets from the ABPI member companies and is published annually. Hence, it is fairly up-to-date but there are wide variations in how adverse reactions are treated by different drug manufacturers. Some seemingly list everything that has ever been reported, whilst others identify only the well established reactions; but again these are just lists with little indication of frequency or clinical importance. There are also some serious errors and omissions regarding adverse reactions in the data sheets and, although this has been recognised for some years[106], little has been done to correct them. This is particularly the case with drugs which have a product licence of right and have not yet been dealt with by the Committee on Review of Medicines (CRM). For example, the 1983/84 data sheet[105] for Uromide (sulphacarbamide 500mg + phenazopyridine 50mg) includes a statement that "the product is extremely well tolerated and no adverse conditions have been reported". In comparison, under phenazopyridine, the 9th edition of Meylers Side Effects of Drugs[107] (see below) reads "nephrotoxicity has now been established, a single report of hepatic damage has appeared, the formation of vesical concrements has also been described, methaemoglobinaemia and haemolytic anaemia can occur".

Meylers Side Effects of Drugs is probably the most authoritative and useful secondary source of information on adverse drug reactions. It was first published in 1952[108] and the 9th edition[107] appeared in 1980. An edition or volume is now published every four or five years, summarising and evaluating the reports in the literature over that period and consolidating this with the older information, often referring back to previous editions for more detail. In an attempt to keep more up-to-date, these major works

have been supplemented by annuals since 1977, the latest one[109], Annual 6, being published in 1982. The collection is now becoming rather bulky but the main disadvantage is the price, both the 9th edition and Annual 6 cost over £60. Other drawbacks are that, despite the annuals, the information is still a year or two out of date and a more critical approach to the literature reviews could be adopted in some cases. However, of 100 observed side effects some French workers have shown that the single reference source which mentioned most (76) was the 9th edition of Meyler and that this, plus the other Meylers, also provided better coverage (81) than any other two reference sources[110]. For a drug information centre or other unit regularly dealing with adverse drug reaction reports and enquiries Meylers Side Effects of Drugs is an essential reference work.

One other book worthy of mention is the Textbook of Adverse Drug Reactions edited by Dr. D. M. Davies[111], the second edition of which was published in 1981. Davies includes an excellent introduction to the subject covering history, epidemiology, pathogenesis, detection and investigation; most of the subsequent chapters are devoted to the various body systems affected by adverse drug reactions, e.g. skin disorders, eye disorders, blood disorders, etc. These are well written and original references are widely quoted but, as with any book, it can never be right up-to-date and is not entirely comprehensive.

A problem with all of these books is the time-lag between a reaction being reported in the literature and its inclusion in such publications, this is a particular problem with new drugs and newly reported reactions with established drugs. This is largely overcome in two ways, firstly by

abstracting services and, secondly, by "on-line" literature searching. A number of abstracting publications are available, for example "Inpharma" and "Reactions", both of which are published by ADIS Press, Australia. "Inpharma" is available weekly and has the shortest time lag but only a small part has been devoted to adverse drug reactions since the introduction in January 1980 of "Reactions" which is available two-weekly and deals exclusively with adverse drug reactions. There is also "Clin-Alert" which also covers only adverse drug reactions, it is published two-weekly by Science Editors Inc., Louisville, Kentucky, U.S.A., but appears to have a longer lag time and is less useful in the author's experience. All these abstracting services are valuable in providing fairly recent information from a wide range of journals but their cost probably confines them to specialist units.

On a similar note there is the National Abstracting Scheme which is a co-operative venture by a group of drug information pharmacists in the U.K. This was formally started in 1977 as a low cost scheme to meet the needs of drug information pharmacists[112], although it drew together a number of smaller schemes already in existence. The Scheme has some 16,000 papers key worded and abstracted on microfiche at the end of 1982 and about 30% of these concern, at least in part, adverse drug reactions[113]. Approximately 85 journals are scanned by the participating pharmacists[112], the choice of journals having changed considerably since the start of the scheme[113]. The time-lag between a paper appearing and being abstracted is about two weeks for the weekly core journals and a month or more for others[112,113]. Apart from the selected journals, CSM

publications, such as Current Problems, and some DHSS circulars are also included. The Scheme has provided a useful source of information but will be easier to use in the near future when a cumulative microfiche index appears and considerably more valuable when it is available on-line as "Pharmline" through a computer bureau sometime in 1983.

"On-line" literature searching of commercially available databases, such as MEDLINE and RINGDOC, has in recent years become available to drug information pharmacists[114]. However, these facilities only partly overcome the time-lag, as it takes at least six months for a paper to be indexed and incorporated in such databases. They are also not entirely comprehensive in journal coverage, particularly with conference abstracts and proceedings. In an examination of six databases for publications on cimetidine it was shown how some performed better in particular areas, e.g. pharmacological papers, clinical papers, abstracts or reviews, and that more than one database was needed to approach 100% recovery[115].

In the search for adverse drug reaction reports two other problems are worthy of comment. Firstly, the indexers who compile the systems apply certain selection criteria to restrict the number of index terms used, and this may result in some drugs or adverse reactions not being indexed if they are a secondary part of the paper. For example, a paper describing reports received by the Australian Drug Reactions Advisory Committee[116] included references to the following drugs and adverse reactions:

Drugs

Trimethoprim-sulphamethoxazole
Amoxycillin
Ampicillin
Sodium diatrizoate

Propranolol
Erythromycin
Methyldopa
Metoprolol
Thioridazine
Fluphenazine
Intralipid
Dextropropoxyphene
Troxidone
Paramethadione
Sodium aurothiomalate
Chloramphenicol
Althesin
Phenylbutazone
Disopyramide

Reported reactions

Rash
Pruritus
Urticaria
Nausea
Vomiting
Dizziness
Headache
Fever
Hypotension
Diarrhoea
Anaphylactic-type reactions
Blood dyscrasias
Thrombocytopenia
Leucopenia, and others

The index terms used on MEDLINE for this paper were as follows:

Adolescence
Adult
Aged
Australia
Child
Child, preschool
Drug interactions
Drug therapy/*ADVERSE EFFECTS
Human
Infant
Infant, newborn
Middle age
Poisoning

Thus, owing to the superficial indexing, this paper would not have been identified by a MEDLINE search for any of the adverse drug reactions discussed.

Secondly, there is the problem of false drops. If a search is conducted using the appropriate terms for the desired drug and adverse reaction, a list of papers should be obtained. However, in practice they do not all necessarily describe or refer to the selected drug causing the reaction. A good practical example of this is as follows: A search was conducted for reports of Henoch-Schonlein Purpura (HSP) associated with cimetidine; the search strategy used produced three references from MEDLINE, none of which described HSP due to cimetidine. The three references obtained were:

1. A reported case of HSP in which the patient was later given cimetidine for a gastric ulcer[117].

2. A review of urticaria and urticarial vasculitis where cimetidine was mentioned as a treatment for chronic idiopathic urticaria[118].

3. A description of two cases of post-transfusion purpura where one of the patients was given intravenous cimetidine for a bleeding duodenal ulcer[119].

Thus, each of these references was a false drop because there was no way of linking the drug (cimetidine) with the adverse reaction (HSP). If this had been done, no references would have been obtained. This problem can

be overcome by more sophisticated indexing techniques but these are only currently employed within the pharmaceutical industry.

Some national drug monitoring centres publish lists or summaries of the spontaneous adverse reaction reports that they receive. The CSM, for instance, produced in 1977 a Register of Adverse Reactions which listed the reports that it had received between 1964 and 1976 for each drug and these were also cross-referenced under reactions. This publication has not been repeated but it is possible to obtain similar updated lists for each drug, either directly from the CSM or through the ABPI. Unfortunately, both the Register and the updated listings are simply lists of reported reactions and do not indicate what, if any, other drugs the patient was receiving, or give any judgment as to the causal relationship between drug and reaction. Some of the overseas monitoring centres are more helpful in these respects, in particular the Australians produce an impressive paperback which also includes details of causality[120], see also Chapter 6. Similarly, the Dutch and Swedish bulletins, which are produced frequently, include useful additional information such as patients' age and sex and other drugs taken. However, in most cases it is difficult to draw meaningful conclusions from this type of undigested data and some are difficult and time-consuming to search. Such registers and bulletins are only of value to specialist adverse drug reaction units and the West Midlands Group is now beginning to index them on their recently acquired micro-computer to overcome the problem of searching.

Another information source frequently consulted by drug information pharmacists is the pharmaceutical companies. If the company was

responsible for the development of the drug and now collects data from around the world, it should in theory know more about the adverse reaction profile than anyone else. Available sources of information within companies include reports from pre- and post-marketing clinical trials in the U.K. and overseas, spontaneous reports from practitioners, results from any postmarketing surveillance studies, communications from drug regulatory authorities and a wide range of literature and "on-line" searching facilities.

The drug information pharmacist's contribution

Leach[121] in 1978 described drug information services in the U.K. and analysed the types of enquiries received by eight regional units. At times there were more enquiries about adverse drug reactions than anything else but it was noted that many enquirers seemed reluctant to report novel effects to the CSM. The mean proportion of enquiries relating to adverse reactions in 1976 from the eight units was 20.6%, the range being from 10.3 to 28.5%. Further figures for the number of such enquiries were obtained from eleven of the Regional drug information centres for 1977, 1978 and 1979, see Figure 22. Between 8% and 32%, mean 18%, of questions concerned adverse drug reactions including overdoses and poisoning, thus providing a very similar picture to Leach's earlier analysis. These figures represent a vast number of questions about adverse drug reactions coming to drug information centres each year, a mean of over 2,600 per annum, based on three years' figures, to the eleven centres alone. This emphasises the important role of drug information centres in dealing with adverse drug reactions.

In the West Midlands Region it has been shown that requests to drug information pharmacists for information about adverse drug reactions can lead to the reporting of reactions to the CSM[86], see also Chapter 2. A more detailed appraisal of the role of the West Midlands Regional Drug Information Centre (based at Good Hope Hospital) in this respect was undertaken, see Figure 23. The mean proportion of enquiries relating to adverse drug reactions between 1976 and 1981 was 14.1%, range 10.2 to 20.9%, which is slightly lower than that shown by Leach and the 1977 to 1979 data from eleven Regional drug information centres, see Figure 22. The higher proportion of adverse reaction enquiries for the West Midlands Centre in Figure 22 compared to Figure 23 is because overdose and poisoning enquiries were included only in the former. The reporting of adverse drug reactions from Good Hope Hospital could be monitored through the West Midlands Adverse Drug Reaction Study Group and the number of yellow cards received is also shown in Figure 23. The majority of these reports followed an enquiry to the drug information centre at Good Hope[122], see also Figure 6. A mean of nearly 10% of adverse reaction enquiries resulted in a yellow card being completed.

Some enquiries about adverse reactions received by drug information centres are of a general or academic nature but many concern a specific patient. The latter type of question frequently being asked to assist the physician with the differential diagnosis between an adverse drug reaction and a spontaneously occurring disease or to assist treatment by removal of a possibly offending agent. A number of drug information centres were asked to record all adverse reaction enquiries and, if they concerned a specific patient, to note some further details on a form

provided, see Appendix 8. Forms were returned from nine centres and 140 of the questions recorded related to a particular patient, see Figure 24. A surprisingly small number of enquiries, 16 (11%), concerned new drugs, i.e. those marked by the black triangle symbol (▼). A much larger number, 89 (64%), concerned adverse drug reactions that were either not mentioned in the data sheet or were not well established. This implies that doctors were asking the drug information centres about unusual or less common reactions or were using the service to exclude an adverse drug reaction as a possible diagnosis. In both instances this was good use of the drug information centres' resources to the patients' benefit and the drug information pharmacist would be making a direct contribution to patient care by providing the right information.

In response to 56 of the 140 enquiries a yellow card was supplied for the doctor to report the reaction. Where not supplied, this was generally because after discussions it was decided that the event was not, after all, drug-related. Of the 56 yellow cards supplied at least 30 were completed and sent to the CSM; this figure may have been higher as outside the West Midlands Region (as were centres UHW, LGI, Y and H) the report could have gone directly to the CSM without the drug information pharmacist knowing. Two main reasons why the doctor did not complete the yellow card were identified. Firstly, there was a feeling that this was unnecessary, as the reaction was already recorded in the literature, albeit only as one or two reports in some cases, and secondly, the causal relationship between the drug and the event was not certain, other causes not being excluded.

Figure 22 : Adverse drug reaction enquiries received by eleven Regional Drug Information Centres

Regional Centre	% adverse drug reaction enquiries			Mean number/year/centre (based on 1977/1978/1979)
	1977	1978	1979	
East Anglia	17%	13%	19%	107
Mersey	28%	22%	28%	109
Northern	15%	19%	13%	152
North Western	30%	31%	31%	400
S.E. Thames	16%	16%	17%	447
South West	9%	32%	20%	156
Trent	20%	17%	24%	404
Wessex	16%	16%	14%	151
West Midlands	16%	17%	18%	355
Northern Ireland	10%	8%	12%	93
Wales	12%	12%	11%	260
			Total	2634/year

Figure 23 : **Adverse Reaction Enquiries and Reports from the West Midlands Regional Drug Information Centre at Good Hope Hospital**

	1976	1977	1978	1979	1980	1981	Totals 1976-1981
Total number of enquiries	1,956	2,050	2,064	2,156	2,339	2,381	12,946
Adverse reaction enquiries	201	264	259	300	488	312	1,824
Adverse reaction enquiries as % of total	10.2%	12.8%	12.5%	13.9%	20.9%	13.1%	14.1%
Number of reactions reported*	21	42	43	33	21	21	181
Percentage of enquiries resulting in reports	10.4%	15.9%	16.6%	11.0%	4.3%	6.7%	9.9%

*i.e. No. of yellow cards received from Good Hope Hospital by the West Midlands Adverse Drug Reaction Study Group

Figure 24 : Adverse drug reaction enquiries relating to specific patients

Drug Information Centre	No. of enquiries	No. involving new drugs	No. not in data sheet or well established	Yellow Card supplied	Yellow Card completed
GH (Regional)	21	2	14	19	8
UHW (Regional)	30	3	24	9	6
LGI (Regional)	15	3	11	4	1
NC (Area)	13	2	3	7	3
SO (District)	28	3	18	5	5
QEH (District)	11	0	6	3	1
Y (DGH)	4	1	2	2	2
H (DGH)	6	1	5	3	1
SM (Psychiatric)	12	1	6	4	3
Totals	140	16 (11%)	89 (64%)	56 (40%)	30 (21%)

Key

GH = Good Hope Hospital
UHW = University Hospital of Wales
LGI = Leeds General Infirmary
NC = New Cross Hospital
SO = Selly Oak Hospital
QEH = Queen Elizabeth Hospital
Y = York District Hospital
H = Huddersfield Royal Infirmary
SM = St. Matthew's Hospital
DGH = District General Hospital

CHAPTER 5

THE WARD PHARMACIST'S CONTRIBUTION

Introduction

Over the past fifteen years an increasing number of hospital pharmacists in the U.K. have been taking their skills from the pharmacy out to the wards. This has been a vital step in the development of a more clinically orientated role for the pharmacist. The function of ward pharmacy services was summarised at a workshop held in 1980 and one of the roles identified was monitoring for adverse drug reactions[123].

The ward or clinical pharmacist's role in monitoring adverse drug reactions in hospitals has been highlighted since the early 1970's by a number of workers in the U.S.A.[54,65-67,69,72] and more recently by some in the U.K.[80], as reviewed in Chapter 1. By going to the wards, the pharmacist is able to identify adverse drug reactions, assist with the reporting, documentation and follow-up of cases and educate nursing and medical staff. The ward pharmacist is also able to realise a most important role, that of helping to prevent adverse drug reactions by encouraging safer prescribing and administration of drugs. The comprehensive adverse drug reaction programme[67] outlined in Chapter 1 is useful reading for ward pharmacists who could use it as a basis for developing their own role in monitoring, reporting and prevention.

Identification of adverse drug reactions

It is proposed that ward pharmacists could identify adverse drug reactions in the course of their ward visits in the following ways:

i) Medication changes - Discontinuation of drugs or dosage reductions have previously been suggested as a means for pharmacists to identify adverse drug reactions[54,65,67,69]. Such changes should be noted by ward pharmacists when reviewing each patient's prescription sheet and may have been made because of suspected adverse drug reactions. The pharmacist should determine if this was the case by examining the patient's notes, using their ingenuity, and if necessary asking the appropriate medical and nursing staff. Many discontinuations of short-term therapies, such as antibiotics or analgesics, will obviously not be due to adverse reactions, but dosage reductions and discontinuation of drugs usually used for long-term treatment should raise the pharmacist's suspicions.

ii) Additions to therapy - Certain drugs or groups of drugs may be prescribed to treat or alleviate the symptoms of adverse drug reactions; some examples are given in Figure 25, although this is not intended to be a comprehensive list. Certain new additions to therapy, as well as discontinuations and dosage reductions, should alert ward pharmacists to possible adverse drug reactions[67,74]. This has been explored further in relation to antihistamines and anti-diarrhoeal preparations, see later.

iii) Requests for information - Drug Information Pharmacists may identify reactions in this way in the course of their work, and this has already been considered, see Chapter 4 and Figure 24. However, most questions about adverse drug reactions arise at ward level and are frequently put to the ward pharmacist by nursing and medical

staff. The ward pharmacist may be able to provide the answer or will, if necessary, refer the enquiry to the local Drug Information Centre. Sometimes the ward pharmacist will be told about an adverse drug reaction that has occurred and this may or may not be followed by a question. There is also a system in some Australian hospitals where ward staff notify the pharmacists about possible adverse reactions by special alerting cards, see Chapter 6.

iv) Patient contact - Patients frequently relate their adverse experiences of drug therapy, both past and present, to the pharmacist as they discover someone with a real interest in drugs. This may occur in a number of situations; for instance, at the patient's bedside whilst on ward rounds with clinicians; when the pharmacist is reviewing the prescriptions if they are placed at the end of the bed; if the pharmacist interviews the patient on or soon after admission to hospital to determine their drug history; and if the pharmacist counsels patients about their drug regime on discharge from hospital or at out-patients. Close co-operation with the appropriate medical staff is particularly desirable in this area, in particular what the patient tells the pharmacist, what the pharmacist tells the patient and what the doctor has already told the patient.

A simple form listing these means of identifying adverse drug reactions was designed for ward pharmacists to record such identifications made in the course of their work, see Appendix 9. The forms were used over a period of about one month in 1980 by ward pharmacists at the Queen

Elizabeth Hospital, Birmingham, and the Derbyshire Royal Infirmary. Sixty-seven adverse reactions were identified, 14 independently by two methods, making a total of 81 detections, as summarised in Figure 26.

Discontinuation of a drug or drugs was the most common means of identifying reactions and the 18 cases where a suspected reaction was identified in this way are listed in Figure 27. As can be seen, the majority were well established reactions to the drug or drugs concerned. Reduction of dosage revealed six reactions; for example the characteristic fine tremor that occurs with high oral doses of salbutamol, nystagmus and sedation which are dose-dependant effects of phenytoin, and nausea and vomiting with digoxin. One possible reaction - sedation and lethargy with phenytoin and phenobarbitone - was identified because the timing of doses had been altered. Although these were clearly means by which ward pharmacists could identify reactions, they all meant that the doctor had already recognised them as adverse drug reactions and had acted accordingly.

Additions to patients' therapy identified eight reactions, the new prescription being an antihistamine for the treatment of a drug-induced rash in all cases. The majority of rashes were due to antibiotics or an antibacterial agent (co-trimoxazole) but one was a photosensitivity rash related to chlorpromazine. Prescription changes as a whole revealed a total of 33 reactions and this was more than any of the other methods.

Requests for information identified only 9 possible reactions and, as seen with questions going to drug information centres (Figure 24) these mainly

concerned reactions that were not well established or known. Examples included systemic lupus erythematosus (SLE) syndrome with acebutolol, corneal microdeposits with amiodarone, macrocytic anaemia with perhexiline and nightmares with propranolol. As with the drug information centres, medical staff were making good use of the ward pharmacist's knowledge and skills in locating information.

Twenty-one reactions were mentioned to the ward pharmacist by medical (14) and nursing (7) staff which implies that the pharmacist's interest in adverse drug reactions was recognised. Direct contact with patients revealed nine possible reactions; for instance, headaches with minocycline, nausea with cephradine and two patients mentioned dyspepsia with ibuprofen.

In addition to the suggested ways of identifying reactions, two further means were found. In seven cases adverse drug reactions were recorded in the patient's notes and were seen by the ward pharmacists and in two cases possible adverse consequences of therapy were recognised from the bedside charts. The examples of the latter were glycosuria in a patient receiving dexamethasone and hypotension in a patient taking chlorpromazine.

This study proved that ward pharmacists could easily identify adverse drug reactions by a number of means in the course of their normal ward visits. Although in many cases the reactions had already been recognised by the medical staff, the pharmacist may still have a role in advising on the management of the reaction or, more particularly, in reporting it to

the CSM. It was thought that only six of the 67 reactions identified above were reported on a yellow card, see Figure 28. A general reluctance on the part of the medical staff to report adverse reactions to the CSM was encountered throughout, especially with the common and well established reactions. The six reactions actually reported were all associated with new drugs or were unusual or serious occurrences with more established agents.

Identification of reactions by monitoring certain additions to therapy

Further work was also undertaken at the Derbyshire Royal Infirmary to investigate whether monitoring certain additions to therapy would identify adverse drug reactions. A list of drugs that may be prescribed to treat or alleviate the symptoms of adverse drug reactions appears in Figure 25. From this list anti-diarrhoeal preparations and antihistamines were selected because they are frequently prescribed and were considered likely to reveal reactions. Naturally, these drugs will often be prescribed for other reasons and the purpose of the study was to determine whether it was worth monitoring them in order to identify adverse drug reactions.

Ward pharmacists visiting several wards at the Derbyshire Royal Infirmary reported new in-patient prescriptions for anti-diarrhoeal preparations and antihistamines. Each patient's prescription and notes were then reviewed and details of all drugs, diagnoses, etc., were recorded. The reason for prescribing the anti-diarrhoeal preparation or antihistamine was established either from the notes or by asking the medical or nursing staff.

Thirty-three patients receiving anti-diarrhoeal preparations were reviewed and four different preparations were encountered, namely oral codeine phosphate, kaolin and morphine mixture, Lomotil (diphenoxylate 2.5mg + atropine sulphate 25mcg) and loperamide; the number of prescriptions for each of them is shown in Figure 29. One preparation was prescribed in 28 cases but five patients received two, making a total of 38 prescriptions. In four of the patients receiving two preparations the initial prescription was changed but in one case the patient was receiving two concurrently. In 22 of the 38 prescriptions (58%) the preparations were given for the treatment of diarrhoea but in 16 cases codeine phosphate was being used as an analgesic; all but one of these were on the neurosurgical wards. The possible aetiology of the diarrhoea was estblished in each case and four basic causes were found, namely drugs, radiotherapy, nutrition (tube feeds) and concurrent diseases. In several instances the cause of the diarrhoea was not known for certain and in such cases the most likely of the four basic causes was allocated.

Diarrhoea was considered to be probably or possibly due to drugs in 10 cases (26%); the anti-diarrhoeal preparation prescribed and the implicated drug or drugs are shown in Figure 30. Diarrhoea was thought to be due to radiotherapy in three cases, tube feeds (Clinifeed) in two instances and concurrent diseases in seven.

About one quarter of the prescriptions for anti-diarrhoeal preparations identified a possible or probable case of drug-induced diarrhoea. However, if the use of codeine phosphate as an analgesic was excluded, the proportion of cases with drug-induced diarrhoea would have been much

higher - 10 out of 22 (45%). It would thus appear to be worthwhile for ward pharmacists to monitor new prescriptions for anti-diarrhoeal preparations to identify cases of drug-induced diarrhoea, with the exception of codeine phosphate used on neurosurgical wards.

The only antihistamine studied was chlorpheniramine. Prescriptions for others, notably promethazine hydrochloride, were found to be single doses given for pre-operative medication and were thus excluded. Of the 14 patients prescribed chlorpheniramine that were reviewed, 10 were found to have skin rashes which were probably due to drug therapy. The drugs implicated were antibiotics in six cases and frusemide, Lomotil, phenobarbitone and phenytoin in the other four, see Figure 31. Four patients were given chlorpheniramine for skin conditions unrelated to drugs, see also Figure 31. Although this was a small sample of patients, it can be seen from the high proportion of drug-induced skin rashes discovered that monitoring new prescriptions for antihistamines would be an effective way for ward pharmacists to identify such reactions. A pharmacy based study in the U.S.A. showed that monitoring new prescriptions for another antihistamine, diphenhydramine, was an effective means of detecting suspected hypersensitivity reactions[74].

The adverse reactions identified in these studies were all established reactions to well-known drugs and were, therefore, probably not worth reporting to the CSM, see later. However, in the cases where the reaction was probably due to the drug and particularly with the skin rashes, the ward pharmacist, in collaboration with the medical and nursing staff, should ensure that the patient's notes and future prescriptions are

marked appropriately and that the patient is aware of which drug they should avoid and why. Diarrhoea and rashes with newer drugs will also be identified in the same way by ward pharmacists, albeit less frequently. In such cases the reaction may well be worth documenting and reporting to the CSM.

Other drugs that may be prescribed to treat or alleviate the symptoms of adverse drug reactions, as listed in Figure 25, would also be worthy of similar investigation. It would also be valuable to compare the numbers and types of reactions identified by ward pharmacists in this way with the other means of identification as in Figure 26.

Reporting, documentation and follow-up of reactions

Once an adverse drug reaction has been identified the ward pharmacist in conjunction with the medical staff should decide whether it should be reported to the CSM and whether any particular follow-up is necessary. Reporting well established reactions, such as ampicillin or co-trimoxazole related rashes is of little or no value to the CSM. It might be argued that, if everyone reported such cases, it would reveal the true incidence of the reaction. However, this is naive because it is improbable that everybody will report, and accurate figures for the number of patients treated are not available. Furthermore, asking medical staff to co-operate in the reporting of such reactions might also irritate and alienate them from reporting more important cases.

On the yellow card the CSM requests reports of "all reactions to recently introduced drugs and serious or unusual reactions to other drugs" but

further guidance appears necessary from the author's experience. The following additional guidelines for reporting might be helpful to both pharmacists and medical staff:

i) All reactions associated with drugs marked by the black triangle symbol (▼) in the BNF[104], Data Sheet Compendium[105] and MIMS[124]. This symbol indicates that the product is recently introduced and special reporting to the CSM is requested. It was introduced in 1973 in an attempt to improve reporting, and new drugs, drugs with new indications, routes or formulations or new combinations of potent drugs are kept in this category usually for four years.

ii) Serious reactions associated with all drugs: examples include death and life-threatening events, such as anaphylactic or anaphylactoid reactions, any blood dyscrasia, hepatitis, jaundice, Stevens Johnson syndrome, SLE, renal failure, etc.

iii) Unusual reactions associated with any drugs - this is probably best interpreted as those not mentioned in the current data sheet for the product. This does not necessarily mean that the reaction has not been previously reported but, as the number of reports increases, the more likely the CSM are to insist on its inclusion in future data sheets.

iv) If there is doubt as to whether a report should be sent the rule should be "if in doubt - report"[62] or, if available, advice could be

sought from a local reporting centre such as the West Midlands Group.

Ward pharmacists should take the initiative and suggest that, if a reaction falls into one of the above categories, it should be reported. One of the main problems in persuading doctors to report is that a relationship between the drug and the adverse event is rarely clear cut and they are generally reluctant to report mere suspicions. If this is the case, the ward pharmacist should determine whether other likely causes have been excluded or are still being investigated. If they have been, or are not going to be excluded, the pharmacist must emphasise the importance of reporting events and, if necessary, should complete a yellow card themselves and then obtain the doctor's approval and signature before sending it to the CSM. As previously described, see Chapter 2 and Figure 6, this was done in 24% of a sample of reports coming from three hospitals in the West Midlands[86]. Clearly, the ward pharmacist will need both tact and skill when adopting this approach and it is probably desirable that they have already built a foundation of confidence and trust with the medical staff on their wards.

Reactions reported to the CSM should be as well documented as practically possible; however, from the author's experience of reports received by the West Midlands Adverse Drug Reaction Study Group the quality of reports leaves a lot to be desired. Although the yellow card looks straightforward to complete, the following may be useful points to consider when reporting a reaction:

i) Write legibly or print.

ii) Patient details - full name, hospital number, sex, age, body weight (and height or surface area with reactions to cytotoxic drugs).

iii) Relevant previous medical history and concurrent conditions, e.g. allergies, atopy, adverse drug reactions, renal function and liver function.

iv) Drugs - route, dosage, date started, indication, whether stopped as a result of reaction and exact timing with acute reactions, i.e. interval between giving drug and patient experiencing reaction.

v) Reaction - clear clinical description, timing, course of events, severity, outcome and treatment.

vi) Relevant laboratory findings - with units, normal ranges and dates, e.g. biochemical and haematological parameters and plasma levels of drug, if determined.

vii) Dechallenge/rechallenge - what was the effect of stopping the drug and, if attempted, the results of re-exposing the patient to the drug.

viii) Alternative causes of reaction - those excluded and those not excluded.

This list may look frightening but it is intended to assist rather than deter reporting. With increasing experience in case documentation the task should become easier and ward pharmacists should gradually gain confidence and an appreciation of what information is required.

In some cases particular follow-up can add considerably to the quality of a report and it may be worth waiting for such data before forwarding the yellow card to the CSM. Examples may include a more detailed drug history obtained from the general practitioner, exclusion of other possible causes and waiting sufficient time to assess the effect of drug dechallenge. Such follow-up can also be done by the ward pharmacist, particularly the drug history, but they must be aware that waiting a long time for data can take the impetus away from reporting.

The publication of a description of an adverse drug reaction in the literature can sometimes be of value. This is particularly the case when the reaction has not previously been published or if the case throws new light on an established problem. However, there should be reasonable grounds for suspecting that the drug has caused the reaction and the description should include the minimum information elements as outlined by Jones[97] and developed as a checklist, see pages 76 and 77. If the pharmacist has been involved in searching the literature or documenting and following up drug history or other details, the publication should list them as an author alongside the medical staff involved.

It may also be desirable in the case of non-generic medicines for a report of an adverse drug reaction to be sent to manufacturers as well as the CSM. Recently, the CSM has started to provide the ABPI with computer printouts of limited details from yellow cards (FO'X') for distribution to the appropriate member companies. However, this data is limited and there is a delay of about nine months before the manufacturers receive the information. If contacted for information about a possible adverse

reaction, the manufacturers may be able to provide useful data and comment, see Chapter 4, but they also have both legal and moral obligations to obtain further details. They will hence ask for clinical details, if contacted, and will probably send a form of their own for completion. If the pharmacist contacts a manufacturer, he or she should be prepared for such questions and have the necessary clinical facts available. Completing a second adverse reaction reporting form is a further chore, but it will assist the staff in the pharmaceutical company to evaluate their products and may be helpful to practitioners requesting information from them in the future. Companies are prepared to receive reports from pharmacists, providing they are well documented, but may wish to address certain questions to the doctor involved, notably his opinion on the causal relationship between product and reaction.

Prevention of adverse drug reactions

One of the basic reasons for pharmacists visiting the wards and monitoring patients' drug therapy is to help prevent adverse drug reactions. This is achieved in several ways. The pharmacist should ensure that each drug and its route of administration, formulation and dosage is appropriate to the individual patient's needs. These points require consideration of factors which might predispose patients to adverse drug reactions, for instance age, previous medical history, concurrent diseases, renal impairment, liver failure and other medications.

Ward pharmacists can make their task easier in some of these respects by asking the Clinical Chemistry Department to provide daily lists of

patients with specified abnormal values to facilitate their identification by the ward pharmacists[125,126]. This has been done at the Queen Elizabeth Hospital since 1979; results for patients with serum creatinine levels greater the 120μmol/l and serum potassium values of less than 3.5mmol/l or greater than 5.0mmol/l were produced from the Clinical Chemistry computer on a daily basis. The high levels of creatinine enabled identification of patients who had renal impairment and the ward pharmacists paid particular attention to the drugs and doses used in these patients, drawing any problems to the attention of the medical staff. Similarly, with the serum potassium results, if hyperkalaemia was identified the ward pharmacist would check that patients were not still receiving potassium salts or potassium sparing diuretics or both! Surveys conducted earlier at the same hospital showed that the prescribing of potassium or potassium sparing diuretics sometimes continued despite hyperkalaemia[127]. If hypokalaemia was identified, it would be checked that suitable potassium supplementation had been commenced and that the patient was not receiving more than one drug that could cause hypokalaemia. Soon after starting the daily clinical chemistry printouts it was noted that a surprising number of patients on the neurological ward were developing hypokalaemia. It was found that they were all patients with multiple sclerosis receiving corticotrophin (ACTH), together with a thiazide diuretic to prevent ACTH induced oedema. This combination was undoubtedly causing the hypokalaemia. This was pointed out to the medical staff and after discussion the thiazide diuretic was changed to amiloride, a potassium sparing diuretic, with a resultant decrease in the incidence of hypokalaemia on the ward.

Ward pharmacists can also help prevent adverse drug reactions by educating and advising medical and nursing staff. For instance, when a new or unfamiliar drug is used on the ward, the pharmacist should say what adverse reactions are recognised and when they are likely to occur. The ward pharmacist can also advise on how certain adverse drug reactions might be recognised at an early stage, e.g. by monitoring urine and renal function with potentially nephrotoxic drugs and by regular checking of the prothrombin time or ratio in patients receiving warfarin and drugs that might potentiate or inhibit its anticoagulant effect. In the case of drugs where a therapeutic range for plasma levels is established, the ward pharmacist should suggest when the measurement of such levels would be appropriate and advise on the interpretation of results. In this way the toxicity of certain drugs can be avoided, for instance aminoglycoside antibiotics, aminophylline and phenytoin.

Some of the above points were illustrated in a retrospective survey of gentamicin prescribing conducted by the author at East Birmingham Hospital in 1978. One-hundred-and-fifteen courses of gentamicin received by 101 patients were reviewed[128]; in five patients there were significant rises in serum creatinine consistent with the administration of gentamicin. In each case this was associated with excessive doses of the drug and/or unacceptably high serum levels. Such rises in serum creatinine are a sign of nephrotoxicity and should be recognised by ward pharmacists who should take appropriate action to reduce the dose of gentamicin. In the same study it was found that prescribed doses of gentamicin were far from optimal; patients of moderate to high body weight with normal renal function tended to receive too little, whereas patients with impaired renal

function frequently received too much. Out of 38 patients with renal impairment (serum creatinine >115μmol/l), 15 (39%) were given a dose greater than that recommended by the Mawer nomogram[129]. Gentamicin serum levels were determined in only 7 of these 15, the mean first trough level for this group was 5.9mg/l (range 4.2 to 8.4) and the mean first peak level was 10.8mg/l (range 6.1 to 14.0). Serum levels should have been determined in all these patients, and excessively high levels found in the 7 patients given doses greater than those recommended by the nomogram, confirm this. These patients were clearly at risk of gentamicin toxicity but this could be minimised by ward pharmacists ensuring that appropriate doses are prescribed and that serum levels are monitored.

Figure 25 : Examples of drugs that may be prescribed to treat or alleviate the symptoms of adverse drug reactions

Drug or group of drugs	Possible Adverse Drug Reaction treated
Antihistamines	Rashes and other allergic-type reactions
Potassium supplements	Hypokalaemia
Anticholinergic drugs	Extra-pyramidal effects
Antacids	Dyspepsia
Antiemetics	Nausea/vomiting
Purgatives	Constipation
Anti-diarrhoeal preparations	Diarrhoea
Vancomycin	Pseudomembranous colitis
Benzodiazepines	Agitation/insomnia
Diuretics	Oedema/fluid retention

Figure 26 : Ways in which Adverse Drug Reactions were identified by Ward Pharmacists

Means of Identification	No. of instances
Prescription changes:	
Drug discontinued	18
Dosage reduced	6
Timing of doses altered	1
Additions to therapy	8
Requests for information by:	
Medical staff	8
Nursing staff	1
Other professional contact with:	
Medical staff	14
Nursing staff	7
Patients	9
Other means:	
Recorded in notes	7
From bedside charts	2
Total	81

Figure 27 : Suspected adverse reactions identified by discontinuation of drugs

Drug discontinued	Suspected adverse reaction
amiloride	dehydration
amoxycillin	maculopapular rash
ampicillin	rash
ampicillin + cloxacillin	extensive erythematous rash
clotrimazole pessaries	vaginal irritation
co-trimoxazole	generalised erythematous rash
co-trimoxazole	rash
disopyramide	urinary retention
Eugynon 30	deep vein thrombosis
guanethidine	diarrhoea
indomethacin	haematemesis
lincomycin	diarrhoea
Madopar	nausea and dizziness
methyldopa	drowsiness
Moduretic	hyperkalaemia
phenytoin	dizziness and nausea
rifampicin	vomiting
Slow-K	coughing and inability to swallow

Figure 28 : Adverse drug reactions identified by ward pharmacists and subsequently reported to the CSM

Drug(s)	Adverse reaction
acebutolol	SLE syndrome
amiodarone	corneal microdeposits
benoxaprofen	photosensitivity
Minovlar	deep vein thrombosis
minoxidil	hirsutism
doxorubicin, cytarabine, thioguanine and prochlorperazine	agitation and restlessness - coincided with this chemotherapy regimen on two occasions

Figure 29 : Review of 38 inpatient prescriptions for antidiarrhoeal preparations

Antidiarrhoeal preparation	Reason for prescription				
	Diarrhoea possibly/probably due to:				Analgesia
	Drugs	Radiotherapy	Nutrition	Disease	
Codeine Phosphate (23)	2	1		4	16
Kaolin & Morphine Mixture (7)	6		1		
Lomotil (2)	1			1	
Loperamide (6)	1	2	1	2	
All preparations (38)	10	3	2	7	16

Figure 30 : Details of the ten cases of drug-induced diarrhoea

Anti-diarrhoeal preparation prescribed	Drug(s) probably or possibly causing diarrhoea
codeine phosphate	cephradine
codeine phosphate	Ferrogradumet
Kaolin and morphine mixture	cephradine
Kaolin and morphine mixture	cephradine
Kaolin and morphine mixture	ampicillin + flucloxacillin
Kaolin and morphine mixture	flucloxacillin + ferrous sulphate
Kaolin and morphine mixture	amoxycillin
Kaolin and morphine mixture	ferrous gluconate
Lomotil	Ferrogradumet
loperamide	amoxycillin

Figure 31 : Review of 14 inpatient prescriptions for chlorpheniramine

Indication for chlorpheniramine	Probable aetiology of indication
	Drug related
Skin rash and swollen jaw	Amoxycillin
Skin rash	Ampicillin
Diffuse erythematous macular rash on trunk	Ampicillin
Skin rash	Ampicillin
Allergic rash	Ampicillin
Rash on face and trunk	Erythromycin
Itchy rash	Frusemide
Skin rash	Lomotil
Erythematous maculopapular rash	Phenobarbitone
Skin rash	Phenytoin
	Not drug related
Pruritus	Eczema
Pruritis	Eczema
Rash	Senile pruritus
Pruritus	Starched bed sheets

CHAPTER 6

ADVERSE DRUG REACTION REPORTING IN AUSTRALIA

The arrangements for reporting adverse drug reactions in Australia are similar to those in the U.K. and a description[130] appears in "Monitoring for Drug Safety". The Australian Drug Evaluation Committee (ADEC) has a sub-committee known as the Adverse Drug Reactions Advisory Committee (ADRAC) which supervises the voluntary reporting of reactions. A blue reporting form, similar to the CSM yellow card, is used and the Committee also encourages public hospitals to submit discharge summaries concerning patients in whom an adverse drug reaction was suspected.

One way in which ADRAC differs from the CSM is that it seeks reports from pharmacists and recognises their role in hospital monitoring programmes[130]. The pharmacist's role in such schemes goes beyond recording data, the pharmacist acting as a monitor[131,132] in a similar way to those in the BCDSP. Another significant feature of ADRAC is that it provides better feedback to the professions. A cumulative list of reactions reported, which includes an assessment of causality, is published periodically in paperback[120]. There are also annual reports in the Medical Journal of Australia which briefly summarise the reactions notified and comment on matters of current interest. For instance the 1981 report, which appeared in January 1983, included notes on mianserin-associated white cell disorders, mebhydrolin agranulocytosis and neutropenia, immediate reactions to measles vaccine, sulphasalazine infertility,

bromocriptine and pleuropulmonary changes and possible carcinogenicity of commonly used drugs[133].

The role of the hospital pharmacist is clearly acknowledged by ADEC, the following passage appearing in their notes on adverse drug reaction monitoring in Australian hospitals:

> "In other hospitals, pharmacists - particularly ward pharmacists - are responsible for reporting to the Committee. Pharmacists in hospitals are an important resource in detecting, documenting and reporting adverse drug reactions. As ward pharmacists they may be the first to detect problems, and on noting changes in drug orders they may jog the conscience of the medical staff to ensure that adverse drug effects are adequately described in the progress notes. It is, however, important that they co-ordinate their activities in this field closely to those of their medical colleagues."

In some hospitals, e.g. Royal Brisbane Hospital, Royal Adelaide Hospital, Queen Victoria Medical Centre and Box Hill Hospital, there are simple alerting cards on which the medical or nursing staff record the patient's name and possible reaction to notify the ward or clinical pharmacist of a suspected adverse drug reaction[134,135]. In response to such a card, the pharmacist in some hospitals takes responsibility for reporting, completes a blue reporting form and forwards it to ADRAC[134]. Figure 32 shows the number of adverse reaction reports received by ADRAC from 1978 to 1981 inclusive[133]. Unfortunately, the proportion of the hospital reports

submitted by pharmacists is unknown, although it is thought to be high[134]. However, it should be noted that the percentage of hospital reports is consistently higher than in the U.K., nearly 50% in Australia, see Figure 32, compared to around 30% in the U.K., see Figure 8. This higher level of reporting from hospitals could be due to the efforts of pharmacists in Australia.

A comparison between reports submitted to ADRAC by doctors and pharmacists has recently been made by the 1982 I.C.I. travelling fellow from the U.K.[134,135]. A sample of reports received by ADRAC between January and September 1982 from 36 hospitals (maximum 3 per hospital) were assessed. Seventy-five reports from hospital pharmacists were randomly selected and matched for drug and adverse reaction with 75 reports from doctors. Each report was scored on eleven data fields - patient identification, age, sex, height, weight, treatment, outcome, sequelae, date of onset, drug therapy and adverse reaction description. One point was scored for each field except the last two which were marked out of three, thus making a maximum possible score of 15 for each report. It was straightforward to allocate an objective score in all but the last field, hence to avoid bias on behalf of the worker and to give a better judgment, the adverse reaction description was assessed as unsatisfactory, satisfactory or good by Dr. John McEwen, the secretary of ADRAC. The respective scores for the two groups are shown in Figure 33. Although the reports from doctors scored a slightly higher average mark, there was no statistically significant difference between the reports from pharmacists; the two areas where doctors did score rather more were patients' height and weight. Most important, and

perhaps surprising, was that the score for the description of the adverse reaction was identical for both groups. It can be concluded from this matched sample of blue cards that reports completed by hospital pharmacists are of equal quality to those submitted by doctors.

Figure 32 : Source of adverse drug reaction reports received by ADRAC (1978 to 1981)

Year	Source of Reports					Totals
	Hospitals	Private medical practitioners	Community pharmacists	Dentists	Others	
1978	1139 (47%)	1080 (45%)	103 (4%)	19 (1%)	67 (3%)	2408
1979	1309 (49%)	1077 (40%)	65 (3%)	18 (1%)	217 (8%)	2686
1980	1113 (44%)	1063 (42%)	90 (4%)	17 (1%)	220 (9%)	2503
1981	1118 (52%)	865 (40%)	68 (3%)	15 (1%)	98 (5%)	2164

Figure 33 : Scores allocated to a matched sample of reports submitted to ADRAC

Data field	Hospital Pharmacists' Reports		Doctors' Reports	
	score	percentage	score	percentage
Patient Identification	74	98.7%	73	97.3%
Age	73	97.3%	74	98.7%
Sex	73	97.3%	75	100%
Height	13	17.3%	40	53.3%
Weight	31	41.3%	43	57.3%
Treatment	64	85.3%	61	81.3%
Outcome	70	93.3%	71.5	95.3%
Sequelae	45.5	60.7%	50	66.7%
Date of onset	63.5	84.7%	64.5	86.1%
Adverse reaction description	147.5/225	65.6%	147.5/225	65.6%
Drug therapy	191/225	84.9%	198/225	88.0%
Total No. of reports	75		75	
Total score	845.5		897.5	
Average score	11.27 (75.2%)		11.97 (79.8%)	

CHAPTER 7

DISCUSSION AND CONCLUSIONS

Discussion

There is no such thing as a totally safe drug, the safety of a drug is always relative to its benefits or potential benefits. On one hand the serious adverse reactions frequently encountered with many cancer chemotherapeutic agents e.g. blood dyscrasias, severe vomiting and alopecia, are acceptable if these drugs can prolong life by inducing remission. On the other hand, such adverse drug reactions are unacceptable in treating minor illnesses or symptoms, i.e. the gravity of the condition being treated determines the margin of allowable risks. However, the mirage of a truly "safe" drug has dominated public expectations and Governments have responded by demanding ever more costly and time-consuming screening of potential agents before tests can be started in man[136]. Exactly what risks are acceptable cannot, therefore, be easily defined but risk is an inevitable fact of life and it is worth considering when action is taken outside the area of drug safety. Fatal incidents presenting risks of 1:1,000 per person per year or less, e.g. cigarette smoking and motorcycling, require immediate action to reduce such hazards, suggesting that this level is socially unacceptable. Fatal incident levels of 1:10,000 per person per year cause public money to be spent for their control and fatality risks of 1:100,000 per person per year are still considered candidates for action[137]. Certain very rare serious adverse drug reactions, e.g. chloramphenicol-induced aplastic anaemia which has an incidence of

approximately 1:30,000, can alter doctors' attitudes and prescribing habits. In the case of chloramphenicol, it is now infrequently prescribed in the U.K. and U.S.A. for minor or moderately severe infections because there are effective and "safe" alternatives but in Haemophilus influenzae meningitis, which is rapidly fatal, it is still used as the risk appears acceptable in the light of the severity of the condition.

It is only possible to identify the common adverse reactions of a new drug from clinical trials, hence monitoring must continue after it has been marketed. This has been borne out over the years, notably with practolol, more recently with benoxaprofen (Opren) and very recently (March 1983) with zomepirac (Zomax)[138]. There have also been recent examples in other countries, e.g. ticrynafen (Tienilic Acid) was withdrawn in the U.S.A. in 1980 due to hepatitis which occurred in approximately one in 500 patients but which required tens of thousands of patients' experience before the relationship was identified[139]. However, the withdrawal of a drug is fortunately a rarity and exemplifies the extreme situation. What happens more often is that the true adverse reaction profile of a drug slowly emerges over its first few years on the market and, as it does, this is recorded in the data sheet and standard reference texts.

The current methods of monitoring adverse drug reactions fail broadly in two ways; firstly some do not detect previously unrecognised adverse reactions and, secondly, others are slow to identify new reactions. Following the experience with practolol, a lot of attention was paid to postmarketing surveillance schemes[26,27,28,29,140] but none of these

proposed schemes, independent of the pharmaceutical industry, has actually materialised. Dr. Inman's scheme[31], based on his earlier ideas[26], commenced as a pilot study only in 1981/1982. In the meantime, pharmaceutical companies have been organising their own PMS schemes. In adverse drug reactions it has been recognised that "bias exists everywhere but the difference is that the bias of the drug industry is always in one direction"[141] and it would not be surprising to find this where an interested party (a pharmaceutical company) is looking at the safey of its own product. There has certainly been criticism of industry based PMS, a recent example being the suggestion that the in-house surveillance study for Kalspare (chlorthalidone + triamterene) was a "marketing ploy"[142]. A recent survey of sixty PMS schemes organised by pharmaceutical companies showed them to be ineffective compared with spontaneous reporting in producing hypotheses related to previously unknown adverse drug reactions[30]. Their use in accurately quantifying previously known reactions was also found to be limited[30]. PMS must be conducted by bodies independent of the pharmaceutical industry if it is to appear free from such bias but such bodies have been slow to come forward and prove themselves effective. Even then, PMS may still only be of limited value and it will not detect very rare reactions.

The second type of failure is that very large numbers of patients are exposed to a drug before hazards are identified and publicised. This was particularly the case with benoxaprofen which came to the market in a blaze of publicity including radio and newspaper articles telling patients that it was a major advance in the treatment of arthritis and encouraging them to ask their doctor to prescribe it[143]. The explosive

marketing of Opren resulted in an estimated 500,000 patients receiving the drug in the two years it was on the U.K. market[144] before its product licence was suspended on 4th August 1982. In this period the CSM had received 3,500 reports including 61 deaths[145] before the action was taken. It could be argued that the CSM were slow to act and this was the view given in the first of the two BBC Panorama programmes entitled "The Opren Scandal". Although the common side effects of benoxaprofen, notably photosensitivity and onycholysis, were recognised fairly early, their high frequency was not fully appreciated. However, it was not until April and May 1982 that the first deaths of elderly patients due to cholestatic jaundice associated with benoxaprofen were reported in the literature[146,147], although these were quickly followed by other reports. The number of reports received by the CSM indicated that the yellow card system had worked but with better reporting both in terms of quantity and quality the problems would have been recognised earlier.

The same failing appears to have occurred with zomepirac, although it is too early for really objective comment. An estimated one million patients in the U.K. and 20 million worldwide had received the drug before its withdrawal by the manufacturers on 7th March 1983 because 1,100 reports of side-effects in the U.S.A., including five deaths from anaphylactoid reactions, in patients taking the drug[138]. Surely the problem should have been identified well before these numbers of patients had been reached? About two weeks following the withdrawal of zomepirac it was said that the CSM had received 512 reports of adverse reactions, five of which were fatal[148] but there had been some

earlier warning signals. Several anaphylactoid reactions to the drug were reported in American journals[149-153], the first being in April 1981[149], and in November 1982 the manufacturers wrote to doctors in the U.K. about the possibility of hypersensitivity reactions to the drug[138]. The West Midlands Group had also received ten reports of acute anaphylactoid or urticarial reactions[154] but they were unsuccessful in getting a letter about these published in either the British Medical Journal or The Lancet in December 1982. It is likely that zomepirac will be re-introduced[148] but better voluntary reporting would have led to earlier recognition and quantification of the problem of anaphylactoid reactions and may have avoided the sudden and dramatic withdrawal of the drug.

The delay in recognising adverse drug reactions sufficiently serious to necessitate withdrawal of practolol, benoxaprofen and zomepirac and serious adverse reactions with many other drugs must be overcome to prevent damage to patients, reduce the costs of such damage and avoid loss of patient confidence and litigation. Postmarketing surveillance schemes are both ineffective and expensive, although Inman's scheme at Southampton may be suitable for a limited number of new drugs. A scheme such as the BCDSP is very expensive, will not provide a rapid meaningful answer and can also handle only a few drugs. The simplest, most effective and cheapest solution is to improve the voluntary reporting of adverse reactions, which in the U.K. means improving the yellow card system. This system has had its critics over the years and recently Venning[158] noted that it made no contribution to the first alerting of 18 important adverse reactions studied by him and reported

in a series of articles[155-159]. However, in response to this, the yellow card system was defended by Inman[41] who noted that only three of the drugs quoted by Venning could have been tested by the system. Furthermore, although there was a serious failure with practolol, this occurred not because of any fault in the system but because people did not use it[41]. The yellow card system is a vital source of data on adverse drug reactions and it is the only way of identifying rare reactions. The problems are that gross under-reporting persists and more could be done with the data collected.

One possible way of increasing the number of reactions reported to the CSM would be to make reporting by doctors mandatory. Reporting has been compulsory in Sweden since 1975 and this produced a 25% increase in reports; since 1973 it has been compulsory to report fatal or life-threatening reactions in Norway and this was extended in 1979 to include new or unexpected reactions and those leading to serious sequelae[160]. However, such a move would almost certainly antagonise doctors in the U.K. and would not have the desired effect or improve the quality of the yellow cards received. Improvement, however, could be achieved in other ways, both in the number and quality of reports. Some of these methods will be proposed and developed. Firstly, the system for collecting reports should be devolved to the Regions in a manner similar to the West Midlands Group whilst retaining centrally the prime responsibility for analysis of reports. Secondly, pharmacists should be more involved in the reporting process, initially by encouraging doctors to report and document cases but in some instances by identifying reactions and taking responsibility for reporting themselves. Thirdly, by

improving arrangements at the CSM to cope with the increased volume of reports but more particularly to speed up analysis of data and provide good quality, rapid feedback to practitioners.

The case for regionally devolved, adverse reaction, reporting schemes can be built around the work of the West Midlands Group over the past ten years as previously described in Chapter 2. This has been successfully followed by Leicester (Appendix 4), the Northern Region (Appendix 5) and most recently by Wales[93]. There is evidence that regional groups have increased the number of adverse drug reactions reported; this has been achieved by heightening awareness, involving pharmacists and making reporting easier, possibly even by telephone[42]. The quality of reports should also improve as a result of local follow-up. Local feedback in the form of bulletins, etc., would be welcomed by doctors and pharmacists and would give a further incentive to reporting. Feedback to physicians, showing that their reports were being carefully observed and evaluated, was considered important by Koch-Weser et al[161]; continued emphasis on adverse drug reactions probably increasing the index of suspicion and focussing attention on the problem.

The above suggestion serves to improve the collection of data; local analysis may be of some value but it is essential that reports are quickly passed on from the Regions to the CSM for central analysis. Regional schemes are in no way a substitute for the CSM, their role is to enhance it. Such schemes only exist at present where there has been considerable local interest and pressure to set up a system. If they are to be implemented by all other Regions in the current financial climate

some incentive will have to be offered. Money would need to be provided to fund schemes in some Regions and a case would have to be made for this, but they should not be very expensive. For several years the West Midlands Group consisted of a Staff Pharmacist half-time and the part-time contribution of a lecturer in clinical pharmacology. The least costly and perhaps most effective way to set up a new regionally devolved, adverse reaction reporting scheme would be to base it in a Regional Drug Information Unit. Links with clinical pharmacologists may already exist but, if not, they would need to be established for the assessment of reports and to demonstrate that the scheme was a joint venture between doctors and pharmacists. The scheme that has developed in Leicester over the past five years is an excellent example of how limited local resources can be used effectively to centralise reporting, provide feedback and involve clinical pharmacologists (see Appendix 4).

Some pharmacists will clearly be involved directly in organising and running Regional schemes, their role being that of providing drug information, encouraging reporting and preparing bulletins and other feedback, etc. This should stimulate other hospital pharmacists to accept a role in adverse drug reaction monitoring and reporting at a more local level. All drug information pharmacists have a key role to play in regionally devolved reporting schemes judging by experience in the West Midlands where they were the most active members of the Group and provided a stimulus to reporting at hospital level. Drug information pharmacists must be aware of the available information sources on adverse drug reactions and appreciate the scope and

limitations of these, see Chapter 4. They must also realise the anecdotal nature of many published adverse reaction reports and adopt a critical approach to these, the minimal information elements proposed by Jones[97] and developed in this thesis could be useful in this respect. Around 20% of enquiries to Drug Information Centres concern adverse reactions, see Chapter 4, hence this is an important method of identifying cases and encouraging reporting. Yellow cards were completed following about 10% of adverse reaction enquiries to the Drug Information Centre at Good Hope Hospital, see Figure 23. Perhaps this would be a reasonable ratio of adverse reaction enquiries to reports for other centres to aim for and, if achieved nationwide, it would result in a substantial increase in reporting.

Ward pharmacists can also make a vital contribution whether or not a Regional scheme exists. They need to be aware that 3 to 5% of acute admissions are due to adverse drug reactions[51-56] and they should be alert for such patients being admitted to their wards. They must also recognise that adverse drug reactions commonly occur in hospitalised patients[53,54,57,59,60] and should know how to identify such reactions. For instance, by noting medication changes (discontinuation of drugs and dosage reductions) and certain additions to therapy, also that requests for information from medical or nursing staff and patient contact may reveal reactions, see Chapter 5. Ward pharmacists are in a good position to identify adverse reactions because they are near to the nursing staff and patients and should be in close contact with medical staff. In a recent review of clinical pharmacy services from Edinburgh, 51 out of a total of 331 queries (15.4%) handled by clinical pharmacists concerned

adverse effects[162], the highest proportion being from the medical unit (21.8%). Far more adverse effect queries arose when pharmacists were on consultant ward rounds, both medical and surgical, in comparison to ward pharmacy visits[162]. This illustrates the importance of pharmacists attending ward rounds but may also mean that the ward pharmacists were missing some adverse effects that they should have encountered on normal ward visits. The system in some Australian hospitals where medical or nursing staff use a simple alerting card to notify the ward pharmacist of a suspected adverse drug reaction should rectify this and would be well worth trying in U.K. hospitals (see Chapter 6).

When an adverse reaction has been identified, the ward or drug information pharmacist should assess whether a report is appropriate. The guidelines on pages 101 and 102 could be useful in this respect but, if necessary, the regional reporting centre could be consulted. Where a report is appropriate, the pharmacist should suggest this to medical staff or complete a yellow card themselves and then obtain the doctor's approval and signature. Experienced hospital pharmacists could be given responsibility for reporting adverse drug reactions themselves, see also below. Judging by the comparison of reports received from doctors and pharmacists in Australia, this should not detract from the quality but may well increase the quantity of reports, see also Chapter 6. If hospital pharmacists did take on this responsibility, the reporting must still be done in conjunction with the medical staff who should at least be aware that a report has been sent. This approach could be regarded as controversial in the U.K. but it appears to have worked well in Australia.

However, before pharmacists could report reactions themselves, a change of policy at the CSM and a wider recognition of the pharmacist's role by doctors and their professional bodies is needed. Both of these points are probably major obstacles to pharmacists reporting reactions, whereas motivation, ability and local agreement are generally not. From the national survey, Chapter 3, there is no doubt that pharmacists want to be more involved in adverse reaction monitoring and reporting. As there is now more and more clinically orientated postgraduate education for hospital pharmacists, an increasing number should be capable of making good reports. However, there is probably a need for short specialised courses in completing yellow cards but these could be organised by the Regional groups. One further problem is that managers and administrators may see the increased role of pharmacists in this area as requiring additional manpower which they would be reluctant to fund at present. Any increased involvement would probably have to come from within current establishments which means that pharmacists would have to work harder, manage their time better or relinquish some more traditional roles, such as manufacturing or outpatient dispensing. It may be difficult to argue locally for more staff to support increased involvement as the benefits would be more likely to be felt nationally, although a link-up with local audits of drug usage may be beneficial. To justify an increase in pharmacy establishment would probably also require more involvement in other clinical areas, such as pharmaco-kinetic monitoring, patient counselling and total parenteral nutrition.

The CSM has been a target of much criticism over the years but this is not surprising as, whatever decision they make, it will not please

everyone. Media interest has also increased, every hint of a possibly dangerous side-effect is now widely broadcast with varying degrees of competence and responsibility. A number of Members of Parliament also keep a close watch on such situations and make various speeches about protecting the public. The CSM certainly does not have sufficient resources to achieve what many of its critics think it should; however, this is not a criticism of the CSM but of Government for not providing adequate funds. Mr. Jack Ashley M.P. has a point when he compares the trifling £1 million spent on the CSM per year with the £1,000 million spent on the drugs that it monitors[163]. Professor Finney, a member of the Adverse Reactions Sub-committee since 1964, makes a similar point in a recent paper[8] and a letter to "The Times"[164] in which he tells how proposals to obtain proper computer facilities to handle the extensive records at the CSM were repeatedly refused or delayed indefinitely for reasons of cost. Finney goes on to say "if we are to have a proper system for protecting the community from drug dangers (which are bound to arise from time to time) we must recognise that the operation cannot be run on a shoestring"[164]. The message is clear, if the government wants to help drug safety by improving the CSM, they must be prepared to pay for it. The most cost effective method of improvement would be to improve the yellow card system. Improved feedback to practitioners, both in terms of speed and quality, would be welcomed and would be a further stimulus to better reporting.

In the parliamentary debate on Opren (27th January 1983) the Minister for Health revealed that the CSM was actively considering the possibility of accepting adverse reaction reports from pharmacists to add to the

data that was received from doctors[163]. This statement is to be welcomed, as it may signal a change in attitude but "actively considering" does not necessarily mean that the response will be positive. Furthermore, how prepared is the profession to accept this responsibility? From the evidence presented herein, hospital pharmacists, particularly drug information pharmacists and ward pharmacists, have shown both interest and capability in this respect and would perform the task well. However, the national survey (Chapter 3) showed that monitoring schemes involving pharmacists were not planned in the majority of areas, even over the next five years.

Close liaison with medical staff is important in order to continue and possibly enhance a good professional interface and to check whether diseases which could have caused the adverse event have been excluded. For instance, it would be folly to report a case of hepatitis as being drug-induced until any results from virology requested to exclude hepatitis B, and possibly hepatitis A, had been returned. As ADEC acknowledges in the notes on pharmacists reporting reactions in Australia - "it is, however, important that they (pharmacists) co-ordinate their activities in this field closely to those of their medical colleagues", see Chapter 6. When pharmacists complete yellow cards themselves, the reports must be of at least equal quality to those submitted by doctors, hence it may be better initially to restrict reporting to experienced drug information and ward pharmacists. After a period of such restriction, reporting by pharmacists should be assessed as other hospital pharmacists are trained in the role. If the profession is given the responsibility, it must not fail in carrying it out with competence. There is now a strong

case for the implementation of at least a pilot scheme where hospital pharmacists in the U.K. are allowed to report reactions to the CSM themselves.

The monitoring and reporting of adverse reactions by general practice pharmacists is, however, a different matter, although this is even more important in the community, as around 90% of drug usage is outside hospitals. The main involvement of U.K. general practice pharmacists in adverse reaction monitoring previously envisaged, is the identification of patients on certain drugs, i.e. the compiling of a cohort[28,165,166]. There is no reason why pharmacists could not do this but it is only a clerical function and hardly demanding of professional responsibilities. What further role could they play? In Australia, community pharmacists can report adverse drug reactions to ADRAC but, as can be seen in Figure 32, the number of reports received is low, less than 100 per annum. Very little is published describing the role of community pharmacists in the U.K. monitoring adverse drug reactions. Shulman et al[167] described a system which involved keeping patient medication record cards and recording allergic reactions, the prescription of two or more drugs known to interact and drugs used when contraindicated. One of the aims of such recording was to prevent adverse drug reactions. Such a system is highly commendable and in 53 cases, over a three-year period, the general practitioner changed the prescription after being contacted by the pharmacist.

In a survey of 453 general practitioners, only 3.9% stated that they would use pharmacists as a source of information on adverse effects and

contra-indications[168]. The same survey showed that the most popular source of such information was MIMS[124] (75.7% of respondents[168]). This was most surprising as MIMS does not list adverse reactions! It also clearly showed that general practitioners cannot have much regard for pharmacists' knowledge about adverse drug reactions but at the same time they cannot be very discerning themselves. Another, more recent, survey of 131 general practice pharmacists in Northern Ireland[169] showed that they frequently provided information to patients about adverse drug reactions but considerably less often to other health care professionals. The first step towards community pharmacists having a greater role in adverse drug reaction monitoring and reporting must, therefore, be to improve the interface with general practitioners and obtain recognition of their role as providers of drug information. This will take motivation and effort and many such pharmacists will require further education and training in the field.

Another vital step towards an increased role for the community pharmacist is the keeping of patient medication records. Drug histories recorded for 51 patients admitted to hospital were compared with the medication records kept by a general practice pharmacist in Ross-on-Wye[170]. The two records provided identical information in 43% of cases, the pharmacist's record cards were more informative in 30% and less informative in 28%. This small study thus showed a potential contribution that such records could make but the full value will not be realised until there are much closer links between community pharmacists, their hospital colleagues and general practitioners.

The general practice pharmacist is likely to identify possible adverse drug reactions in similar ways to ward pharmacists, e.g. by noting changes in patients' medication and new prescriptions for antihistamines, etc., see Chapter 5. When this occurs, the pharmacist should notify the general practitioner and, if appropriate, suggest that a yellow card be completed. Only if this becomes a common practice and the general practitioner recognises the pharmacist's interest and role can the latter be allowed to report. It is even more important than in hospitals for community pharmacists to co-ordinate their activities with doctors, as it is likely that they will be unaware of relevant facts concerning cases of suspected adverse drug reactions. Before general practice pharmacists should be involved in reporting, there is a need for them to accept medication record keeping as the norm, to develop closer professional relationships with general practitioners and to undergo more clinically orientated education and training.

The most feasible scheme for general practice, and possibly even for hospitals, would perhaps be to have a system of "special reporting" for a small number of drugs. The normal yellow cards could be used in the same way but pharmacists and doctors should be particularly alert for any adverse events occurring in patients on the chosen drugs, thus lowering the threshold for reporting. The drugs chosen would be recently marketed, new chemical entities, probably with a rapid uptake by patients, i.e. like benoxaprofen, and would stay in the "special reporting" category for a period of 2 to 3 years. A system along these lines called the Intensified Adverse Drug Reaction Reporting Scheme (IADRRS) exists in New Zealand and has included drugs such as perhexiline, sodium

valproate and cimetidine[171]. The event profiles that IADRRS has shown for these drugs in New Zealand are very similar to those which have emerged in the world literature[171]. Unfortunately, the time scale that the New Zealand scheme would take to provide a warning or give an assurance of safety is too long because of the limited population exposed to the drugs in that country. However, such a scheme would provide a much quicker answer in the U.K. and would merit a pilot study which included the involvement of pharmacists.

Conclusions

Hospital pharmacists can make a useful contribution towards the monitoring and reporting of adverse drug reactions by several means. Ward pharmacists have been shown to be capable of identifying reactions and can encourage reporting to the CSM at ward level. They can certainly act as a catalyst in this respect but could also be given responsibility for completing yellow cards themselves. Pharmacists in Australia have proved themselves capable in this respect and a pilot scheme where experienced U.K. hospital pharmacists are allowed to report reactions to the CSM is proposed. Drug information pharmacists have an important role in providing useful and critical answers from the mass of available information on adverse drug reactions. When questions concern specific patients, they can also encourage the reporting of cases and may similarly be given the responsibility for reporting in some instances.

Further devolution of the yellow card scheme along the lines of the West Midlands Group is desirable. This would increase the number of reports and improve their quality whilst retaining the main responsibility for analysis of data with the CSM. The devolution would be best achieved through the Regional Drug Information Centres with some involvement of clinical pharmacologists. Close collaboration is needed between the ward and drug information pharmacist and between the latter and regional reporting centres. However, the pharmacist's role must not be seen in isolation, they must co-ordinate their activities with the appropriate medical staff.

In the U.S.A. it has been suggested that hospital pharmacists should spearhead an organised programme to reduce the complications of drug therapy, the pharmacist becoming a strong and effective third force so that optimal drug services will be acceptable to physicians and available to patients[172]. This suggestion could also be adopted in the U.K. and many hospital pharmacists are keen to do more, both in terms of reporting and preventing adverse drug reactions. Some have shown their capabilities in these respects, but more planning is required to progress on a wider front and achieve full recognition of the pharmacist's role. The development of a parallel role for general practice pharmacists will be slower as certain fundamental steps, such as keeping patient medication records, improving the interface with general practitioners and receiving more clinically orientated education, have yet to be widely taken.

LIST OF APPENDICES

APPENDIX 1 : CSM yellow card

IN CONFIDENCE — REPORT ON SUSPECTED ADVERSE REACTIONS

1. Please report all reactions to recently introduced drugs and serious or unusual reactions to other drugs. (Vaccines, dental or surgical materials, IUCDs, absorbable sutures, contact lenses or associated fluids should be regarded as drugs).
2. Record on the top line the drug you suspect of causing the adverse reaction.
3. Record all other drugs, including self medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Do not be deterred from reporting because some details are not known.
5. Please consider the possibility of interaction.

NAME OF PATIENT (To allow linkage with other reports for same patient. Also give record number for hospital patient)	SEX	AGE OR DATE OF BIRTH	WEIGHT

DRUGS* (Give brand name if known)	ROUTE	DAILY DOSE	DATE STARTED	DATE ENDED	INDICATIONS
*For Vaccines give Batch No.					

REACTIONS	STARTED	ENDED	OUTCOME (e.g. fatal, recovered)

ADDITIONAL NOTES

REPORTING DOCTOR

Name.....

Address.....

Tel No. .....

Signature.....

Date.....

APPENDIX 2 : Sample page from West Midlands Adverse Drug Reaction Study Group Bulletin (No. 14, January 1982)

NERVOUS SYSTEM

I Drug	II No. of Reports received	III Description of Reaction	IV Other drugs possibly responsible	V Contributing factors	VI Classification (Degree of certainty)	VIII Hospital reporting reaction
Amitriptyline	3	Status Epilepticus, 2° twilight state			A1	Manor, Walsall
		Loss of co-ordination Depersonalisation, slowing of thought and action			A1	G.P.
		'Pins & needles' in left hand		Carpel Tunnel Syndrome	B	G.P.
Buprenorphine	2	Withdrawal syndrome			A1	G.P.
		Itching, erythematous rash covering whole body			C	Selly Oak
Carbamazepine	2	Generalised erythematous rash			A1	Dudley Road
		Neutropenia, diplopia, nausea, vertigo	Erythromycin	Toxic levels of carbamazepine	C A1	Good Hope
Chlorpromazine	1	Agranulocytosis - fatal	Fluspiriline		A1	Manor, Walsall
Clopenthixol	1	Cholestatic jaundice			A1	East Birmingham
Dothiepin	1	Generalised urticaria			A1	Highcroft
Droperidol	2	Epileptiform fit			A1	Solihull
		Hypotension	Papaveretum		A1	Dudley Road
Enflurane	2	Renal failure	Tobramycin		C	Q.E.H.
		Renal failure	Tobramycin		C	Q.E.H.
Fluphenazine	1	'Bright' vision, blushing, feeling of embarrassment			C	G.P.

APPENDIX 3 : Key to Table of Reported Reactions

1. Drugs are grouped according to the body system they act on - as in the BNF - and they are listed by their approved names.

2. If more than one drug could have been responsible for the reaction, the reaction is listed under the drug most likely to have caused it, and the other drugs are listed in column IV.

3. Drug interactions are listed under both drugs.

4. CLASSIFICATION

   A - Causal relationship probable - appropriate time sequence, etc.

   A1 - reaction previously well documented.

   A2 - reaction not established.

   B - Causal relationship unlikely

   C - Insufficient data for classification or other cause cannot be excluded.

   D - Drug interactions

   D1 - probable or well known

   D2 - possible or not established

APPENDIX 4 : The local adverse drug reaction reporting scheme in Leicester

Since 1978 staff at the Drug Information Centre, Leicester Royal Infirmary, have actively encouraged and centralised the reporting of adverse drug reactions in a similar way to the West Midlands Group. Yellow cards with self-addressed envelopes attached are distributed to three district general and two psychiatric hospitals and, when completed, are returned to the Drug Information Centre. Each report is scrutinised for completeness and acknowledged, together with a brief review of the literature concerning the adverse drug reaction reported. The quality of this feedback is good, it involves an explanation of likely mechanisms and references to previous similar reports including others on file. Over 90% of the reports received are from hospitals and it is estimated that pharmacists are involved in about 50% of them. The scheme has been described by Hudson[173,174].

The number of reports dealt with since the inception of the scheme is shown in Table 1 along with the number of reports received by the CSM from hospitals in Leicester. There was a substantial increase in the number of reports to the CSM in 1979 and 1980, the latter being estimated from figures provided in September 1980, see Table 1. This could be explained by the existence of the local reporting scheme from 1978 onwards. Unfortunately, final figures for 1980 and those for 1981 and 1982 were not available from the CSM.

Table 1 : Hospital reporting of adverse drug reactions in Leicester

Year	No. of reports received by Leicester Drug Information Centre	No. of reports received by CSM from hospitals in Leicester
1973		12
1974		14
1975		33
1976		19
1977		33
1978	21	39
1979	36	65
1980	64	65 (estimated)
1981	53	unknown
1982	57	unknown

Since January 1982, a further development has been to include a formal input by local clinical pharmacologists[174]. Their role has been to assess causality in selected reports (20 out of 57 in 1982) according to the specific operational criteria of Karch and Lasagna[4]. The reports are classified as "probable", "possible", "unlikely" or "conditional" and, should additional clinical or drug information be required for this assessment, the request is relayed back through the Drug Information Centre.

Other features of the scheme include a yellow sheet (white copy overleaf) explaining why reactions should be reported and how this is done. There is also a written procedure to advise the local hospital pharmacists how to deal with reports and an annual list of reported adverse drug reactions is produced. The quality of the reports has improved since the start of the scheme[175] and it is interesting to note that four out of the 20 reports assessed by a clinical pharmacologist in 1982 have been published[176,177,178,179].

Do you suspect an ADVERSE DRUG REACTION?

* 10 - 15% of all acute medical inpatients suffer an adverse effect to their medication

* Drug reactions that we know little about should get reported to the Committee on Safety of Medicines (CSM). Currently the CSM receive notification of only about 10% of all reactions that ought to be reported

WHY REPORT?

* Knowledge of the side effects of new drugs is unavoidably incomplete during the first few years after they have come onto the market.

  Clinical trials to demonstrate the effectiveness of a new drug involve relatively small numbers of patients, so do not necessarily pick up uncommon side effects.

  Some adverse effects only occur after patients have been taking the drug for several years.

  Clinical trials may not include special groups of patients such as the elderly or those with several diseases.

  Adverse reactions often resemble naturally occurring disorders and so may be difficult to recognise.

* If doctors report their suspicions the large amount of data collected can help provide estimates of how common a particular reaction might be.

WHAT SHOULD DOCTORS REPORT?

* New drugs, especially those with a ▼ in the BNF or drug data sheet.

  Even minor symptoms with these drugs ought to be reported.

  Even suspicions should be reported. If in doubt, report.

* Serious or unusual reactions to older drugs, but not common less serious reactions eg penicillin rash.

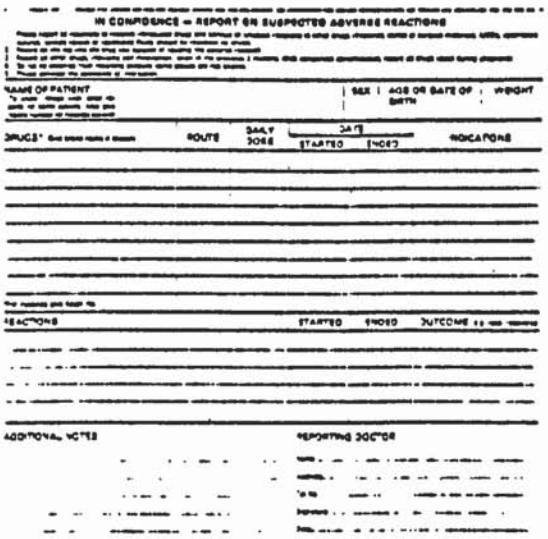
  If in doubt, contact a pharmacist or ring the Drug Information Centre, Leicester Royal Infirmary, Ext 491.

* Unexpected symptoms arising from drug overdosage can be reported to the CSM and these will be passed on to the National Poisons Information Service.

Do you suspect an ADVERSE DRUG REACTION?

For HOW TO REPORT see overleaf

HOW TO REPORT



* The CSM supply YELLOW CARDS for this purpose. These should be available on all wards. Supplies can be obtained from the Pharmacy Department or from the Drug Information Centre, (Leicester Royal Infirmary, Ext 491).

* The yellow card should be filled in completely with all relevant details as requested on the card.

Any pharmacist or the Drug Information Centre will be pleased to help

Please return the yellow card to the Drug Information Centre in the envelope attached to it. This is to enable a local record of adverse reactions to be maintained.

* Your adverse reaction report will be acknowledged with a report from the Drug Information Centre and your findings will be forwarded to the Committee on Safety of Medicines.

* CONFIDENTIALITY will be retained within the scheme, as it is by the Committee on Safety of Medicines.

By contacting any PHARMACIST or the DRUG INFORMATION CENTRE, up to date published and unpublished information on particular adverse drug reactions can be obtained.

YOU CAN HELP towards this scheme and WE CAN HELP YOU

LEICESTERSHIRE HOSPITALS DRUG INFORMATION SERVICE
in conjunction with - Leicestershire Hospitals Pharmacy Service
The Departments of Medicine and Therapeutics, University of Leicester
The Department of Clinical Pharmacology, Groby Road Hospital

APPENDIX 5 : Adverse drug reaction reporting in the Northern Region

A regional adverse reactions reporting scheme similar to the West Midlands Group was started in the Northern Region in June 1981. The scheme is organised by the Regional Clinical Pharmacology Unit and the Regional Drug Information Service, both of which are housed in the Wolfson Building, Royal Victoria Infirmary, Newcastle-upon-Tyne. Doctors are asked to report suspected adverse reactions on re-addressed yellow cards which are returned to the Wolfson Unit for assessment, follow-up and local feedback and are then passed on to the CSM. Feedback has been provided in the bi-monthly "Drug Newsletter" and a list of drugs regarded as "new" for the purpose of adverse reaction reporting is provided.

Doctors are also encouraged to report by telephone, in which case a yellow card is prepared and sent to the reporting doctor for signature and insertion of any missing items. The number of reports received is shown below and summaries of the first one hundred and later of the second hundred reports have also been produced.

The philosophy behind a regional reporting scheme as outlined when the scheme was launched[180] are worth noting:

1. Regional reporting can be publicised widely and repeatedly by existing lines of communciation within the Region, at minimal cost and such publicity should significantly increase the number of cases notified on yellow cards.

2. It will complement and improve the Region's existing information services dealing with adverse reactions, acute poisoning and drug therapy.

3. It will produce information that can be linked with Regional figures on drug usage, enabling the incidence of adverse reactions to be calculated more accurately than has usually been possible in the past.

4. It will facilitate research on particular adverse reactions.

Number of reports received by Northern Regional Scheme

Dates	No. of reports received	Breakdown of reports		
		G.P.s	Hospitals	Others
June 1981 - June 1982	340	166	172	2
July 1982 - April 1983	319			
Total (in first 22 months of scheme)	659			

Pharmaceutical Officer's
Name and address

APPENDIX 6 : Questionnaire

Please tick the appropriate box for each question

1. Supply of C.S.M. yellow cards ?

1.1. Do the pharmacy departments in your Area keep a supply of yellow cards ?

YES ☐ SOME ☐ NONE ☐

1.2. Are yellow cards available on the wards in hospitals in your Area ?

YES ☐ SOME ☐ NONE ☐

1.3. Do ward pharmacists in your Area carry a small supply of yellow cards ?

YES ☐ SOME ☐ NONE ☐

2. Completion of C.S.M. yellow cards ?

2.1. Do pharmacists in your Area ever recommend that reports of adverse drug reactions should be sent to the C.S.M. ?

FREQUENTLY ☐ SOMETIMES ☐ RARELY OR NEVER ☐

2.2. Do pharmacists in your Area ever complete a yellow card themselves and then obtain the doctors' signature ?

FREQUENTLY ☐ SOMETIMES ☐ RARELY OR NEVER ☐

2.3. Are pharmacists in your Area informed by the medical staff of reports sent to the C.S.M. ?

FREQUENTLY ☐ SOMETIMES ☐ RARELY OR NEVER ☐

2.4. Do you attempt to channel reports to the C.S.M. via a pharmacy department or drug information unit in your Area ?

YES ☐ NO ☐

If YES about how many reports a month go to the C.S.M. in this way ?

3. Adverse drug reaction monitoring schemes

3.1. Do any schemes exist in your Area whereby pharmacists are involved in:

a) encouraging reporting of adverse reactions to the C.S.M. ? YES ☐ NO ☐

b) monitoring patients on a particular drug or drugs ? YES ☐ NO ☐

c) other adverse reaction monitoring schemes ? YES ☐ NO ☐

If YES to 3.1 (a) (b) or (c) please could you give brief details of the pharmacists role.

3.2. Are any monitoring schemes involving pharmacists planned?
YES (IN THE NEXT YEAR) ☐ YES (IN THE NEXT 5 YEARS) ☐ NO ☐

3.3. Would you like to see your pharmacists more involved in:
Adverse drug reaction reporting to the C.S.M.? ☐
Other schemes for monitoring adverse reactions? ☐
How do you think this might be achieved?

3.4. Are there any pharmacists with a particular interest in adverse drug reactions employed by your Authority?

NAMES	HOSPITAL

3.5. Are there hospitals in your Area which might be interested in participating in pilot schemes for development of adverse reaction monitoring in the near future? Whom should I contact?

NAMES	HOSPITAL

4. West Midlands Adverse Drug Reaction Study Group

4.1. Were you aware of the existence and work of the West Midlands Adverse Drug Reaction Study Group? YES ☐ NO ☐

4.2. Would you like further information concerning the Group?
YES ☐ NO ☐

4.3. If you are not already on our mailing list would you like to receive our bulletin? YES ☐ NO ☐

Any additional comments.

APPENDIX 7 : **Raw data from questionnaire on the hospital pharmacist's involvement in adverse drug reaction reporting and monitoring**

Table 1 : Availability of yellow cards - Replies to questions 1.1, 1.2 and 1.3

Availability	All Replies (119)			Areas/Health Boards (76)			Districts/Hospitals (43)		
	Yes	Some	None	Yes	Some	None	Yes	Some	None
In Pharmacy Departments	97	15	7	62	13	1	35	2	6
On wards	32	44	43	23	33	20	9	11	23
Carried by ward pharmacists	19	30	70	13	23	40	6	7	30

Table 2 : Completion of yellow cards - Replies to questions 2.1, 2.2 and 2.3

Pharmacist's involvement	All Replies (119)			Areas/Health Boards (76)			Districts/Hospitals (43)		
	frequently	sometimes	rarely or never	frequently	sometimes	rarely or never	frequently	sometimes	rarely or never
Pharmacist recommends a report	21	83	15	16	54	6	5	29	9
Pharmacist told of report sent	12	69	38	9	42	25	3	27	13
Pharmacist completes report	1	19	99	1	15	60	0	4	39

Table 3 : Pharmacists' current involvement in reporting and monitoring schemes
Replies to questions 3.1(a), (b) and (c)

	All Replies (119)		Areas/Health Boards (76)		Districts/Hospitals (43)	
Pharmacists' involvement	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Encouraging reporting to CSM	36	83	30	46	6	37
Monitoring patients on particular drugs	20	99	13	63	7	36
Other monitoring schemes	8	111	6	70	2	41

Table 4 : Pharmacists' future involvement in adverse drug reactions reporting and monitoring schemes
Replies to questions 3.2 and 3.3

Question	All replies (119)	Areas/Health Boards (76)	Districts/Hospitals (43)
"Are any schemes with pharmacists planned?"			
Yes - in next year	13	9	4
Yes - in next 5 years	27	22	5
No	79	45	34
	Yes	**Yes**	**Yes**
"Would you like to see pharmacists more involved in:"			
Adverse reaction reporting to the CSM	84	60	24
Other adverse reaction monitoring	69	52	17

Table 5 : Answers relating to the West Midlands Group
Replies to questions 4.1, 4.2 and 4.3

Question regarding West Midlands Group	All Replies (119)			Areas/Health Boards (76)			Districts/Hospitals (43)		
	Yes	No	No answer	Yes	No	No answer	Yes	No	No answer
Aware of West Midlands Group	81	32	6	56	15	5	25	17	1
Require further information	82	26	11	46	20	10	36	6	1
Wish to receive bulletin	88	11	20	50	9	17	38	2	3

APPENDIX 8 : The contribution of drug information - recording form

The contibution of Drug Information

Could you please keep a running record of questions concerning adverse reactions received by your centre.

DRUG(S)	ADVERSE EFFECT	IF THE QUESTION CONCERNED A SPECIFIC PATIENT:			WAS THE YELLOW CARD COMPLETED? IF NOT WHY?
		LIKELIHOOD OF EFFECT BEING DRUG INDUCED	OUTCOME: DRUG STOPPED, CONTINUED, ETC.	WAS A YELLOW CARD SUPPLIED	

APPENDIX 9 : Detection of reactions by ward pharmacists - recording form

Methods of detection:

A Drug discontinued
B Dosage reduced
C Addition to therapy eg. antihistamine
D Mentioned by patient
E Request for information (please state by whom)
F Told by nursing staff
G Told by medical staff
H Other - please specify

DRUG (S)	REACTION OR EVENT brief description	HOW DETECTED please code	FOLLOWED UP? yes/no	REPORTED? yes/no

APPENDIX 10 : Additional material

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